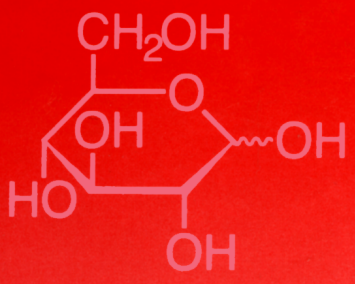
SPECIALIST PERIODICAL REPORTS

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Carbohydrate Chemistry

Monosaccharides, Disaccharides and Specific Oligosaccharides

A Review of the Literature Published in 1998

Volume 32

senior reporter R.J. FERRIER

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ROYAL SOCIETY OF CHEMISTRY

ISBN 0-85404-228-8
ISSN 0951-8428

A catalogue record of this book is available from the British Library

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Typeset by Computape (Pickering) Ltd, Pickering, North Yorkshire, UK
Printed by Athenaeum Press Ltd, Gatehead, Tyne and Wear, UK

Preface

Happily, for this Volume, we hope to have been able to return roughly to our normal production schedule and to have avoided the undue delay in publication of Volume 31 which was brought about by the inordinate pressure under which one of our team had to operate. Fortunately this was temporary, but it did highlight the complexity of the task of bringing together the work of extremely busy people and our complete dependence on each one. Another factor on which we rely heavily is modern communication without which a group as geographically dispersed as ours could not function.

The addition to the reporting team of Rob Field and Ravi Kartha, University of St. Andrews, and Matthew Tilbrook, University of Western Australia, has helped with the abstracting and writing tasks appreciably, and I am indebted to them for their cooperation and contributions. Keith Clinch has completed his role as Reporter which he has held since Volume 25, and I very readily record my gratitude to him.

As a team we are concerned at how little the structure of our presentation has changed over the years while the subject has undergone revolution – particularly through the birth of glycobiology – and we are conscious of the need to adapt. We will try to do this, but must find means of limiting and defining the range of the subject material that is covered. Already this is becoming increasingly problematical with the limits extremely difficult to identify in newer topics such as dendrimer and combinatorial chemistry as well as in such traditional areas as cyclitol and nucleoside work.

R.J. Ferrier
June 2000

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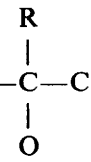
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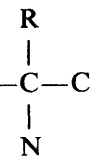
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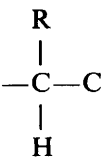
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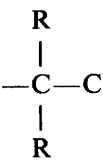
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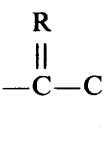
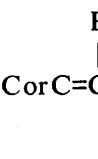
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Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ade	adenin-9-yl
AIBN	2,2-azobisisobutyronitrile
All	allyl
Ar	aryl
Ara	arabinose
Asp	aspartic acid
BBN	9-borabicyclo[3.3.3]nonane
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CD	circular dichroism
Cer	ceramide
CI	chemical ionization
Cp	cyclopentadienyl
Cyt	cytosin-1-yl
Dahp	3-deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.5.0]undec-5-ene
DCC	dicyclohexylcarbodi-imide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBALH	di-isobutylaluminium hydride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dmtr	dimethoxytrityl
e.e.	enantiomeric excess
Ee	1-ethoxyethyl
ESR	electron spin resonance
Et	ethyl
FAB	fast-atom bombardment
Fmoc	9-fluorenylmethylcarbonyl

Fru	fructose
FTIR	Fourier transform infrared
Fuc	fucose
Gal	galactose
GalNAc	2-acetamido-2-deoxy-D-galactose
GLC	gas–liquid chromatography
Glc	glucose
GlcNAc	2-acetamido-2-deoxy-D-glucose
Gly	glycine
Gua	guanin-9-yl
Hep	L-*glycero*-D-*manno*-heptose
HMPA	hexamethylophosphoric triamide
HMPT	hexamethylphosphorous triamide
HPLC	high performance liquid chromatography
IDCP	iodonium dicollidine perchlorate
Ido	idose
Im	imidazolyl
IR	infrared
Kdo	3-deoxy-D-*manno*-2-octulosonic acid
LAH	lithium aluminium hydride
LDA	lithium di-isopropylamide
Leu	leucine
LTBH	lithium triethylborohydride
Lyx	lyxose
Man	mannose
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
Mem	(2-methoxyethoxy)methyl
Mmtr	monomethoxytrityl
Mom	methoxymethyl
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
NAD	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NeuNAc	*N*-acetylneuraminic acid
NIS	*N*-iodosuccinimide
NMNO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
ORD	optical rotatory dispersion
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Phe	phenylalanine
Piv	pivaloyl
Pmb	*p*-methoxybenzyl

Pr	propyl
Pro	proline
p.t.c.	phase transfer catalysis
Py	pyridine
Rha	rhamnose
Rib	ribose
Ser	serine
SIMS	secondary-ion mass spectrometry
TASF	tris(dimethylamino)sulfonium(trimethylsilyl)difluoride
Tbdms	*t*-butyldimethylsilyl
Tbdps	*t*-butyldiphenylsilyl
Tipds	tetraisopropyldisilox-1,3-diyl
Tips	triisopropylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
Tfa	trifluoroacetyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
Thr	threonine
Thy	thymin-1-yl
Tips	1,1,3,3-tetraisopropyldisilox-1,3-diyl
TLC	thin layer chromatography
Tms	trimethylsilyl
TPP	triphenylphosphine
Tps	tri-isopropylbenzenesulfonyl
Tr	triphenylmethyl (trityl)
Ts	toluene-*p*-sulfonyl (tosyl)
Ura	uracil-1-yl
UDP	uridine diphosphate
UDPG	uridine diphosphate glucose
UV	ultraviolet
Xyl	xylose

1
Introduction and General Aspects

Boons has edited a multi-author book 'Carbohydrate Chemistry' which deals mainly with many topics of interest to synthetic chemists concerned with mono- and oligo-saccharide chemistry,[1] while David has authored one which serves as a basis for studies of the carbohydrates for chemists, biochemists and biologists.[2]

IUPAC-IUBMB recommended rules for the nomenclature of glycolipids have appeared.[3]

Advances in Carbohydrate Chemistry and Biochemistry, Vol. 53 has chapters dealing with tin-containing intermediates in carbohydrate chemistry,[4] synthesis aspects of selenium-containing sugars[5] and antibodies with specificity for monosaccharide and oligosaccharide units of antigens.[6] It also records appreciations of the work of John E. Hodge, Allene R. Jeanes and Harriet L. Frush.

Reviews of general significance have been written on the transformation of D-fructose, L-sorbose and isomaltulose, *i.e.* the most accessible ketoses, into starting materials for industrial synthesis,[7] and the use of carbohydrate 'building blocks' for the synthesis of pharmaceuticals.[8] A review of papers covering advances in protecting group chemistry published in 1997 includes sections on the protection of diols, amines, carboxylic acids and phosphates – all with significance for carbohydrate chemists.[9]

Many reviews relevant to the topics covered in the body of the Reports are referred to at the beginning of the chapters; others to have appeared relate to: cyclodextrins (a complete issue of *Chemical Reviews* has been devoted to them),[10] the chemistry of neutron capture therapy (sugar derivatives having linked carboranes are the significant compounds),[11] biosensing with polymer vesicles having biorecognition molecules on their surfaces (sialic acids, for example)[12] and carbohydrate–selectin interactions (including the identification of the Sia Le^x groups which determine the binding).[13]

Two other somewhat general topics to have been reviewed are the production of enantiopure bioactive molecules by biotransformations (*e.g.* cyclopentene and cyclohexa-1,3-diene derivatives),[14] and the use of hypervalent iodine reagents in carbohydrate chemistry (mainly addition and oxidation reactions of glycals).[15]

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2
Free Sugars

1 Theoretical Aspects

The anomeric effects in 2-methoxytetrahydropyran, 2-deoxyribose and glucose have been investigated by use of class II force field calculations,[1] and *ab initio* quantum mechanical methods including continuum solvation have been employed to study the intrinsic exocyclic hydroxymethyl rotational surface for β-D-glucopyranose as well as the α/β energy difference for D-glucopyranose.[2]

Mathematical calculations for predicting saccharide–saccharide interactions under vacuum and in aqueous solutions indicated very strong interactions for β-D-glucopyranose/β-D-glucopyranose, α-D-glucopyranose/α-D-fucopyranose and sucrose/β-D-glucopyranose.[3]

2 Synthesis

Mixtures containing up to 30% aldopentoses were obtained when formaldehyde and catalytic amounts of known intermediates of the prebiotic pathway were incubated with lead salts.[4]

A section on the preparation of ketosugars *via* ketosugar phosphates was included in a review on the use of aldolases in synthesis.[5] A kinetic study on the aldolase-catalysed condensation of various electrophilic aldehydes with pyruvate (**1**→**2**) showed that there is no advantage in the use of preformed phosphates (compounds **1**, R = PO_3^{2-}).[6]

The mechanism of the condensation of sugar-aldehydes and -ketones with Dondoni's reagent [2-(trimethyl)thiazole] has been examined with particular attention to the fact that the reactions of ketosugars are accelerated by addition of equimolar quantities of a free aldose or a non-sugar aldehyde.[7]

Efficient hydrolysis (yields 80–90%) of ethyl thioglycosides has been achieved with Bu_4NIO_4 and 70% aqueous triflic acid in acetonitrile.[8]

2.1 Tetroses to Hexoses. – L-Threose derivative **3** has been synthesized from L-tartaric acid in four standard steps, as a useful precursor of homochiral, functionalized, long-chain alcohols **4**.[9] Further tetrose derivatives suitable for chain-extension, such as **5**, have been obtained by radical cleavage of the C-1–C-2 bond in pentofuranose derivatives on exposure to (diacetoxyiodo)benzene

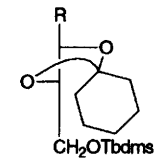
Carbohydrate Chemistry, Volume 32
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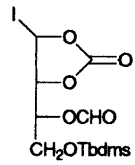
R = H or PO_3^{2-}
X = H, OH, OEt, Cl

1

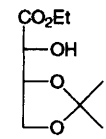
2



3 R = CHO
4 R = R'CH~OH
R' = All, Bu^n, propargyl *etc.*



5

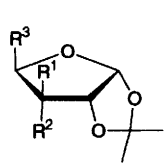


6

and iodine (see Vol. 31, Chapter 2, ref. 7).[10] The syntheses of D- and L-threose- and -erythrose-derivatives modified at the 2-position from D-isoascorbic and L-ascorbic acid *via* intermediate **6** and its enantiomer, respectively, are referred to in Chapters 5 and 12.

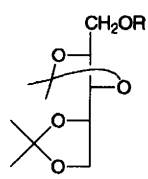
Pentodialdose derivatives **7**, obtained from D-glucose by conventional methods, were converted to 5-monodeuterated pentose derivatives **8** with *S*/*R*-ratios from 4:1 to 1:7.4 by reduction with $LiAlD_4$ in the presence of various ligands. The use of these compounds in the preparation of 5′-monodeuterated nucleosides is covered in Chapter 20.[11]

The key operation in the preparation of L-xylose from xylitol was the lipase-mediated enantioselective deacetylation of the racemic cyclic acetal **9** to give the L-enantiomer **10**, whereas preparation of the L-fucose precursor **12** involved controlled, lipase-mediated mono-acetylation of the galactitol-derived cyclic acetal **11**.[12] Addition of nitromethane to D-xylose by an

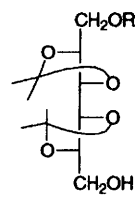


R^1, R^2 = H, OBn

7 R^3 = CHO
8 R^3 = CHDOH



9 R = Ac (racemate)
10 R = H (L-enantiomer)



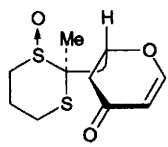
11 R = H (*meso*)
12 R = Ac (L-enantiomer)

improved procedure and exposure of the 1-deoxy-1-nitroalditol thus formed to Nef conditions (aq. NaOH, then aq. H_2SO_4) gave simple access to D-idose.[13] ^{11}C-Labelled aldononitriles, obtained from D-arabinose by chain-elongation with $NH_4{}^{11}CN$ on a solid support, furnished D-[1-^{11}C]glucose on reductive hydrolysis with Raney nickel/formic acid (radiochemical yield >95%).[14]

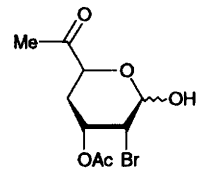
The biosynthesis of apiose is referred to in Chapter 18.

A new method for epimerizing free sugars *via* 1,2-*O*-stannylene derivatives has been exploited in a practical synthesis of D-talose from D-galactose. The process is equilibrium driven and favours the structure with an axial OH-group at C-2.[15]

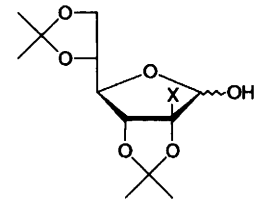
Stereocontrolled, Lewis acid-promoted addition of Danishefsky's diene (*E*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene) to *syn*-2-formyl-2-methyl-1,3-dithiane-1-oxide furnished compound **13** which is amenable to functionalization of the enone grouping and may thus serve as intermediate in the synthesis of unusual deoxy- and deoxyhalosugars, *e.g.* **14**.[16] The preparation of a 2-deoxy-D-*xylo*-hexose derivative from cycloheptatriene is referred to in Chapter 12.



13

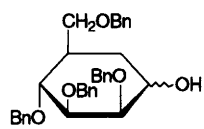


14

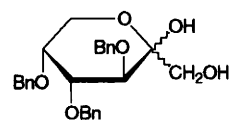


15 X = H
16 X = D

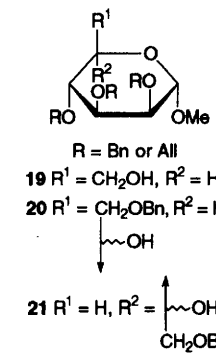
The hydrogen atoms α to the unprotected anomeric centres in certain sugars are readily exchanged on heating in dioxane–THF–Et_3N–D_2O (4:4:2:3), often with considerable stereoselectivity as demonstrated by the deuteration **15**→**16** which proceeded almost quantitatively.[17] The direct conversion of aldohexoses to hex-2-uloses in the presence of samarium iodide and oxygen (see Vol. 30, p. 5, ref. 23) has been improved by replacing THF as solvent with THP. The yield of the transformation **17**→**18**, for example, increased from 44 to 88%.[18]



17



18

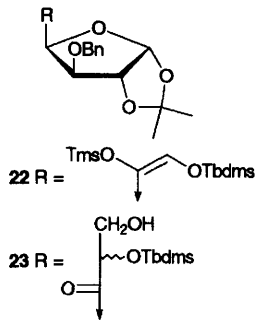


R = Bn or All
19 $R^1 = CH_2OH$, $R^2 = H$
20 $R^1 = CH_2OBn$, $R^2 = H$
21 $R^1 = H$, R^2 = OH / CH_2OBn

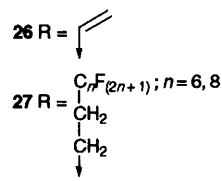
The introduction of ^{17}O at C-2, C-4 and C-6 of D-glucose has been effected by irreversible, stereoselective benzoylation of appropriately protected precursors either by displacement of a triflate group with ^{17}O-labelled sodium benzoate or by reaction of a free hydroxyl group with ^{17}O-labelled benzoic acid under Mitsunobu conditions, then debenzoylation.[19]

2.2 Chain-extended Sugars. – A facile synthesis of D-*gluco*-hept-2-ulose from D-mannose is referred to in Part 4 of this chapter (ref. 50).

2.3.1 Chain-extension at the 'Non-reducing End'. Suitably protected methyl α-D-mannnopyranosides **19** were oxidized (Swern) and chain-extended with benzyloxymethylmagnesium chloride to give the C-5 epimers **20**, as well as small quantities of the C-5 epimers **21**. Conversion of these heptosides to monophosphates is covered in Chapter 7.[20] One-carbon extensions have also been achieved by indium trichloride-catalysed, asymmetric aldol condensations with formaldehyde; the D-glucose-derived silyl enol ether **22**, for example, furnished heptos-5-ulose derivative **23**.[21]



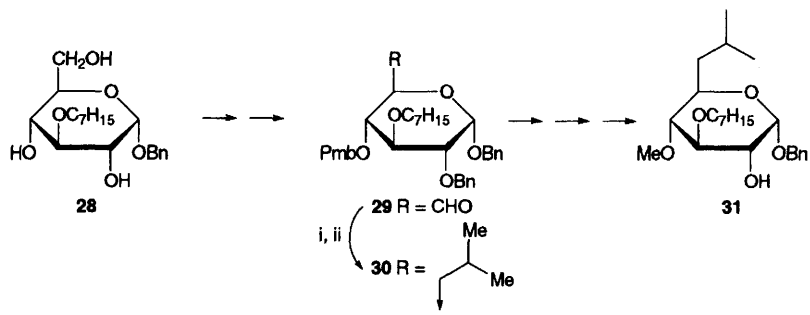
24 R = CHO
25 R = $C_nF_{(2n+1)}$; n = 1, 4, 6



Addition of fluorinated-alkyl organometallics to carbohydrate aldehyde **24** gave access to higher deoxyfluoro-sugars **25**,[22] and the related compounds **27** have been prepared by addition of fluorinated-alkyl halides to terminal alkene **26** in the presence of dithionite as initiator.[23]

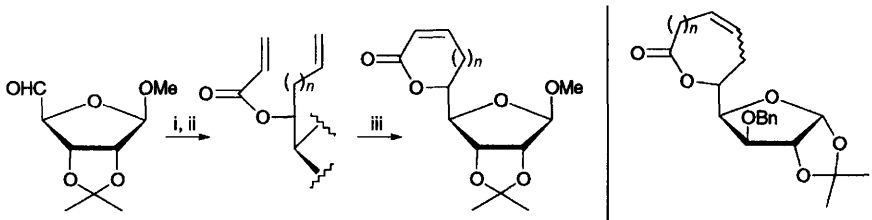
The branched chain-extension in the synthesis of compound **31**, a D-glucose-based potential mimetic of the bioactive cyclic dipeptide hapalosin, from benzyl 3-*O*-heptyl-α-D-glucopyranoside (**28**) has been accomplished by Wittig reaction of aldehyde **29** to give **30**, as indicated in Scheme 1.[24]

Treatment of pentodialdose derivative **32** with vinylmagnesium bromide or allyltrimethylsilane, followed by acryloyl chloride, gave the di-ω-unsaturated



Reagents: i, Pr^iPPh_3I, Bu^nLi; ii, $PhSO_2NHNH_2$, aq. NaOH, $MeOCH_2CH_2OH$

Scheme 1



32 **33** $n = 0$ or 1 **34** $n = 0$ or 1 **35** $n = 4$ or 8

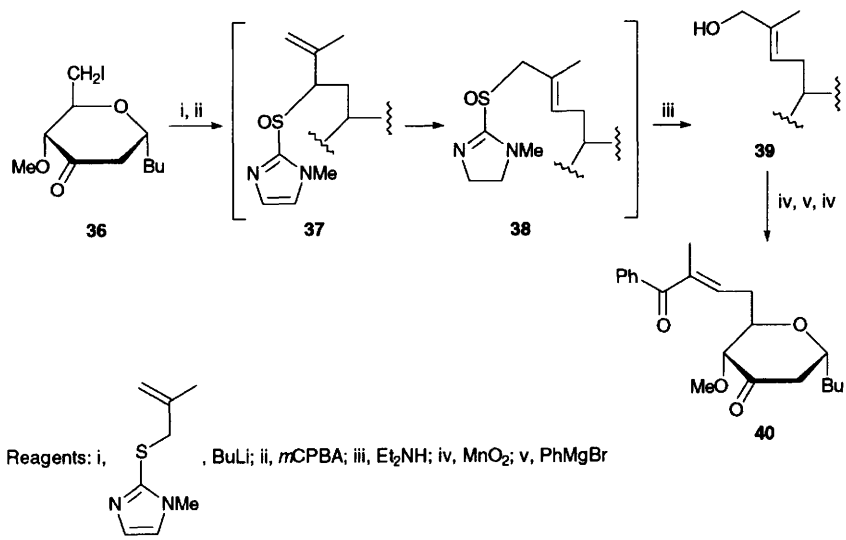
Reagents: i, CH_2=CHMgBr or CH_2=$CHCH_2$Tms, BF_3•OEt_2;
ii, CH_2=CHCOCl, Et_3N, DMAP; iii, Grubbs' catalyst, $Ti(OPr^i)_4$

Scheme 2

higher sugar esters **33**, which underwent ring-closing metathesis in the presence of Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium] and titanium tetraisopropoxide to afford α,β-unsaturated γ- or δ-lactones **34** (Scheme 2).[25] A similar approach was used to produce the unsaturated macrocyclic lactones **35**.[26]

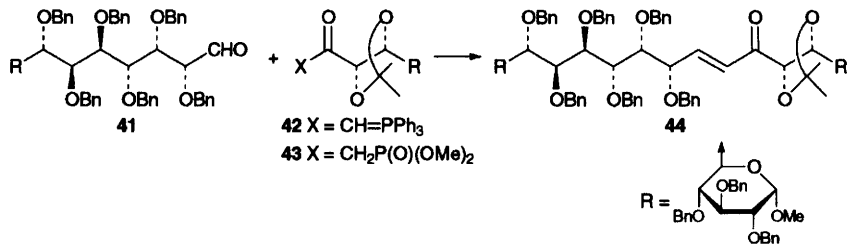
A multi-step synthesis of compound **40**, a model for the lower periphery of the macrocycle antibiotic maytansine, involved alkylation of an allylic sulfide anion by 6-iodide **36** (obtained in five steps from D-glucal) for introduction of a branched four-carbon extension (Scheme 3). Oxidation to sulfoxide **37** with concomitant 2,3-sigmatropic rearrangement and thiophilic trapping of the resulting sulfenate ester **38** furnished allylic alcohol **39**. Grignard methodology was used in the further elaboration to target **40**.[27]

Wittig condensations of various sugar dialdehyde derivatives with sugar derived phosphoranes or phosphonates gave higher sugar dialdoses. Condensation of the C_{12}-dialdehyde **41** with the C_9-phosphorane **42**, for example, produced the C_{21}-dialdose **44** (Scheme 4). This reaction had to be conducted at



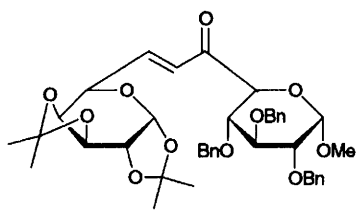
36 **37** **38**

Scheme 3

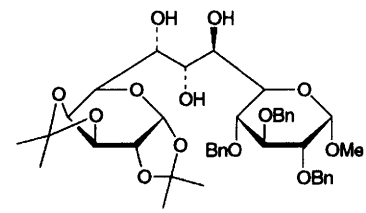


Scheme 4

13 kB, whereas the more nucleophilic phosphonate **43** reacted at atmospheric pressure, giving rise, however, to elimination by-products.[28] A series of C_{12}- or C_{13}-dialdoses, *e.g.* **46**, were prepared by similar condensations between C_5- or C_6-sugar dialdehyde derivatives and three different C_7-phosphoranes or phosphonates to give enones, in this case **45**, followed by highly stereoselective reduction of the carbonyl group ($ZnBH_4$) and osmylation.[29]

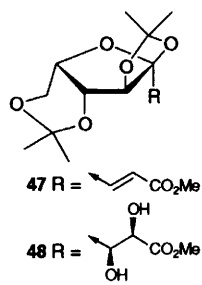


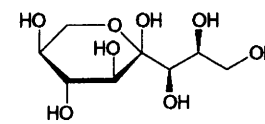
45



46

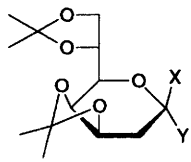
2.3.2 Chain-extension at the 'Reducing End'. The stereoselective osmylation of L-*xylo*-oct-2-ene-4-ulofuranonate (**47**) proceeded with high selectivity in favour of diol **48**, which was isopropylidenated, then reduced with LAH to give, after deprotection, L-*glycero*-D-*galacto*-oct-4-ulose (**49**).[30]



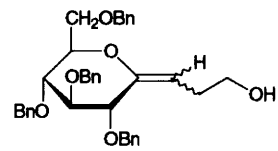


49

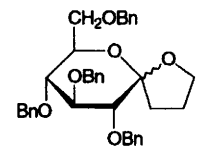
Alkyl ketosides **53** were available by opening of the mixed spiroepoxides **52** with alcohols in the presence of $ZnCl_2$ (only α-anomers were produced). The isomeric mixture **52** was obtained by oxidation of the known *exo*-glycal **51** with dimethyldioxirane, and a considerable improvement in the synthesis of **51** from lactone **50** by use of a Peterson olefination instead of reaction with Tebbe reagent has been reported.[31]



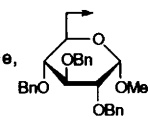
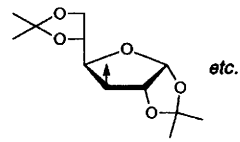
50 X, Y = =O
51 X, Y = =CH_2
52 X, Y = 
53 X = CH_2OH, Y = OR



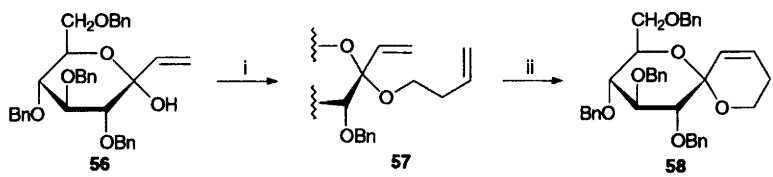
54



55

R = Me,  ,  *etc.*

Saturated spiroketals **55** have been prepared by acid-promoted cyclization of substituted *exo*-glycals **54** (the synthesis of **54** and similar substituted *exo*-glycals by use of a Ramberg–Bäcklund rearrangement is covered in Chapter 13).[32] Unsaturated spiroketals with [5,7]-, [5,6]-, [5,5]- and [5,4]-ring systems, *e.g.* compounds **58**, have been synthesized by ring-closing metathesis in the presence of Grubbs' catalyst, as illustrated in Scheme 5. The required di-ω-unsaturated compounds **57** were obtained by addition of vinyl- or allylmagnesium chloride to perbenzylated D-gluconolactone, then use of the products **56** in the glycosylation of terminally unsaturated alcohols.[33]



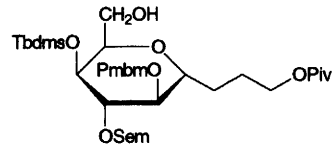
56 **57** **58**

Reagents: i,  , K-10, ii, Grubbs' catalyst, toluene

Scheme 5

Two-carbon chain-extensions of protected free sugars by reaction with amide-stabilized sulfur ylides and of unprotected aldoses by reaction with a *in situ*-generated phosphorus ylide, furnishing acyclic products, are referred to in Chapter 16. Also covered in Chapter 16 are the related chain-extensions, (i) of 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-D-mannitol by use of a lithiated disilylthioacetal leading to KDO; (ii) of a D-glucopyranosyl oxocarbonium ion, formed from the corresponding glycosyl fluoride by use of 2-(trimethylsilyloxy)furan, leading to a dec-2-enonic acid γ-lactone derivative; (iii) of hexonic acid chlorides by use of anions of dialkyl malonate leading to branched-chain 2-deoxyoctulosonic acid derivatives.

A new strategy for the synthesis of *C*-glycosides of phenols and the synthesis of *C*-glycoside **59**, representing a nine-carbon segment of the marine natural product okadoic acid, from small, non-carbohydrate molecules are referred to



59 Pmbm = *p*-methoxybenzyloxymethyl

in Chapter 3. The synthesis of 6-thio-*N*-acetylneuraminic acid from a mannose precursor involving a three-carbon chain-elongation by condensation with oxalacetic acid, followed by decarboxylation, is covered in Chapter 11, and a stereocontrolled, Lewis acid-catalysed aza-Cope rearrangement of *N*-glycosyl homoallylamines to afford chain-extended aminosugars in Chapter 18.

3 Physical Measurements

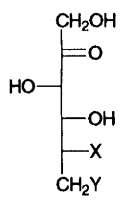
The pK_a values of aldohexoses have been determined by capillary electrophoresis.[34] Aqueous solutions of glucose, fructose, sucrose and trehalose, respectively, at concentrations from 0.2 to 70% have been investigated by modulated differential scanning calorimetry to measure the apparent heats of melting and freezing as well as the melting and freezing point depressions as functions of concentration.[35] The interaction of D-glucose with sodium monoborate has been studied by use of the isomolar solution method.[36]

The kinetics of the decomposition of sucrose in impure sugar solutions have been studied in acid media over a range of temperatures. Whereas the rate constant was affected by both temperature and pH, the presence of non-sugar contaminants appeared to have no effect.[37]

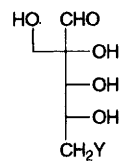
4 Isomerization

In a kinetic study on the non-enzymic glucose–fructose isomerization new measurements of the thermodynamic equilibrium constant at different temperatures were compared to literature data; an enthalpy value of 8.5 kJ mol^{-1} has been derived.[38]

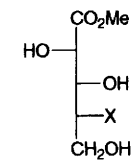
The $Ca(OH)_2$-promoted epimerization of chito-oligosaccharides to produce Man*p*NAc-containing derivatives is covered in Chapter 9.



60 X = OH, Y = OBn or N_3
61 X = N_3, or OBn; Y = OH
62 X = Y = OMe or X = N_3, Y = F



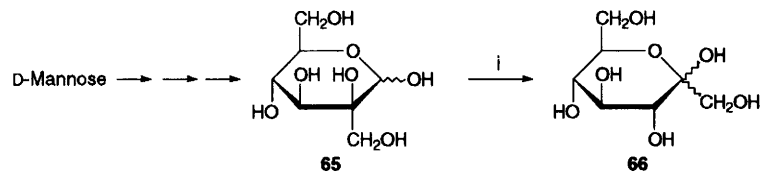
63 Y = N_3 or OBn



64 Y = N_3 or OBn

D-Glucose has long been known to isomerize to D-mannose under the influence of $[Ni(H_2O)_2(tmen)_2]Cl_2$ in methanol with an interchange in the positions of C-1 and C-2 (see L. London, *J. Chem. Soc.*, 1987, 61; Vol. 21, pp. 4/5, ref. 23), and it has now been shown that 5-azido-5-deoxy-D-glucose undergoes a similar epimerization with skeletal rearrangement, furnishing 5-azido-5-deoxy-D-mannose when exposed to $Ni(Me_4en)_2Cl_2$ in methanol.[39] Analogous rearrangements have been observed in the case of D-fructose and the C-6-modified D-fructose derivatives **60**, which gave **63**; the C-5-modified D-fructoses **61**, on the other hand, were degraded to the D-arabinonic acid derivatives **64**, and the C-5/C-6 modified compounds **63** gave complex reaction mixtures.[40]

The molybdate-mediated Bilik rearrangement of 2-*C*-hydroxymethyl-D-mannose (**65**) to D-*gluco*-hept-2-ulose (**66**), which results in a 2:23 equilibrium mixture, has been exploited in a facile synthesis of the latter compound from D-mannose (Scheme 6).[41]



Reagents: i, Molybdic acid

Scheme 6

An improved procedure for the direct isomerization of hexoses to hex-2-uloses by use of SmI_2/O_2 is referred to in Part 2.1 of this chapter (ref. 18).

5 Oxidation

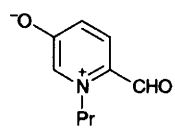
The kinetics and mechanisms of the oxidation of reducing sugars in alkaline media by Pt(IV)[42] and by OsO_4[43] have been investigated. The former study included aminosugars and methyl ether derivatives. A mechanism has been proposed for the oxidation of D-arabinose, D-xylose and D-galactose to the respective glyconic acids by NBS in acidic solutions under Pd(II)-catalysis.[44] Pyranose dehydrogenase from *Agarius bisporus* oxidized D-galactose at C-2 and D-glucose at C-2 as well as C-3 to give D-*lyxo*-hexos-2-ulose and D-*eythro*-hexos-2,3-diulose, respectively.[45]

6 Other Aspects

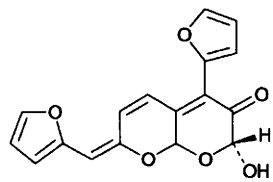
An overview of old and new methods for the chemical transformation of the most accessible and inexpensive ketoses, namely D-fructose, L-sorbose and isomaltulose, into synthetic building blocks for industrial application has been published.[46]

A two-step synthesis of 4-hydroxy-3-methoxybenzaldehyde (vanillin) from D-glucose has been developed using a recombinant *E. coli* biocatalyst to convert the sugar to vanillic acid and a fungal aryl aldehyde dehydrogenase for the reduction of the acid to vanillin.[47]

6-Formyl-1-propylpyridinium-3-olate (**67**) has been isolated from the Maillard reaction of D-glucose and D-fructose with propylamine.[48] The most intensely coloured products of the Maillard reaction of pentoses have been characterized by colour dilution analysis. Among the 20 compounds detected was the previously unknown tetracyclic product **68**.[49,50] The catalytic effect of the ions of various metals (Co, Cu, Fe, Mg, Mn, Ni, Zn) on the degradation of D-glucose to 4-hydroxymethyl-2-furfural has been investigated.[51]



67



68

On treatment with a combination of phenylboronic acid in the presence of the surfactant aliquat 336, fructose, but not glucose or sucrose, formed a boronate anionic complex with a quaternary ammonium counter ion and could thereby be transported from an alkaline solution across a membrane, to be concentrated in the receiving phase at pH 6.[52] In the presence of a hydroxide ion gradient, several free sugars were transported across an anion-exchange membrane against their concentration gradients from a neutral solution cell to a basic one.[53]

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3
Glycosides and Disaccharides

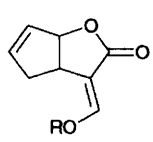
1 *O*-Glycosides

1.1 Synthesis of Monosaccharides Glycosides. – A review has been published on papers dealing with solid-phase syntheses in organic chemistry (Part III) which appeared during the period Nov 1996–Dec 1997. It contains references to the syntheses of glycosides and glycopeptides.[1] A further review on glycopeptides and glycoproteins, with emphasis on recent literature, has also dealt with the synthesis of relevant glycosidic linkages (*O*-, *N*-, *S*- and *C*-bonds are treated),[2] and one on 'disposable tethers in synthetic organic chemistry' has featured several carbohydrate examples, including some that led to glycoside formation.[3] Reviews on enzymic methods are noted in the final part of the following section (1.1.1).

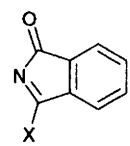
1.1.1 Methods of synthesis of glycosides. Some simple glycosides can be made directly from free sugars by novel approaches. D-Fructose has been converted to the decyl and dodecyl β-D-furanosides *via* the ethyl and butyl analogues (to overcome solubility problems) by direct reaction with the alcohols in the presence of BF_3.MeOH as catalyst.[4] Furanosides of D-glucose, D-galactose, D-mannose, D-glucuronic acid and D-galacturonic acid have been made with long chain alcohols in THF with Lewis acids such as BF_3, $FeCl_3$, $CaCl_2$ as catalysts. Mainly β-products were obtained.[5] On the other hand, butyl α- and β-D-glucopyranosides have been made from the free sugar with H-form zeolites as catalysts, the reactions proceeding *via* the furanosides.[6] The proportions of permethylated furanosides and pyranosides produced by permethylation of L-fucose and D-galactose can be controlled by variation of the conditions used.[7] Reaction of the sodio derivative of tetra-*O*-benzyl-D-glucose with compound **1** (R-Tf) gave diastereomeric glycosides (**1**, R= tetra-*O*-benzyl-α,β-glucose),[8] and in related work chlorinated heterocycles (*e.g.* **2**, X=Cl, and **3**) were similarly treated to give products such as **2** (X = tetrabenzylglucosyloxy) which were tested as glycosylating agents. While none were as good as the glycosyl trichloroacetimidates, this approach has potential for making some α-glucosides.[9]

Peracetylated derivatives of arabinofuranose, galactofuranose and rhamnopyranose, used with tin(IV) chloride, show advantages over the corresponding glycosyl halides for making corresponding glycosides,[10] while the penta-*O*-

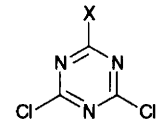
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1



2



3 X = Cl, OMe, OPh, NH_2NHBn

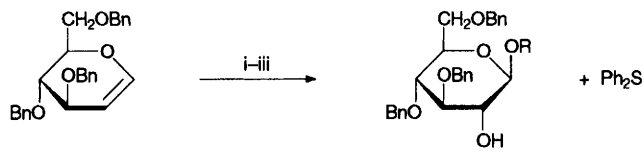
acetyl-gluco-, manno- and galacto-pyranoses, used with iron(III) chloride and alcohols, including sugar alcohols, afford access to corresponding pyranosides in yields greater than 70% and α,β ratios greater than 12:1.[11] In more detailed work, the BF_3-catalysed formation of pyranosides of simple alcohols from penta-*O*-acetyl-β-D-glucopyranose in various solvents has been shown to involve formation of the β-products followed by slow anomerization;[12] $BF_3.Et_2O$ also enhances the rate and efficiency of the $Yb(OTf)_3$-promoted production of glycosides from 1-*O*-acetyl-tetra-*O*-benzyl-α-D-glucopyranose.[13]

Glycosyl 2-pyridinecarboxylates are effective glycosylating agents which can be activated by the mild Lewis acids $Cu(OTf)_2$ and $Sn(OTf)_2$, the former favouring the production of α-glycosides (cf. Vol. 25, p. 16).[14] Related work has used $AgClO_4$–$SnCl_4$ or Cp_2HfCl_2–$AgClO_4$ to activate glycosyl carbonates in α-selective glycosylations,[15] and Mukaiyma and colleagues have developed another highly selective 1,2-*trans*-glycoside synthesis using *p*-chlorobenzylated glycosyl phenyl carbonates as donors.[16] Propargyl β-glycosides ($ROCH_2CCH$), which are obtainable in very high yields from peracetylated sugars, offer an improved route to allyl analogues (partial hydrogenation over Lindlar catalysts),[17] and access to acetoxymethyl glycosides [$ROCH_2O$-$C(O)CH_3$]. These, with alcohols, including carbohydrate alcohols, and BF_3 as catalyst readily give glycosides and disaccharides, acetoxymethyl tetra-*O*-benzyl-β-D-glucopyranoside giving mainly β-products in good yield.[18]

Further interest has been shown in the use of glycosyl phosphates and related compounds for chemical glycosylations. Thus the 1-α- and 1-β-diphenylphosphinates of tri-*O*-benzylribofuranose[19] and tetra-*O*-benzylglucopyranose[20] have yielded glycosides efficiently at −78 °C with TmsOTf as catalyst. In the latter case only β-products were observed and, in this paper, the corresponding glucopyranosyl propane-1,3-diyl phosphate was also shown to be a donor (α,β ratios 1:2). Glycosyl diethyl phosphites act as donors at neutral pH in the presence of $Ba(ClO_4)_2$ in organic solvents. Yields of products (including disaccharides) were in the range 30–95%; α-glucosides predominated in ether and CH_2Cl_2; β-analogues were favoured in MeCN.[21] In related studies tera-*O*-benzyl-D-glucopyranosyl dimethylthiophosphates with alcohols and AgOTf, NIS in CH_2Cl_2, were used to give glycosides (including disaccharides) in high yields with α:β ratios about 3:1.[22] On the other hand, 1,2-*trans*-glycosides were favoured by use of glycopyranosyl phosphoramidates as donors together with TmsOTf or $BF_3.Et_2O$.[23]

Unsaturated sugars, particularly glycal derivatives, continue to be useful starting materials for glycoside synthesis. A novel direct oxidative route to 2-unprotected β-glucosides from tri-*O*-benzyl-D-glucal is illustrated in Scheme 1;

various simple and complex (including carbohydrate) alcohols were used as well as 3-*O*-benzyl-4,6-*O*-isopropylidene-D-glucal and tris-*p*-methoxylbenzyl-D-glucal. Reaction conditions and the proportions of reagents used were carefully monitored.[24] Two papers have appeared on the iodoacetoxylation of glycal derivatives and hence the production of 2-deoxyglycosides. Acetylated glycals with I_2, $Cu(OAc)_2$ give predominantly *trans*-diaxial 2-deoxy-2-iodo-glycosyl acetates and hence, in the case of the tri-*O*-acetyl-D-glucal adduct, 2-deoxy-α-D-glucosides.[25] Related studies with tri-*O*-benzyl-D-galactal have led to 2-deoxygalactosides.[26] Similar additions have been effected by use of polymer-supported SeBr or SeNPhth reagents in the presence of alcohols, followed again by radical reductions to develop the 2-deoxy group.[27] Epoxidation of alkene **4** (Vol. 26, Chapter 3, ref. 148), followed by alcoholysis of the *spiro*-epoxide using $ZnCl_2$ as catalyst, gives only the α-glycosides **5** which may be readily converted to KDO glycosides. Primary and secondary sugar alcohols were amongst those used.[28]

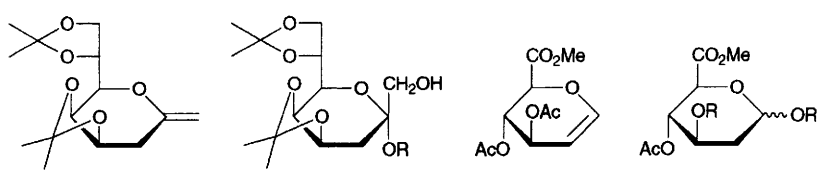


Reagents: i, Ph_2SO, Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine; ii, MeOH (1 equiv.), Et_3N; iii, ROH, $ZnCl_2$

Scheme 1

The glycal → 2,3-unsaturated glycoside reaction has been used to make a 6-deoxy-α-L-talopyranoside of cholesterol by way of the corresponding 2-bromo-2,6-dideoxyaltroside. An intramolecular displacement of bromide gave the required product.[29] Thiem and colleagues have used the rearrangement reaction to couple tri-*O*-acetyl-D-glucal and other glycal derivatives, including pentose and disaccharide compounds, to O-2 and O-1, O-3 of glycerol,[30] and to several long chain alkanols and diols.[31] In an extension of this work the authors encountered an irregularity when working with the D-glucuronic acid-derived glycal **6** because, with some alcohols (ROH), instead of giving the usual 2,3-unsaturated glycosides, it resulted in the 2-deoxy saturated products **7** with the alcohol groups incorporated at C-1 and C-3.[32] Three of the authors of the present Reports have found that water may be the cause of this anomaly.[33] Glycosides obtainable from cyclopropano derivatives of glycals are noted in Chapter 14.

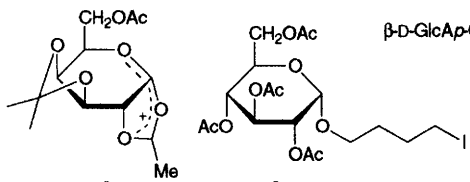
Attention has been drawn to the high tendency of glycosyl donors which react *via* the 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-D-galactose-based carboca-



4 **5** **6** **7**

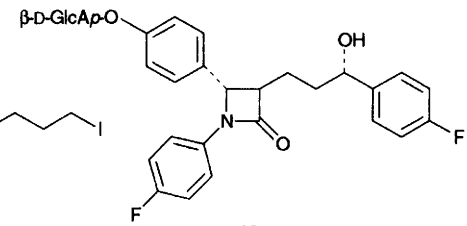
tion **8** to transfer an acyl group from C-2 to the acceptor alcohol during attempted glycosylations. A theoretical study has led to the conclusion that acyl transfer is a kinetic process while reaction to give β-glycosides is thermodynamically controlled.[34]

Glycosyl trichloroacetimidates remain an invaluable group of donors, furanosyl derivatives of glucose, mannose and galactose now having been reported to be good sources of 1,2-*cis*-glycosides.[35] A general reaction of the pyranosyl derivatives of glucose and mannose in THF in the presence of SmI_2 and oxygen involves the solvent, compounds such as **9** being produced in variable yield (18–85%). However, the mannose analogue gives the α-glycosyl iodide predominantly and tetra-*O*-benzylglucose trichloroacetimidate gives the glycosyl α-iodide exclusively.[36] The trichloroacetimidate method has been used to make 2-*O*-(α-D-glucopyranosyl)-*sn*-glycerol (other approaches being used for the β-anomers and 1-substituted analogues),[37] and the β-glucoside of benzaldehyde cyanohydrin [(*R*)-prunasin] (*via* the amido compound which was dehydrated).[38] By use of analogous methods *p*-substituted benzyl α-D-mannopyranosides were made for testing of the inhibition of mannose-sensitive adhesion of *E. coli*,[39] and the β-glucuronide conjugate (**10**) of the cholesterol absorption inhibitor SCH 58235 was made.[40]



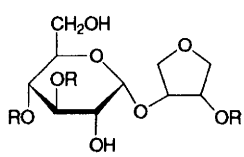
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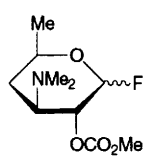


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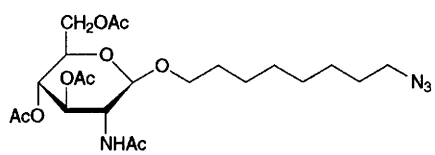
Glycosyl halides still feature prominantly in glycoside synthesis. Fluorides and chlorides can be made by the electrolysis of sugars substituted at all hydroxyl groups except the anomeric in the presence of Ph_3P, CH_2Cl_2 and $PPh_3H.BF_3$ or Bu_4NCl. Weakly nucleophilic alcohols [*e.g.* $HOBu^t$, $HOCH(CF_3)_2$, $HOCH_2CF_3$] also take part in this reaction and give glycosides directly.[41] 6-*O*-Acetyl-3,4-di-*O*-allyl-2-*O*-benzyl-D-glucosyl fluoride was used in the preparation of phosphate **11** which is a novel, potent IP_3 receptor ligand,[42] and the mixed carbonate **12**, a desosamine derivative, was employed for coupling to the macrocycle 10-deoxymethynolide to give YC-17 which is thought to be an intermediate in the biosynthesis of methymycin.[43]



11 R = PO_3H_2



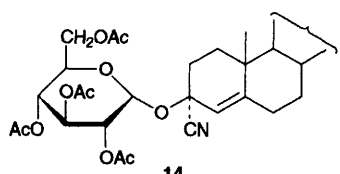
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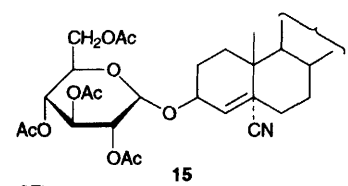
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β-Glycosides of *N*-acetylglucosamine with ω-substituted spacer aglycons (*e.g.* **13**) were made by use of the glycosyl chloride and converted into the ω-NH_2 analogues for coupling.[44] Glycosylation of the conjugated enone 17-*O*-acetyltestosterone with tetraacetyl-D-glucosyl bromide in the presence of $Hg(CN)_2$ and $HgBr_2$ did not give the *O*-substituted enol form, but instead the cyanide ion initially attacked the enone at the carbonyl centre, and also in Michael fashion, to give *O*-nucleophiles which caused the formation of products **14** (37% + 5% β-isomer) and **15** (18%), respectively.[45] The use of glycosyl halides in the synthesis of glycosides related to natural products (Section 1.2) remains commonplace.

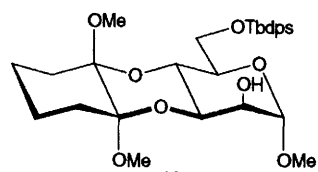
Thioglycosides and analogues such as their sulfoxides, likewise are used very frequently. A valuable comparative study has been carried out on the donor capabilities of *O*-benzyl and *O*-benzoyl protected *S*-ethyl 1-thio-α-L-rhamnopyranoside and the corresponding α-D-mannopyranoside in competitive experiments with the 2-axial alcohol **16** as acceptor. Phenylseleno analogues were also examined. By extensions of the work it was established, for example, that electron withdrawing groups deactivate donors decreasingly when substituted at O-2, O-6, O-4, and O-3. That is, with the exception of those at O-2, the effects are strongest when the groups are near the ring oxygen atom rather than the anomeric centre.[46]



14



15



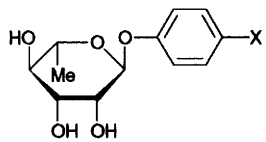
16

Following Fraser-Reid's introduction of pent-4-enyl glycosides, the corresponding *S*-pent-4-enyl thioglycosides have been introduced, the mixed L-rhamnosyl anomers having been used to make *p*-substituted phenyl α-L-rhamnopyranosides (**17**) which are active principles of the leaves of *Moringa oleifera*.[47]

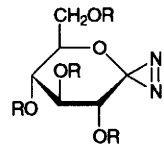
Anomeric sulfoxides, activated by Tf_2O, can rearrange to glycosyl sulfenates which impede glycosylation reactions at low temperature. In consequence, inverse addition of reagents can be beneficial and may help to overcome difficulties some workers have had in using the glycosyl sulfoxide glycosylation method.[48] Other work with glycosyl sulfoxides is covered in Section 1.1.2.

Compounds **18** [R = $CH_2C_6H_4F(p)$, Ac and Bn] have been used to glycosylate TiO_2 surfaces by exposing TiO_2-covered glass slides to solutions of the diazirines in CH_2Cl_2.[49] The benzylated compound was used to glycosylate

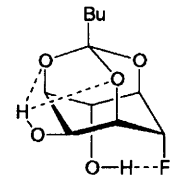
the fluoroinositol **19** and this, together with spectroscopic studies, showed that the illustrated F-hydrogen bond is weaker than the bifurcated bond. Glycosylation occurred preferentially at the more acidic axial hydroxyl group.[50]



17 X = CH_2CN *etc.*



18



19

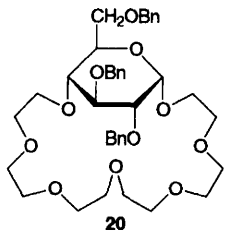
In the area of glycosyl exchange the chiral crown ether **20** was made by building up the appropriate hydroxy-terminating polyoxy substituent at O-4 and glycoside exchanging it with a methyl aglycon by use of TmsOTf as catalyst.[51] Direct transglycosylation has allowed the formation of 2-ethylhexyl-, 1-octyl- and 2-octyl-β-D-xylobiosides from xylan.[52]

Considerable interest continues in the use of enzymes for the synthesis of specific glycosides. A review has appeared on this topic which extended into the preparation of oligosaccharides,[53] while another covered glycosylation by use of glycosidases, glycosyl transferases and whole cells containing these enzymes.[54] Specific glucosides whose syntheses have been reported are benzyl α-D-glucopyranoside (from starch and benzyl alcohol with amylase and an amyloglucosidase from *Rhizopus sp.*),[55] *l*-menthyl α-D-glucopyranoside (from maltose and a glucosidase from *Saccharomyces cerevisiae*),[56] alkyl β-D-glucopyranosides (with almond β-glucosidase)[57] and butyl 6-*O*-(4-phenylbutanoyl)-β-D-glucopyranoside (with the same β-glucosidase coupled with lipase B from *Candida antarctica*).[58] Also 5-phenylpentyl β-D-galactopyranoside has been produced (50% conversion) using a lipid-coated β-galactosidase in supercritical CO_2 with *p*-nitrophenyl β-galactoside as source,[59] and mannosyl transfer between the analogous β-mannopyranoside and methyl β-D-mannopyranoside, -glucopyranoside, -*N*-acetylglucosaminide and 1,5-anhydro-2-deoxy-D-*arabino*-hexitol using a snail β-mannosidase gave mainly β-(1→4) linked disaccharides (<6%) as well as small amounts of other products.[60]

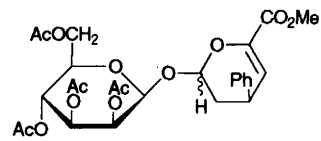
1.1.2 Classes of glycosides. – In this Section different groups of glycosides which have received particular attention are treated. These are β-mannopyranosides, amino-sugar glycosides, glycosides of acyclic compounds, those having aromatic groups within the aglycons and compounds having more than one glycosidically linked sugar.

By treating either *O*-protected phenyl 1-thiomannopyranosides or their derived sulfoxides with PhSOTf Crich and Sun have produced highly reactive α-glycosyl triflates which, with alcohols, afford β-mannosides in excellent yields.[61] In the D-glucose series high yields of products were obtained even with highly hindered alcohols. The anomeric proportions varied from exclusively β to mainly α depending on the specific glycosylating agents and acceptors used.[62] In Chapter 6, 1,2-cyclic ketene acetals with the β-D-*manno*- configura-

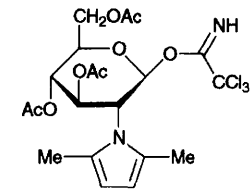
tion are noted. These may be converted into *spiro*-orthoesters which can be made to collapse to β-mannopyranosides, *e.g.* **21**.[63] A more common way of approaching β-mannopyranosides is by way of β-D-glucopyranosides, 2-triflate ester groups of which can be displaced even by hindered alcohols. Ultrasonic irradiation facilitates the reactions.[64]



20



21



22

In the field of amino-sugars 2,5-dimethylpyrroles have been used to protect 2-amino groups and give derivatives suitable as glycosylating agents in oligosaccharide synthesis. For example, compound **22**, made from D-glucosamine hydrochloride by treatment with hexane-2,5-dione followed by peracetylation and then conversion to the glycosyl trichloroacetimidate, has been used to link β-D-GlcNH_2 to several other sugars. The group is compatible with many protecting group manipulations and is cleaved with $NH_2OH.HCl$. *N*-Phthalimido groups can be cleaved in its presence.[65] 2-Azido-2-deoxy-α-D-mannosides have been made from methyl 4,6-di-*O*-benzyl-3-*O*-benzoyl-2-*O*-triflyl-α-D-glucoside by azide displacement, formation of 1,3-anhydro-2-azido-4,6-di-*O*-benzyl-2-deoxy-β-D-mannose and $ZnCl_2$-catalysed alcoholysis of the 4-membered anhydro ring.[66] Stereoselective glycosylation of cyclopentanol with 2-azido-2,6-dideoxygalactopyranose derivatives led to *N*-methyl-D-fucosamine models of neocarzinostatin chromophore.[67] Several perfluoroalkyl α-glycosides of 2-acetamido-2-deoxy-3-*O*-muramyl-D-glucose with peptides linked to the muramyl group have been reported.[68]

A wide range of glycosylated acyclic compounds have been reported; these will be treated according to the lengths of the carbon chains of the aglycons. Penta-(2-aminoethyl)glucose (made from the allyl analogue) has been elaborated into dendrimers by chain extensions involving initial disubstitution at each amino group with amino-functionalized alkyl groups which, in turn, allowed disubstitution.[69] 2-Silylethyl glycosides can be linked by way of 5-pentanoylamido groups bonded through the silicon to solid phase polymers and may be released by acetolysis which gives the glycosyl acetates.[70]

Allyl glycosides have proved very useful for making compounds with C_3 aglycons and also glycolaldehyde glycosides and extended chain compounds. The glycolaldehyde derivatives are made by ozonolysis or hydroxylation followed by periodate oxidation and have been converted into phosphatidylethanolamine-linked α-D-mannolipids which self-assembled into monolayers,[71] thiosemicarbazones which, as Cu(II) and Mn(II) complexes are superoxide dismutase mimics[72] and 2-substituted (NH_2, CN) ethyl glycosides which have been incorporated with glycoconjugate combinatorial libraries.[73]

Hydroxylation of allyl glycosides gives access to 1-substituted glycerols, a naturally occurring β-glucopyranosyl 6-deoxy-6-sulfonato glyceride having been made by this method.[74] Epoxidation, on the other hand, allows access to 3-azido-3-deoxy-1-glycosyl glycerols,[75] and 3-aminopropyl compounds, for use as neoglycoconjugates, have been made by azido-phenylselenation followed by reductive deselenation.[76] Dibromination followed displacement with azide leads to 2,3-diazido compounds,[77] and addition of $I(CF_2)_nCl$ allows carbon chain extension with iodination at C-2 of the aglycon moiety.[78] Radical halogenation on the other hand occurs at the methylene group and consequently gives reactive compounds that readily hydrolyse to the free sugars.[79]

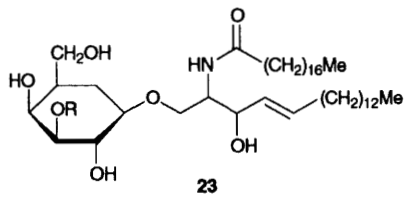
Glycerol with hexadecyl groups at O-2 and O-3 and 2,6-disulfato-3,4-*O*-isopropylidene-β-D-galactosyl at O-1 has been made as a P-selectin inhibitor.[80] Several 2-*O*-glycosylglycerol compounds have been described. Thus, α-D-glucopyranosides having long chain alkyl groups (n = 12, 14, 16, 18) at O-1 and phosphate-linked choline at O-3 have been made for studies of apoptosis,[81] and several 2-*O*-β-D-galactofuranosides carrying ether groups such as tetraisoprenyl at O-1 and O-3, which have self-assembling properties and show liquid crystal properties, have been studied as relatives of components of bacterial membranes.[82,83] Related compounds with 1,3-long chain ether groups and β-D-*N*-acetylglucosamine linked to O-2 by a 3,6-dioxaoct-1,8-diyl bridge have been made as homologous glycero-neoglycolipids.[84] Compounds with a less usual C_3 aglycon are 2-malonyl 2-deoxy-β-D-ribofuranoside and the corresponding 2-deoxy-2-fluoroarabinofuranoside which have been made for conformational analysis purposes.[85]

Enantiomerically pure but-3-en-2-yl glycosides with hydroxy or azido groups at O-1 have been made by trichloroacetimidate coupling to resolved, 1-substituted but-3-en-1,2-diols,[86] and related work led to 1-*O*-mannosylated pent-4-en-1,2- and pent-4-en-1,3-diols.[87] β-Galactosylated 5-hydroxynorvaline, and an α-D-Glc-(1→2)-β-D-Gal analogue, have been converted into glycopeptides related to a fragment of type II collogen.[88]

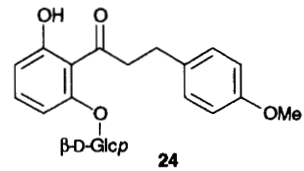
The *N*-(2,2-dimethoxyethyl)-6-hydroxyhexanamido glycosides, *e.g.* β-D-Glc-$O(CH_2)_5$-$CONHCH_2CH(OMe)_2$, represent new derivatives for linking carbohydrates to proteins since the aldehydes obtained on hydrolysis of the acetals can be coupled to give neoglycoconjugates. Such conjugates containing several glucose moieties have been produced.[89] β-L-Fucose, linked by a spacer 6-aminohexyl aglycon to a dipeptide has immunostimulant properties,[90] and several phospholipids have been made from the monoglycosides of decane-1,10-diol, the derived 10-aldehydes and the 10-*N*-(2-aminoethyl)glyceryl phosphates carrying long chain fatty acid and ester group at O-2 and O-3 of the glycerol.[91]

3-(Perfluorooctyl)propyl β-D-glucopyranoside forms relatively stable smectic mesophases.[92] A sulfatase which hydrolyses ester **23** (R = SO_3H) to the alcohol **23** (R = H) has been post-translationally modified to enable it to convert cysteine into α-formylglycine ($CH_2SH \rightarrow CHO$).[93]

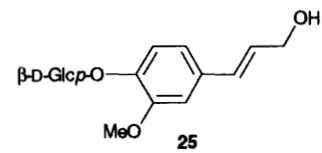
Considerable attention has been given to glycosides having aryl on alkaryl aglycons; these will be referred to in approximate order of their complexity.



23



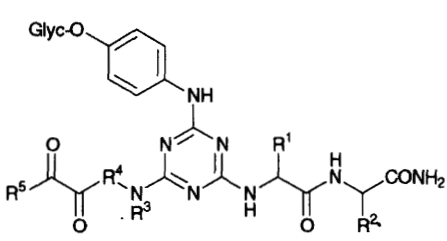
24



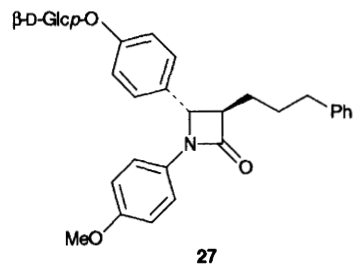
25

Compounds to have been synthesized are: 2-chloro-4-nitrophenyl β-D-galactopyranoside,[94] nitrophenyl glycosides of *N*-acetylneuraminic acid benzyl ester,[95] β-D-glucopyranosyl and β-D-maltopyranosyl derivatives of hydroxybenzoic acid aminoalkyl esters,[96] several analogues of 4′-dehydrophlorizin (**24**) for the development of structure–activity profiles in relationship to enhancement effects on urinary glucose excretion,[97] coniferin (**25**) and several derivatives.[98] In studies of the carbohydrate part of vancomycin a β-glucoside derivative of 2,6-dimethoxyphenol was made using the glycosyl sulfoxide method and the tributyltin derivative of the phenol. Vancosamine was then coupled α-(1→2) to the glucose moiety, again by the sulfoxide procedure, both in the model and in 3,4,6-tri-*O*-acetylglucosyl vancomycin analogues made from the antibiotic itself.[99] Coupling of *p*-aminophenyl glycopyranosides to cyanuric chloride gave access to combinatorial arrays of compounds represented by **26**.[100] The 2-azetidinone glucoside **27**, and corresponding glucuronide, and corresponding compounds with the sugars 6-linked, were tested as cholesterol absorption inhibitors.[101]

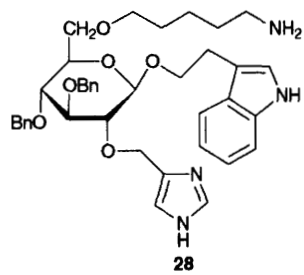
Alkaryl compounds to have been reported are the 2,4- and 2,6-dinitrobenzyl



26



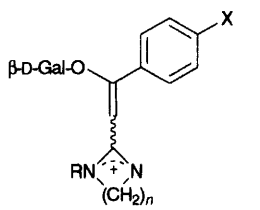
27



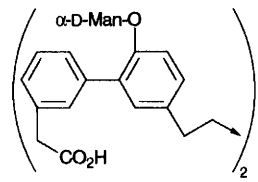
28

β-D-glucuronides,[102] β-D-ribofuranose and β-D-glucopyranose linked by *n*-butyl spacers to *N*- of pyrazinones,[103] and compound **28**, together with β-L-glucose and α-L-mannose analogues which were made as scaffolds for peptidomimetics.[104] Acetobromogalactose together with corresponding ketene aminal compounds gave the glycosyl enol derivatives **29**.[105]

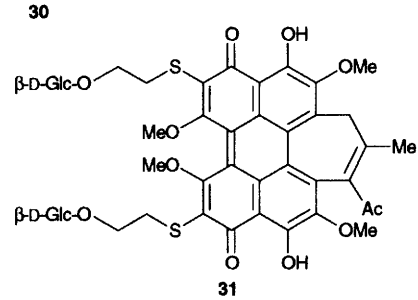
Often for biological purposes considerable attention is being given to compounds containing more than one sugar unit; several are based on aryl or alkaryl systems: the biphenyl-based dimer **30**, which mimics sialyl Le^x-Le^x in a novel type of solution-mediated cell adhesion;[106] the bisglucoside **31** was made from hypocrellin B treated with mercaptoethanol followed by acetobromoglucose,[107] further work (*cf.* Vol. 28, p. 24) has been reported on glycosidically substituted tetraphenylporphyrins, some having one sugar *O*-bonded on each of the phenyl groups and some two,[108] and other studies have produced compounds having sugars on only some of the phenyl substituents.[109] Calix[4]-arenes having *syn*-related (glycosyloxy)phenyl substituents on two opposed rings and *n*-propyloxy groups (all *syn*-related) on all of the rings represent a new class of carbohydrate-containing calixarenes with deepened cavities.[110]



29 X = H, Me, OMe, Br, Cl
n = 2, 3
R = H, Me



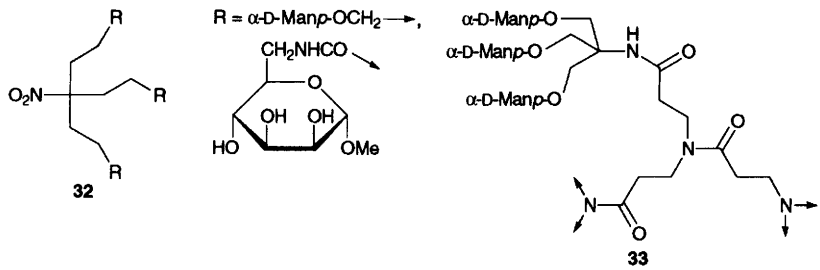
30



31

Ten sulfated and three phosphorylated galactosyl compounds have been made as glycolipid analogues. Each contained two or three *O*-β-D-galactopyranosyl derivatives of 2-*C*-alkylpropane-1,3-diol, 2,2-di-*C*-alkylpropane-1,3-diol or 2-*C*-alkykl-3-*C*-(hydroxymethyl)butane-1,4-diol.[111] Special interest has been taken in compounds containing several α-D-mannose moieties: oligomannopeptoids based on oligoglycines carrying 2-(α-D-mannopyranosyloxyethyl) substituents on N;[112] cluster compounds **32**[113] and compounds derived by extension as indicated in **33**. One, centred on benzene-1,3,5-tricarboxamide, contained 36 mannosyl moieties. The dendrimer structure increased the ability to exhibit binding of concanavalin A to a purified yeast mannan.[114]

Wong and colleagues have reported the solution and solid phase synthesis of glycolipids with GlcNAc bound at different positions and their testing as



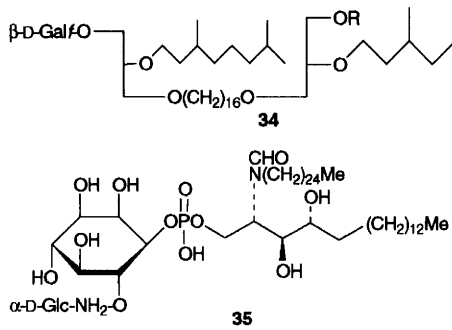
substrates for subtilisin-catalysed glycopeptide condensations.[115] In related work aimed at development of anticancer vaccines Danishefsky's group has reported the synthesis of *O*-serine and *O*-threonine α-glycosides of GalNAc and β-D-Gal-(1→3)-GalNAc from glycals and their conjugation to carrier proteins. In this way a vaccine able to protect mice from prostate cancer was developed and the work has led to clinical trials in humans.[116]

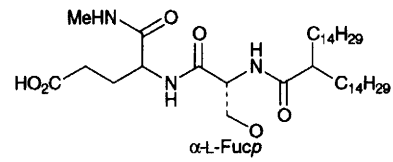
1.2 Synthesis of Glycosylated Natural Products and Their Analogues. – A review has appeared on the synthesis of polyol glycosides and their use in cosmetic production.[117] The unsymmetrical tetraether glycolipids **34** have been prepared by use of the *n*-pentenyl glycoside method[118] (see previous section for related compounds), and several galactosyl ceramides have been reported, α-compounds by use of tetra-*O*-benzyl-α-D-galactopyranosyl fluoride,[119,120] and a β-compound with tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate.[121] In the last case the aglycon was produced by enantioselective cleavage of racemic ceramide acetates. Related, novel cerebrosides which are β-glucosides isolated from starfish have been made.[122]

Appreciable effort continues in the area of synthesis of glycopeptides (see also refs. 115, 116). A dodecapeptide from the β-turn of mouse cadherin 1 was made using solid phase technology and incorporating tetra-*O*-acetyl-α-D-GlcNAc *O*-bonded to serine,[123] and in related work the same sugar *O*-coupled to threonine was incorporated into a decapeptide model for the polymeric domain of RNA polymerase II.[124] NMR evidence indicated that glycosylation caused a 'turnlike' effect. α-GalNAc-containing glycopeptides have already been mentioned,[116] and other work has reported a hexa- and a nona-peptide each carrying two α-D-GalNAc moieties.[125] α-L-Fucopyranosyl selectin inhibitor **34a** has been made by improved methods,[126] and the same workers have reported β-L-fucopyranosyl, α-D-mannopyranosyl[127] and α-L-fucofuranosyl[128] analogues. Wong and colleagues have described parallel syntheses of a library of α-L-fucopeptides as analogues of Le^x.[129]

In the area of *N*-linked glycopeptides a major paper has described the simple preparation of glycosylamines by treatment of free sugars with $(NH_4)_2CO_3$, coupling to give glycosylated asparagines and their incorporation by solid phase methods into T-cell epitope analogues of a mouse haemoglobin-derived decapeptide. The sugars used ranged from GlcNAc, to simple oligosaccharides to branched high-mannose oligosaccharides of glycoproteins.[130]

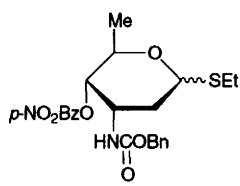
Glycosylinositols to have been prepared are 2-*O*-α-D-galactopyranosyl-D-*chiro*-inositol (a jojoba bean constituent),[131] a sannamycin-like aminoglycoside antibiotic mentioned in Chapter 19 and the aminoglucosyl derivative **35** of a ceramide 1-phosphoinositol.[132]

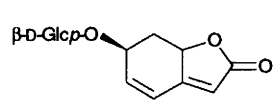


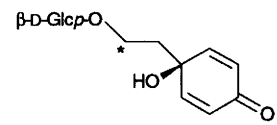


A range of β-D-glucosyl, -galactosyl and -cellobiosyl glycosides of the steroidal cardenolides, pregnanes and 23-nor-5,20(22)*E*-choldienic acid have been described,[133] and compound **36** was used in the glycosylation of three cardioactive steroids in the hope the participation of the carbamate group would lead to good β-selectivity. The best such selectivity obtained was 1.4:1.[134] UDP-Glucuronic acid together with the appropriate transferase was used to make β-glucuronides from estradiol and ethynylestradiol as well as several phenols.[135]

A review has described the isolation, characterization, synthesis and biological activities of the saponins.[136] Six separate sugars have been glycosidically bonded to diosgenin by the trichloroacetimidate method,[137] and the diosgenyl saponins dioscin, polyphyllin D and balanitin 7 have been synthesized.[138] Acetylated glycals have been used in the preparation of betulin 2-deoxy-α-D-, 2-deoxy-α-L- and 2,6-dideoxy-α-L-*arabino*-hexopyranosides.[139]







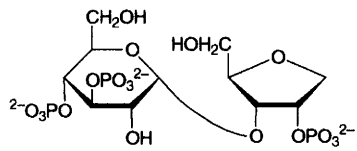
The plant bioregulator phyllanthurinolactone **37** has been made by use of the racemic alcohol,[140] and coroside **38** ^{13}C labelled at the indicated position was made by photooxidation of the corresponding *p*-substituted phenol. It and related cyclohexyl derivatives were required for studies on the biosynthesis of plant phenylethanoid compounds.[141] Glycosylation with a glycosyl fluoride was used to make compound **39** and three analogues with alterations in the furanoid ring as novel IP_3 receptor ligands. IC_{50} values were comparable with that of IP_3 itself.[142]

Diterpene glycoside synthesis has been reviewed[143] and the α-D-arabinopyranoside of alcohol **40** was made and the product converted into cytotoxic marine natural products eleuthosides A and B.[144] Several isoflavone β-D-glucopyranosides have been prepared as antioxidants,[145] and conditions involving the use of acetobromoglucose, ^{t}BuOK and a crown ether have been described for the regio-specific 4′-*O*-β-D-glucosylation of isoflavones.[146] Synthesis of the shark repellant glycoside pavoninin I and analogues have been made using a sulfoxide donor.[147]

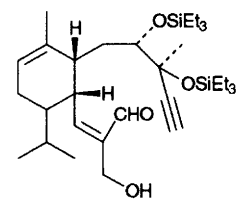
Compound **41**, an analogue of etoposide and NK611, has been made with good β-selectivity by use of a 3-azido-3-deoxy-1-Tbdms glycosylating agent. When the reaction was applied to the 3-epimer, selective α-glycosylation was observed.[148]

In the area of glycosides of *N*-heterocyclic compounds the *O*-α-D-glucosyl[149] and β-D-*N*-acetyl glucosaminyl[150] derivatives of thiamine have been made by enzymic methods, and similarly the α-D-galactopyranoside of the ergot alkaloid **42** has been prepared.[151] Several glycosylated derivatives, *e.g.* **43**, have been made of indolizidinone as Sia Le^x mimics, but none had E-selectin binding activity.[152]

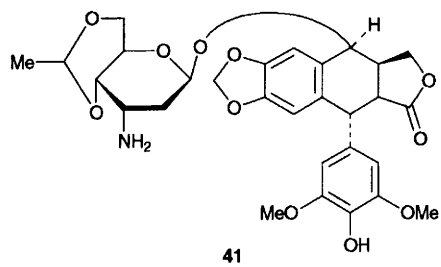
Several glycosides of the ene-diyne **44** (R = H) have been made by use of 2-thioethyl glycosides[153] and used in studies of DNA cleaving in which the sugars serve as DNA recognition elements.[154] Chapter 19 contains reports of glycosylation of other complex compounds conducted during work on antibiotics.



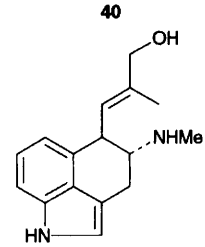
39



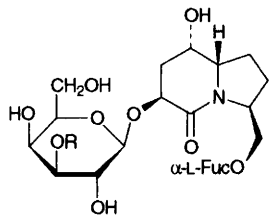
40



41

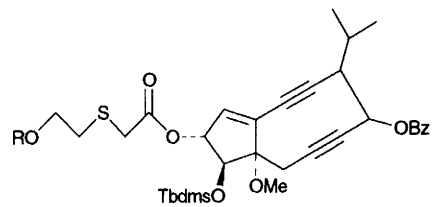


42



R = CH_2CO_2H

43



R = β-D-Glc, β-2-deoxy-D-Glc, β-D-Fuc, β-D-GlcNH$_2$

44

1.3 *O*-Glycosides Isolated from Natural Products. – As always, this section is highly selective with focus mainly on the carbohydrate components or properties of the compounds. Often compounds with novel features in the aglycons are disregarded.

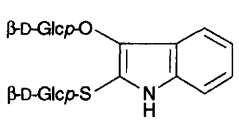
A review has been published on ptaquiloside, a bracken carcinogenic sequiterpene β-D-glucopyranoside,[155] and a new paper has appeared on the isolation of this type of compound.[156] A 2-hydroxy-4-(3-oxobutyl)phenyl-β-D-glucopyranoside 6-dihydroxycinnamoyl ester has been recognized as the major orally available analgesic glycoside in the dried fruit of *Vitex rotundifolia*,[157] and the novel *O,S*-diglucoside **45**, also a plant product, has skin blood flow promoting activities in rats.[158] Four new metabolites related to indole 3-acetic acid which can be obtained from rice bran are compound **46** and its epimer at C-3 and the corresponding cellobiose glycosides.[159] A further cellobioside, which are uncommon in nature, is the apigenin 7-glycoside which was found in the petals of *Salvia uliginosa*.[160] Two novel oleanolic acid saponins containing glucose and methyl glucuronate inhibit excess recruitment of neutrophiles to injured tissue a thousand times more than does Sia Le^x.[161] Further work has been published on leaf-opening substances of plants, two simple phenolic acid glucosides with this function having been isolated from different plants.[162,163]

A known flavonoid L-rhamnoside from the leaves of *Myrcia multiflora* is as potent an inhibitor of rat lens aldose reductase as is the commercial inhibitor epalrestat. Further glycosides available from this plant showed specific glycosidase inhibitory activity.[164]

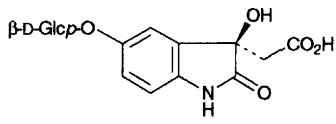
Ethyl β-L-arabinopyranoside can be isolated from the roots of *Hibiscus rosa-sinensis*.[165]

1.4 Synthesis of Disaccharides and Their Derivatives. – This family of compounds has received increased attention and several novel methods have been used for their synthesis. Many of the papers referred to in Section 1.1.1 of this chapter contain material relevant to disaccharide formation and give examples of specific dissaccharide synthesis.

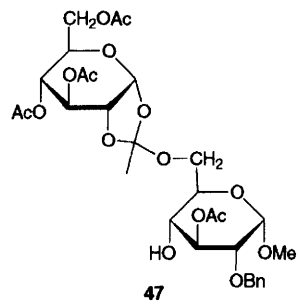
1.4.1 Non-reducing disaccharides. New crystalline and amorphous forms of trehalose have been reported,[166] and an enzymic method gave β-D-GlcNAc-(1↔1) β-D-Man as major product formed from mannose and *p*-nitrophenyl *N*-acetylglucosaminide.[167]



45



46



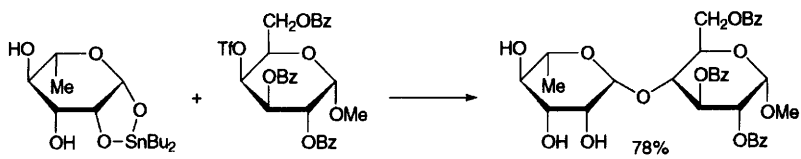
47

1.4.2 Novel synthetic methods for reducing disaccharides. Intramolecular methods have been further developed, and two routes to methyl cellobioside involved linking of a methyl glucoside derivative having a free hydroxy group at C-4 and an *S*-ethyl thioglucoside by 6,6′- and 3,6′-*m*-xylenediyl bridges have been reported. Molecular mechanics calculations indicated that the macrocycle formed in the second case is lower in energy than the first which may explain the higher yield obtained when 3,6′-linking was used.[168]

A useful looking, simple method which may have an intramolecular component involves the production of β-D-glucopyranosyl, -galactopyranosyl and α-D-mannopyranosyl disaccharides *via* the corresponding orthoacetates. For example, compound **47**, obtainable in nearly quantitative yield using acetobromoglucose and methyl 3-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranoside, gave the corresponding gentiobioside with free C-4 hydroxyl group and potentially free C-2 hydroxy group, so this approach appears to have considerable potential for complex oligosaccharide synthesis.[169]

In the area of D-mannosyl disaccharides 3,3-linking of a donor to a benzyl glucoside derivative gave the β-(1→4)-linked product in 66% yield,[170] and the same workers, using malonic or succinic ester linkages, also made disaccharides comprising D- and L-mannose and D- and L- glucose linked 1→4 in four different combinations. Anomeric ratios were variable and depended greatly on the enantiomers used.[171] The Ogawa approach, which uses orthoester functions which include the acceptor species adjacent to the anomeric centres, has been used to make β-fructofuranosides. For example a compound with general structure **48** has given access to methyl 6-*O*-(β-D-fructofuranosyl)-α-D-mannopyranoside in 77% yield.[172]

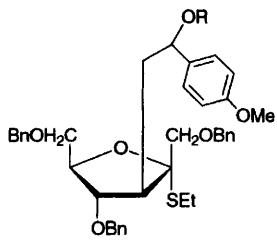
A very novel and different approach involves the use of cyclic 1,2-stannylene sugar derivatives, which have activated nucleophilic anomeric oxygen atoms, to displace triflate ester groups as illustrated in Scheme 2. β-Mannosides were also made (59%) from the illustrated triflate and (57%) from methyl 2,3,4-tri-*O*-benzoyl-6-*O*-triflyl-α-D-glucopyranoside.[173]



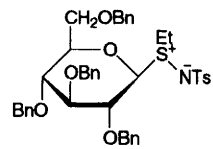
Scheme 2

Several novel glucosyl donors have been employed, each of them affording mainly β-linked products. Mukaiyama and colleagues have found *o*-chlorobenzylated β-glucosyl phenylcarbonate couples with, for example, methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside in the presence of $TrB(C_6H_5)_4$ to give 97% yield of the 1,3-linked glucobioses (α:β, 6:94).[16] Mercury(II) catalysed hydration of propargyl tetra-*O*-benzyl-β-D-glucoside gave the (acetyl)methyl glycoside, which on Baeyer-Villiger oxidation, afforded the (acetoxy)methyl analogue. This reacts with alcohols in the presence of BF_3, the methyl tribenzylglucoside giving 72% yield with α:β ratio 1:3.[18]

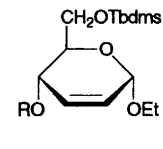
Sulfur-linked compounds continue to be developed as glycosylating agents, compound **49**, made from the ethylthio glycoside with chloramine T, giving high yields of disaccharides with α:β-ratios about 1:3 when activated with $Cu(OTf)_2$, CuO. With the *O*-acetyl protected analogue of **49**, β-products were formed exclusively.[174] Other workers have examined glucosyl phosphorodithioates which, activated with methyl triflate, gave β-linked disaccharides in about 60% yield.[175]



48



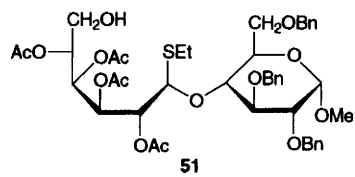
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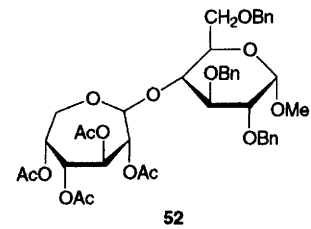
50

Coupling of unsaturated carbonate **50** (R = MeOCO) with sugars *O*-protected except at the anomeric centre in the presence of Pd(0) gave unsaturated disaccharide derivatives (**50**, R = glycosyl) with retention of configuration at the allylic centre. Anomeric selectivity was not high.[176]

Attention should be drawn to a method for synthesizing hexosyl disaccharides with the non-reducing terminal unit in the septanose ring form. Key precursors are hemithioacetals having unsubstituted hydroxy group at C-6, *e.g.* **51**, which cyclize to give septanosyl products (**52** from **51**) on treatment with NIS, TfOH. Other hexosyl compounds can be treated in the same way.[177]



51



52

1.4.3 Reducing glucosyl disaccharides. Opening of 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose with benzoic acid gave means of access to the α-(1→2)-glucobiosyl benzoate,[178] a derivative of α-D-Glc*p*-(1→2)-D-Gal *O*-linked to an amino acid was made for incorporation into a glycopeptide,[179] and a β-D-Glc *p*-(1→2)-D-Fuc was made as an appropriate glycoside for the synthesis of tricolorin A.[180]

Tetrabenzyl-β-D-glucosyl fluoride was used in a Mukaiyama synthesis of laminaribiose [β-(1→3) linked], activation was by use of $TrB(C_6H_5)_4$ and high yields and 10:1 β-selectivities were reported.[181]

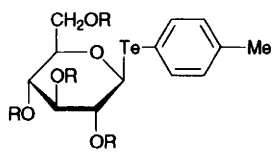
A mutant β-glucosidase/galactosidase from an *Agrobacterium* catalysed transglycosylation from the α-fluorides to a range of mono- or di-saccharide

aryl glycosides to give mainly β-(1→4) linked products.[182] Activation of thioglycosides with $Mg(ClO_4)_2$, *N*-(phenylseleno)phthalimide or PhIO gave syntheses of maltose and isomaltose,[183] and syntheses have been reported of the following maltose glycosides: methyl α (four steps),[184] ethane-1,2-diyl, propane -1,3-diyl and butane -1,4-diyl (α,α-, α,β- and β,β-isomers)[185] and a (carboranyl)methyl compound which was made together with analogous derivatives of several mono- and di-saccharides for use in cancer treatment by boron neutron-capture therapy.[186] Cellobiose 6-sulfate and 6′-sulfate and related compounds have been made by chemical methods.[187]

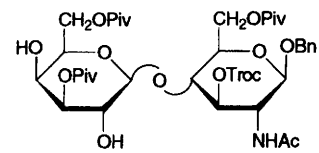
Isomaltose [α-Glc-(1→6)-Glc] can be made very efficiently by use of the telluroglycoside **53** (R = Bn), whereas **53** (R = Bz) gives the β-analogue also efficiently.[188] Solid phase methods on various polymers, including porous glass, involving trichloroacetimidate coupling have also been shown to give gentiobiose.[189]

1.4.4 Reducing galactosyl disaccharides. 2,3,5-Tri-*O*-benzoyl-6-*O*-benzyl-β-D-galactofuranosyl trichloroacetimidate has been used to link β-D-galactofuranose to O-3 of D-galactopyranose, O-6 of D-galactofuranose and O-4 of L-fucopyranose.[190] The synthesis, using a glycosyl acetate as donor and selectively substituted mannono-γ-lactone as acceptor, of β-D-Gal*f*-1→3)-D-Man, which is present in the lipopeptidophosphoglycan of *Trypanosoma cruzi* and the lipophosphoglycan of *Leishmania*, has also been reported.[191]

α-D-Gal*p*-(1→2)-D-Man,[192] β-D-Gal-(1→3)-D-GlcNHR (R = Ac, CHO, EtOCO, $HOCH_2CO$)[193] and β-D-Gal-(1→3)-D-GalNH_2[194] have been made, but most attention has been given to 1,4-linked compounds: α-D-Gal*p*-(1→4)-D-GalA, α-D-Gal*p*-(1→4)-D-Gal-6-NH_2[195] and several compounds based on lactose. Thus lactosides were made as the 3′-sulfates of aryl glycosides carrying amino and amino-acid substituents on the aromatic rings.[196] Considerable attention has been given to lactosamine chemistry, a thermophilic enzyme operating at 85 °C allowing its preparation from lactose and glucosamine (3.2 lactosamine from 8.6 glucosamine with 5.9 of the latter recovered).[197] A further enzymic method used *p*-nitrophenyl β-D-galactopyranoside as galactose source and this work led on to *N*-acetyllactosamine carrying sulfate groups at O-6 or O-6′, these compounds being required as fucosyl acceptors in connection with Le^x studies.[198] A bromonaphthyl glycoside of *N*-acetyllactosamine was made with several related glycosides as a potential inhibitor of a β-(1→4)-galactosyl transferase.[199] By use of specific deoxy UDP-Gal analogues, corresponding deoxylactosamines have been made.[200] Derivative **54** was used to make a mannosyl disaccharide (see below) and also in the preparation of Le^x derivatives.[201]



53



54

1.4.5 Reducing mannosyl disaccharides. Several reports of the synthesis of mannopyranosyl compounds are referred to in Section 1.4.2. See also Section 1.1.2 for methods of preparation of β-mannopyranosides. Two further papers have described the synthesis of 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulose, the disaccharide of bleomycin A2, one using L-xylose as precursor of the L-gulose (*cf.* Vol. 31, Chapter 3, refs. 180, 181),[202] and the other continuing to complete the synthesis of the natural product.[203] Solid phase procedures were used to make derivatives of α-D-Man*p*-(1→3)-D-Man suitable for the development of glycoprotein-related libraries. The products were tested for their ability to interact with C-type lectin of *Lathyrus odoratus*.[204] α-D-Man*p*-(1→4)-α-D-Man has been made as its 2,4-dinitrophenyl glycoside,[205] and β-D-Man*p*-(1→4)-D-Glc by a double inversion reaction applied to the ditriflate of compound **54**.[201] A glycosyl sulfoxide method was used to make the caloproside disaccharide isopropyl 2-*O*-acetyl-5-*O*-(2-*O*-acetyl-β-D-mannopyranosyl)-D-mannonate.[206]

1.4.6 Reducing aminoglycosyl disaccharides. Glucosamine compounds to have been made are β-D-GlcNAc-(1→3)-D-Gal as well as a series of derivatives with F or SH groups at C-3, C-4 or C-6 of the GlcNAc moiety[207] (selective O-3 glycosylation of a 3,4-dihydroxygalactoside being effective),[208] β-D-GlcNAc-(1→3)-L-Rha which occurs as part of the immunosuppressive triterpene glycoside brasilicardin A (see Chapter 22),[209] β-D-GlcNAc-(1→4)-D-Glc (using *N*-dimethylmaleoyl *N*-protection),[210] β-D-GlcNH$_2$-(1→4)-1,6-anhydro-D-GlcNH$_2$,[211] β-D-GlcNH$_2$-(1→6)-D-Glc (solid phase synthesis),[212] β-D-GlcNAc-(1→6)-D-Glc and several analogues,[207] β-D-GlcNAc-(1→6)-D-GalNAc (enzymic),[213] and β-D-GlcNH$_2$-(1→6)-D-GlcNH$_2$ (highly substituted phosphates; analogues of *Salmonella* Lipid A).[214]

α-D-GalNH$_2$-(1→4)-D-Gal was made for inhibition studies of the binding of the pilus protein of *E.coli* to glycolipids,[195] and a 1-phenylseleno 2-azido-2-deoxy-α-mannoside, activated with *cis*-2,3-perfluoroalkyloxaziridine, acts as a specific β-glycosylating agent, β-D-ManNH$_2$-(1→6)-D-Man having been made in this way.[215] α-L-FucNAc-(1→2)-L-Fuc was made by use of a 2-azido-2-deoxy-thioglycoside as glycosylating agent.[216]

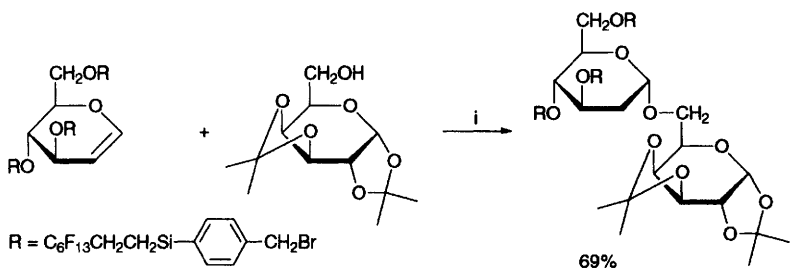
α-L-Aco-(1→2)-Glc (Aco = 3-amino-2,3,6-trideoxy-L-*arabino*-hexose) was made as its *p*-glycylphenyl β-glycoside, part of actinoidin antibiotics,[217] and α-L-Van-(1→2)-Glc (Van = 3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose) was synthesized as its α-2,6-dimethoxyphenyl glycoside, a vancomycin component.[218] The terminal disaccharide of a *Vibrio cholerae* polymer α-D-Per-(1→2)-D-Per (Per = 4-amino-4,6-dideoxy-D-mannose) was prepared as the bis-*N*-2,4-dihydroxybutanoyl derivative for coupling to proteins.[219]

1.4.7 Reducing deoxyglycosyl disaccharides. Fucosyl compounds to have been made are α-Fuc-(1→3)-D-Glc and α-L-Fuc-(1→3)-D-GlcNAc (enzymic methods),[220] α-L-Fuc-(1→3)-D-GlcNAc with various polyhydroxyalkyl and/or sulfate groups at O-4 and/or O-6 as inhibitors of human glioma cell division,[221] and β-D-Fuc-(1→2)- and (1→3)-D-Xyl (enzymic methods).[222] L-Fucose has

also been linked to the rarer sugar 3,4,6-trideoxy-L-*erythro*-hexose [α-(1→2) bond].[223]

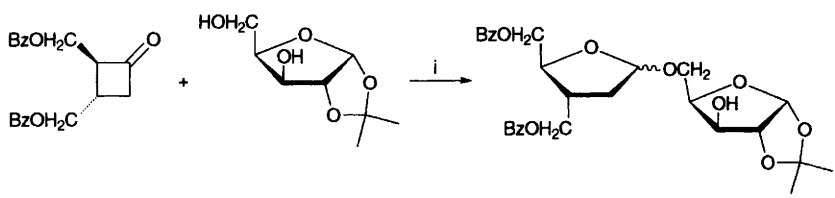
In the L-rhamnose family of compounds α-L-Rha-(1→3)-D-Glc has been made by two groups as (hydroxy[224] and dihydroxy[225]-phenyl)ethyl β-glycosides, α-L-Rha-(1→6)-D-Gal has been reported,[226] and the following rhamnobioses have been described: α-L-Rha-(1→2)-L-Rha with specific deuteration at C-2 of the reducing moiety,[227] and as a rhamnolipid based on this disaccharide made in a one-pot, two-step process from two thioglycosyl rhamnose donors,[228] and α-L-Rha-(1→3)-4-*O*-Me-α-L-Rha made, together with related disaccharides, as fragments of bacterial lipopolysacharides.[229]

Interest continues in developments for the synthesis of anomerically specific 2-deoxyglycosidic disaccharides, and Curran and colleagues have illustrated the value of the fluorous approach in making 2-deoxy-α-glycosides with high selectivity as illustrated in Scheme 3.[230] An alternative approach to the same type of α-linked disaccharide involves the use of 3,4,6-tri-*O*-benzyl-2-*O*-thiobenzoyl-α-D-glucopyranosyl trichloroacetimidate (or the corresponding mannosyl derivative) with TmsOTf-catalysed coupling followed by radical reduction of the thioester group. In this way 2-deoxy-α-D-Glc-(1→3)- and -(1→6)-D-Glc were made.[231] Otherwise, *S*-(2-deoxyglycosyl)phosphorodithioates, activated with $AgClO_4$, give α-products with good yields and selectivity in the (2-deoxy) D-glucose, D-galactose and L-fucose series. 2-Deoxy-α-D-Glc-(1→3)-D-Glc is an example of the compounds made.[232]



Scheme 3

An entirely different approach to 2-deoxyglycosyl compounds is illustrated in Scheme 4. Branched-chain furanosyl compounds formed by way of a furanoid carbene are obtained, but the yields are not good.[233]



Scheme 4

In connection with work on anthracyclinone antibiotics such as cororubicin 2,6-dideoxy-L-*lyxo*-hexose was coupled α-1,4 to deliconitrose (2,3,6-trideoxy-3-*C*-methyl-3-nitro-L-*ribo*-hexose).[234]

1.4.8 Reducing sugar acid glycosyl disaccharides. D-Glucuronic acid as its methyl ester has been α-(1→2) linked to D-Xyl,[235] β-(1→3) linked to D-Gal[236] and GalNAc[237] and β-(1→4) linked to D-Glc.[238] In the last case the oxidation to give the uronic acid was carried out after disaccharide formation.

Several derivatives have been reported of α-D-GalA-(1→4)-D-GalA.[239] (2→8)-Linked Kdo disaccharides have been made for studies of binding with *Chlamydia*-specific monoclonal antibodies.[240] Enzymic methods have yielded α-NeuNAc-(2→6)-D-GalNAc and α-NeuNAc-(2→6)-D-Gal,[241] but chemical procedures were utilized in making α-NeuNAc-(2→3)-D-GalNH$_2$ as a ceramide glycoside.[242]

1.4.9 Reducing pentosyl (and other) disaccharides. From a derivative of D-allal a 1,2-anhydro compound was made and used to give a 3-*O*-(α-D-altropyranosyl)-D-glucal in work aimed at making a trisaccharide repeating unit of Gram −ve bacterial polysaccharides.[243]

Novel routes to α-D-arabinofuranosyl and α-D-lyxofuranosyl disaccharides [*e.g.* α-D-Ara*f*-(1→6)-D-Glc] rely on the preparation of the 2,3,5-furanosyl acetates by ozonolysis of tri-*O*-acetyl-D-glucal and -galactal followed by selective hydrolysis of the derived 4-*O*-formyl pentose triacetates. Coupling of the sugar triacetates with alcohols was done using diphenyl sulfoxide and Tf_2O.[244]

β-D-Xyl-(1→6)-D-GlcNAc was made by enzymic transglycosylation from *p*-nitrophenyl β-D-xylopyranoside,[245] and a β-(1→6) linked apiosyl 1-thioglucoside was used in the preparation of a trimethoxyphenyl glycoside with a cinnamoyl ester group on the branching hydroxymethyl group, this being a natural wood bark product with anti-ulcerogenic properties.[246]

1.5 Disaccharides with Anomalous Linking or Containing Modified Rings. – Carba-β-D-Gal-(1→4)-D-Glc and -D-GlcNAc and the analogues with the two 'saccharide' units NH- rather than *O*-linked have been described.[247] See Chapter 18 for other relevant carba-sugar compounds. Several compounds with heteroatoms other than oxygen within or between the rings have been reported: α-D-Gal-(1→6)-1-deoxynojirimycin (enzymic linking),[248] and two groups have reported hetero-substituted mannobioses as α-mannosidase inhibitors, notably α-D-Man-(1→2)-α-D-Man with S as the ring atom in the non-reducing moiety and as the inter-unit linking atom, and with S in each of these positions separately.[249] The other work has produced α-D-Man-(1→3)-α-D-Man with S as the hetero atom in the 'non-reducing' ring and with NH, S or O in the 'reducing' ring.[250]

Analogues with 1-deoxynojirimycin linked (1→4) to D-Glc or D-Gal by the oximino group (=NO–) are good glycosidase inhibitors,[251] and β-D-Glc has been ester-linked through C-1 to glucuronic acid, and phosphonate ester-

bonded to C-6 of methyl glucoside 6-phosphonate have been made by nucleophilic ring opening of 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose[178]

Ether-linked disaccharides to have been reported are D-Glc-(6→6′)-D-Glc[252] and 2,3-anhydro-D-ribose-(4→4′)-2,3-anhydro-L-lyxose.[253]

Branched-chain disaccharide analogues to have been made are 2-branched 2-deoxy-compounds (by couplings involving 1,2-cyclopropanated sugars),[254] and highly branched disaccharide analogues, *e.g.* **55**, (by triflate displacements).[255]

1.6 Reactions, Complexation and Other Features of *O*-Glycosides. – The mechanism of action of the α-glucosyltransferase of *Protaminobacter rubrum* (with sucrose as the donor sugar) involves rate-limiting glycoside cleavage with a completely protonated oxocarbenium ion-like transition state.[256] β-*N*-Acetylglucosaminidase treatment of allyl α,β-*N*-acetylglucosaminides left the α-anomer unhydrolysed, and this was used to obtain allyl 2-amino-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside, useful for the synthesis of lipid A analogues.[257]

Isopropenyl α-and β-glucopyranosides both hydrolyse under acid conditions exclusively by vinyl ether C–O bond, rather (than C-1–O bond) cleavage, with the α-anomer reacting four times faster than the β.[258] *o*-Nitrobenzyl 2-deoxy-α,β-glucopyranoside, or the analogue with a methyl substituent on the benzyl methylene group, have potential use in syntheses because they undergo fast photolysis and have good stability and solubility in phosphate buffered saline.[259] $Sc(OTf)_3/Ac_2O$ is an efficient reagent for cleaving dioxoxylene linkers from polyethyleneglycol (PEG) polymer supports during oligosaccharide synthesis, and give (acetoxymethyl)benzyl glycosides as by-products.[260]

The alkaline hydrolyses of *p*-nitrophenyl α-D-glucopyranoside, α-D-galactopyranoside and β-D-mannopyranoside are highly selectively accelerated by methylboronic acid with respect to their *trans*-related anomers, suggesting O-1–B coordination enhances the leaving properties of the phenate in 1,2-*cis* complexes.[261] The mechanism of the TmsOTf-promoted anomerization of permethylated glucopyranoses has been examined by NMR and GLC methods. Cyclic and acyclic oxonium ions were concluded to be the key intermediates in the anomerizations of the α- and β-compounds, respectively.[262]

Theoretical studies on epoxide ring opening have been reported which are relevant to the mode of action of epoxyalkyl glycosides, *e.g.* 3,4-epoxybutyl β-D-xylopyranoside, as enzyme inhibitors.[263]

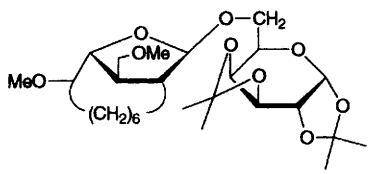
A cage-like compound based on two biphenyl units joined by four diamide linkages binds glycosides in organic solvents.[264]

2 *S*-, *Se*- and *Te*-Glycosides

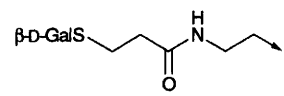
This year has seen the publication of a diverse set of syntheses of thioglycosidic compounds. Several 1-thio-β-D-galactofuranosides have been made from penta-*O*-benzoyl-D-galactofuranose as potential β-galactofuranosidase inhibi-

tors,[265] and many 1,2-*trans*-related alkyl and phenyl 1-thioglycosides of glucose, galactose, mannose and lactose have been prepared from the sugar peracetates and trimethylsilylated thiols with iodine as activator.[266] Otherwise, (trimethylsilyl)thiophenol with ZnI_2 and Bu_4NI give good access to *S*-phenyl α-1-thioglucosides (even from *O*-glycosides), which were converted into D-glucuronic acid thioglycosides.[267] Standard preparations of *S*-alkyl 2-acylamino-2-deoxy-1-thio-β-D-glucopyranosides (acyl being long chain acyl groups) gave compounds whose liquid crystal phases were studied.[268] Tetra-*O*-lauroyl-1-thio-β-D-galactose has been subjected to a set of Michael acceptors, the resulting ketones being reduced to alcohols or reductively aminated with a range of amino acids to give 30 1-thio-β-D-galactosides.[269]

Reaction of glycosyl thiocyanates with CF_3SiMe_3 and Bu_4NF gives trifluoromethyl 1-thioglycosides,[270] and other rather specific compounds to have been reported are aminomethyl 1-thio-α-L-fucopyranoside which, with the *N*-acetyl analogue, is a moderate α-L-fucosidase inhibitor,[271] 2-(*N*-piperidinyl)ethyl 1-thio-β-D-glucoside and -*N*-acetylglucosaminide,[272] and ethyl 2-deoxy-2-*N*-phthalimido-1-thio-β-D-glucopyranoside.[273]

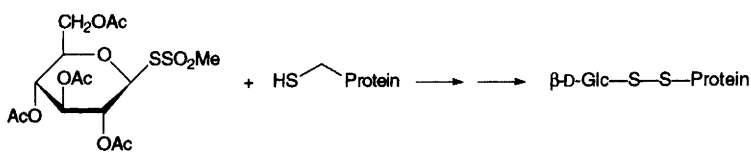


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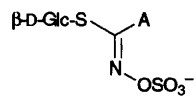
More complex thioglycosides to have been reported are those produced by thioglycosyl coupling with poly(propyleneimine)dendrimers with 4 and 64 reactive amino groups. The coupling involved amide formation using (ω-carboxyalkyl)thioglycosides.[274] *N*-Acetylglucosamine has been disulfide coupled to a protein by use of its 5-nitropyridin-2-yl thioglycoside and a crysteine-containing protein in work on mimics of natural asparagine glycosylation.[275] In important, related research neoglycoproteins were made in which the sites of glycosylation and the specific sugar introduced could be controlled. Cysteine was introduced at four specific sites of subtilisin of *Bacillus lentus* by site-directed mutagenesis and then glucose was *S*-substituted by the reaction indicated in Scheme 5. Partial deacetylation gave a library of compounds.[276] Other combinatorial work was based on differentially *O*-substituted thioglycosides linked to resins.[277] Site selective glycosylation occurred at Lys 15 when (*p*-nitrophenyloxycarbonyl)ethyl 1-thio-β-D-Gal was allowed to react with LA-42b, a 42 polypeptide, and this stabilized the tertiary structure. Presumably the linkage was as shown in **56**.[278]



Scheme 5

In the thiodisaccharide area several compounds based on chitobiose with *S* the inter-unit atom have been reported,[279] and likewise 2,5′-dithiokojibiose and -sophorose[280] and *S*-linked α-D-Glc-(1→3)-D-1-deoxymannonojirimycin and an isomer with S in the glucosyl ring, have been reported,[281] the last pair as potential *endo*-α-D-mannosidase inhibitors. Reference is made to other *S*-linked disaccharides in Section 1.5.

Several arylalkyl and indolylmethyl glucosinolates (**57**) have been made, ultimately from the alkylaryl or indolylmethyl vinylnitro compounds.[282]

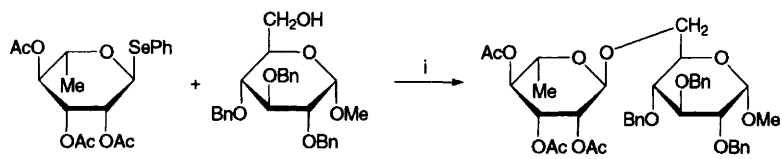


57 A = Aryl, indolylmethyl

The importance of thioglycosides as glycosylating agents is evident from many earlier references to them in this chapter. A comparative analysis of a series of them showed, for example, that *p*-nitrophenyl compounds can remain unreactive while their *p*-acetamido analogues react, and SEt compounds are more reactive than SPh analogues. This complements nicely the armed/disarmed concepts of Fraser-Reid.[283] In related work, the effects of *O*-protecting groups on ethylthio glycosides of methyl glucuronate as glycosylating agents were examined. The 2-benzoate was better than the 2-pivaloate for the 3,4-bis(Tips) compounds.[284]

Phenyl 1,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-fructofuranoside activated by NIS/AgOTf is a suitable reagent for making D-fructofuranosides.[285] Efficient hydrolyses of ethyl thioglycosides have been achieved with Bu_4NIO_4 and 70% aqueous triflic acid in acetonitrile.[285a]

Phenylseleno-glycosides with the single electron transfer (SET) reagent tris(4-bromophenyl)aminium hexachloroantimonate acts as a radical cationic glycosylating reagent (Scheme 6). Quenching reagents indicated that the SET mechanism applies in CH_2Cl_2 but not in some other solvents.[286] See refs. 46 and 215 for other reference to phenylseleno-glycosides and ref. 188 for reference to aryl telluro-glycosides as glycosylating agents.



Reagents: i, $(p\text{-}BrC_6H_4)_3NHSbCl_6$

Scheme 6

3 *C*-Glycosides

3.1 Pyranoid Compounds. – A review has been produced by Chinese authors on methods of synthesis of *C*-glycosides,[287] and a summary of publications

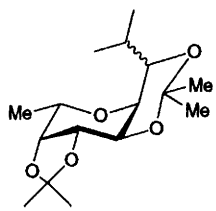
since 1994 on stereoselective procedures has appeared.[288] Tethered approaches to the preparation of *C*-disaccharides have been described in a symposium report.[289]

C-1-Lithiated sugars treated with carbonyl compounds offer a general route to *C*-glycosidic products, and the following examples have been reported: lithiation of 2-acetamido-3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl chloride and treatment of the product with aldehydes or CO_2 gave *C*-bonded α-D-galactosyl secondary alcohols (diastereomeric ratio 1.7:1) or the α-linked carboxylic acid;[290] phenyl 3,4-*O*-isopropylidene-1-thio-α-L-fucopyranoside sulfoxide, lithiated at C-1 by use of MeLi.LiBr, ^{t}BuLi, and the product treated with *iso*-butanal gave mixed α-glycosidic *C*-glycosides (1:1) from which the acetals **58** were made;[291] 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-galactose with lithiotributyltin gave the 1-stannylate derivative and hence the 1-lithio analogue which reacted with aldehydes to give β-*C*-linked secondary alcohols. On the other hand, the α-anomeric *C*-glycosides were made from the α-glycosyl chloride and the α-lithio species derived from it.[292]

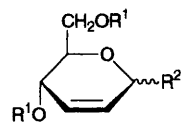
C-1 Carbanionic sugar derivatives can otherwise be made from C-1 sulfones by treatment with SmI_2, and from them α-*C*-glycosides of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactose,[293] α- and β-*C*-glycosides of 3,4,6-tri-*O*-benzyl-D-mannose and D-glucose, respectively,[294] and α-*C*-glycosides of *O*-acetylated Kdn methyl ester[295] have been made.

A different, versatile method of making *C*-glucosides involves *p-tert*-butylphenyl glycosides of 2,3-dideoxy-2,3-unsaturated compounds which, with aryl, benzyl, alkyl, vinyl *etc.* Grignard reagents in the presence of metal catalysts, afford unsaturated compounds of general structure **59**. With $PdCl_2$ α-products are favoured, and β-glycosides are the main products when $NiCl_2$ is used.[296]

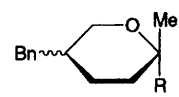
C-Glycosides are now treated approximately in the order of increasing size of their 'aglycons'.



58



59 R^1 = Bn, Tbdms
R^2 = Aryl, vinyl, allyl *etc.*



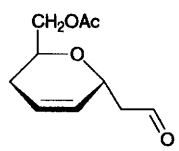
60

Conditions were found for the reductive decyanation and decarboxylation of compounds **60** (R = CN,COO-2-thiopyridyl) such that *cis*- or *trans*-*C*-methyl compounds were made with good selectivity.[297] Radical cyanation of *O*-protected glycosyl bromides or dithiocarbonates by use of *t*-butyl isocyanide, $(Tms)_3SiH$ and AIBN gives α-glycopyranosyl cyanides.[298] The products can be 1-brominated by free radical methods and 1-chlorinated and hence converted to the 1-cyano-1-fluorides by treatment with AgF in MeCN.[299]

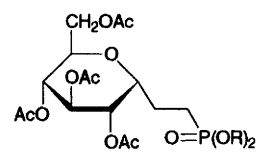
In connection with the building of glycoconjugate libraries the 1-β-*C*-formyl derivative of tetrabenzylglucose has been converted into the aminomethyl

analogue and hence the corresponding isocyanide.[73] 1-*exo*-Methylene compounds ('*exo*-glycals') with one or two substituents on the methylene groups can be made from the corresponding glycosyl methyl (or substituted methyl) sulfones by treatment with base in CBr_2F_2 (Ramberg-Bäcklund reaction).[300] From the products an extensive range of further compounds, *e.g.* ketoses, *spiro*-products, benzyl and hydroxymethyl *C*-glycosides and *C*-linked disaccharides were made.[301] (See later in this section for an example of the dimerization process). Other workers, applying the same reaction, prepared the 1-phenylmethylene *exo*-alkene from tetra-*O*-benzyl-D-mannose and several related compounds and derivatives.[302] Wittig chemistry applied to perbenzylated lactones has been used to give ethoxycarbonyl-substituted *exo*-glycals and hence saturated *C*-glycosides with (ethoxycarbonyl)methyl 'aglycons'.[303] Analogues containing carboxymethyl C-1 groups have been linked to peptides in work focused on building libraries of Sia Le^x analogues in which the NeuNAc, Gal and GlcNAc sugars were replaced by mimics.[304]

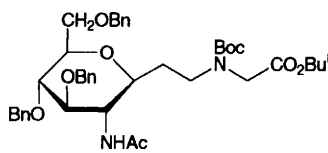
Compound **61** has been made by use of Tbdms vinyl ether and the corresponding glycal and elaborated into a major part of scytophycin C (Chapter 24),[305] and *C*-glycosyl phosphonates of type **62** have been synthesized using the C-1 radical derived from acetobromoglucose and the corresponding vinyl phosphonate.[306] Sugar–aglycon coupling was achieved in the case of compound **63** by reaction of the C-1 lithio derivative (from the Bu_3Sn analogue) with the appropriate 2-aminoacetaldehyde derivative followed by radical deoxygenation of the first formed alcohol.[307] Compound **64** was made by a series of conversions from the diethyl methylmalonate *C*-glycoside to afford conformationally restricted mannosides required for the preparation of selectin antagonists.[308]



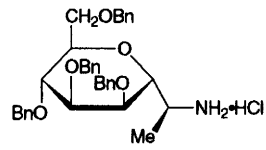
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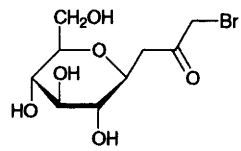
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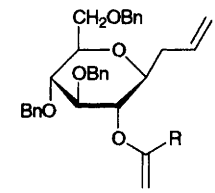
64

Free radical allylation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride with allyltributyltin gave 70% of the α-*C*-allyl compound, but the corresponding *N*-phthalimido bromide gave 40% of the β-glycoside, and 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-mannopyranosyl chloride gave the β-oxazoline only.[309] *C*-Allyl tetra-*O*-benzyl-β-D-glucopyranoside has been used as a source of the new β-glucanase inhibitor **65**,[310] and the corresponding allyl α-*C*-glycoside was employed in the production of a *C*-

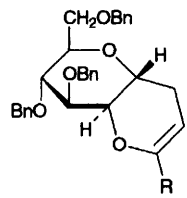
linked glucosphingosine derivative.[311] Compounds **66** (R = H, Me), made by methylenation of the corresponding 2-esters, have been cyclized to give compounds **67** by use of a molybdenum-based reagent, and the products were then extended to give *e.g.* compound **68** which has a structure like those found in 'ladder' toxins.[312] Closely related work by the same authors used a 2-hydroxy-β-*C*-3,3-dimethoxypropyl glucoside to derive a stereoisomer of **67** and an isomer of **68**.[313] *C*-Fucoside **69**, made as a Sia Le^x analogue, binds E- and P-selectins as well as does the parent tetrasaccharide.[314]



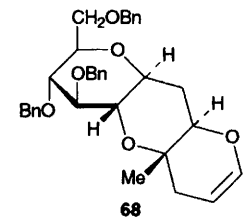
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66



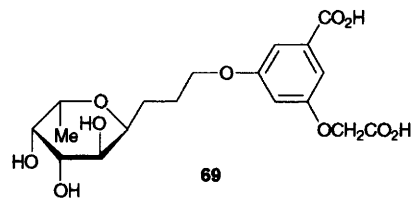
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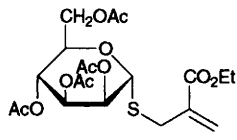
68

Opening of the α-D-*gluco*-epoxide derived from an *O*-substituted D-glucal with tributylisobutenylstannane with tributylstannyl triflate as catalyst gave the 2-hydroxy-β-*C*-isobutenyl glycoside (66%, α:β < 1:20).[315] Methyl 3-methyl-enebutanoate-4-yl *C*-glycosides can be derived from *O*-protected glycosides or glycosyl fluorides by treatment with the corresponding trimethylsilyl derivative and a Lewis acid. α-*C*-Glucosides and -galactosides were made in this way and from them the analogues glycosylated β-ketoesters, butenolides and dihydro-pyrones were prepared.[316] Related 2-methylenepropanoate-3-yl *C*-glycosides can be obtained by triphenylphosphine-induced sulfur extrusion (with configurational retention) from such compounds as the thiomannoside derivative **70** (52%).[317] High chiral induction occurred on the formylation of various 2-*O*-substituted propenyl 3,4,6-tri-*O*-benzyl-β-D-*C*-glucopyranosides. When OH or OAc were present in the propenyl group only *R*-products, *e.g.* **71**, were formed.[318] Irradiation of a glycosyl cobalt complex (Chapter 17) in the presence of maleic anhydride and diphenyl disulfide caused addition of glycosyl and phenylthio radicals to the double bond of the anhydride, and the product, oxidized with MCPBA, gave the *C*-glycosidic anhydride **72**.[319] Treatment of the 4,6-di-*O*-acetyl-2,3-unsaturated α-*C*-diethyl allylmalonate glycoside with $Pd(PPh_3)_4$ gave the bicyclic product **73**.[320] Spiro-bicyclic compounds having both *C*- and *O*-linking to the anomeric centre are treated as chain extended compounds in Chapter 2.

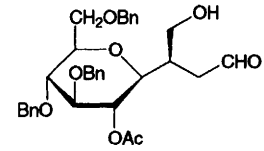
A set of α-galactose-based *C*-linked neoglycopeptides has been designed to



69

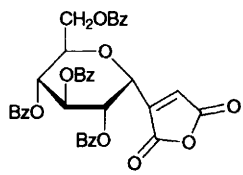


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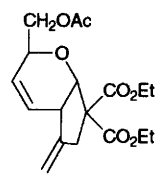


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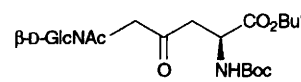
explore the importance of subsite-assisted carbohydrate binding interactions,[321] and several reports have described *C*-glycosides of amino-acids, which are *C*-analogues of glycosylserines : β-*C*-glucosyl compounds involving D-[322] and L-serine,[322,323] α-[324–326] and β-[325,327] *C*-galactosyl and α-*C*-*N*-acetylgalactosaminyl[328] compounds containing L-serine. Likewise several compounds having 5-carbon amino-acid aglycones, which are isosteres of *N*-glycosylated asparagine, have been made: the β-*C*-glucosyl and -galactosyl compounds[329] and a β-*C*-*N*-acetylglucosaminyl compound having a carbonyl group at C-4 of the aglycon, *i.e.* compound **74**.[330]



72

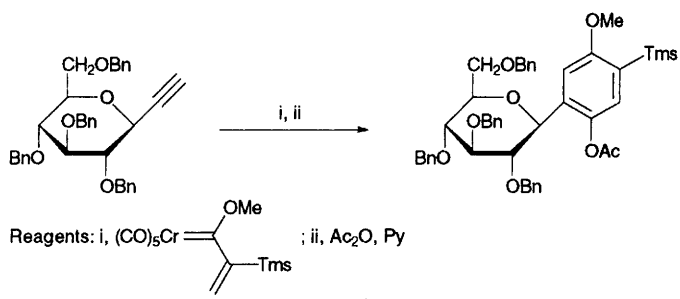


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74

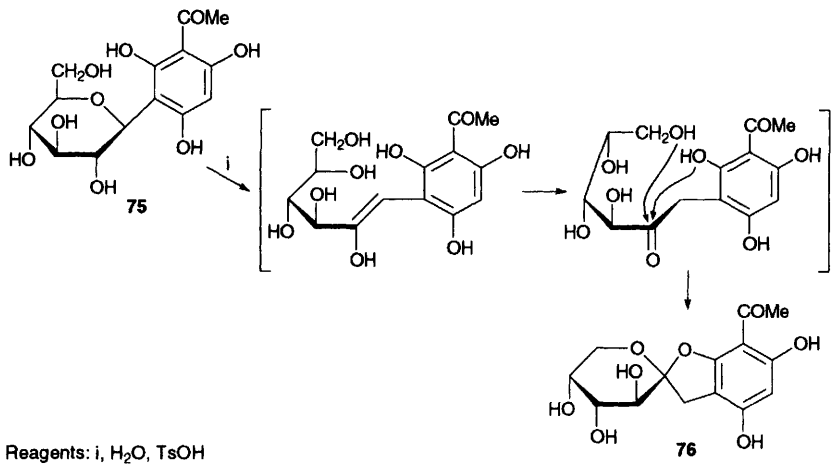
Aryl *C*-glycosides continue to attract attention, and a new approach to their synthesis involves benzannulation between Fischer alkenyl carbene complexes and acetylenic sugars as illustrated in Scheme 7. Otherwise a chromium diene derivative, made from a 1-formylglycal, has been similarly coupled with trimethylsilylacetylene.[331] A more usual application involves coupling of



Scheme 7

glycosyl acetates with aromatic compounds with the powerful $SnCl_4$, AgOTf as catalyst, the process being successful with *N*-phthalimido sugars, NeuNAc and ribofuranose acetates.[332]

An interesting rearrangement occurred when the activated *C*-glycoside **75** was treated in acid water, the product being the D-*arabino*-compound **76** (Scheme 8). No mechanism was proposed, but it is here suggested that an Amadori-like rearrangement may have been involved as illustrated.[333] Amongst aryl *C*-glycosidic compounds to have been made as Sia Le^x mimetics are **77** and **78** (sugar = D-Gal, D-Rib, D-Xyl, L-Rha, D-Fuc).[334]



Reagents: i, H_2O, TsOH

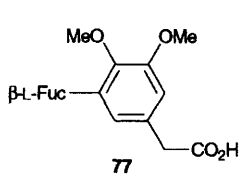
Scheme 8

A striking finding is that unprotected 2-deoxy-sugars with phenols or naphthols and TmsOTf/$AgClO_4$ or TmsOTf alone give the corresponding unprotected *O*-hydroxyaryl β-*C*-glycosides in high yields and with high stereoselectivities.[335,336] Highly efficient *C*-glycosylations were also reported using *O*-protected compounds such as methyl 3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranoside.[336] Diglycosylation of highly activated aromatic compounds can be effected, by similar methods, compounds **79–82** having been made by two-step processes, A and B representing the sites of glycosylation.[337,338]

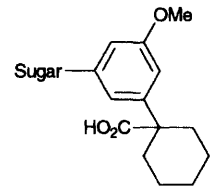
In more complex chemistry, carminic acid **83** synthesis was completed by application of tetra-*O*-benzyl-α-D-glucopyranosyl trifluoroacetate with BF_3 as catalyst.[339] An antibody generated against compound **84** showed α-mannosidase activity.[340]

By use of tetra-*O*-benzyl-D-glucosyl fluoride and a Grignard reagent 2-*C*-D-glucopyranosyl-*N*-methylpyrrole was made,[341] and in the course of the work ribofuranosyl and 2-deoxyribofuranosyl aromatic *C*-glycosides were produced. 1,2-Anhydro-3,4,6-tri-*O*-benzyl-D-mannose, coupled with a lithiated derivative, was used to make 2-*C*-α-D-mannopyranosyl-indole which is the basic unit of a new type of glycopeptide found in human Rnase.[342]

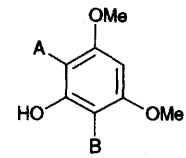
Appreciable work has been carried out on *C*-linked disaccharides. Compounds formed without additional *C*-bridges are treated first. Quantitative



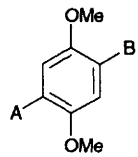
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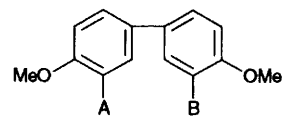
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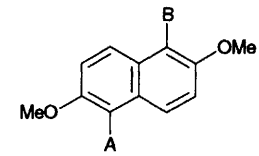
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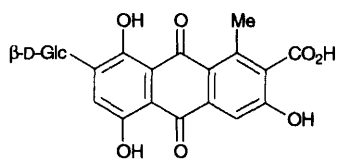
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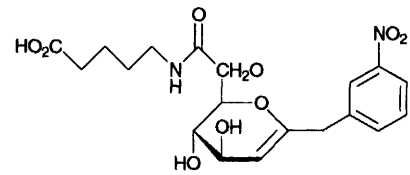
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82

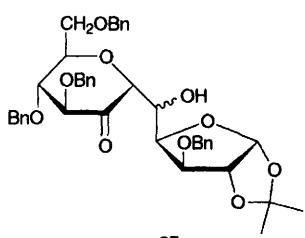


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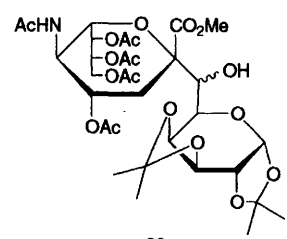


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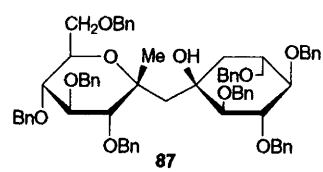
synthesis of C–C-linked glycosyl dimers have been effected electrochemically,[343,344] and the α,α-, α,β- and β,β- isomers of the tetra-*O*-acetylglucopyranosyl dimer were made in 74% yield and in the proportions 1.5, 3.0, 1.0 by SmI_2 treatment of tetra-*O*-acetyl-β-D-glucopyranosyl 2-pyridylsulfone.[345] The 6,6′-linked D-galactose dimer has been made from a 6-deoxy-6-iodo derivative.[343] Dihydroxylation of the known 1,2-*C*-linked mono-unsaturated dimers of tri-*O*-acetyl-D-glucal, -D-galactal and -L-fucal led with good selectivity to 1,2-*C*-linked pyranosylpyranoses.[346] Reaction of the 2-keto phenyl thioglycoside with the 5-aldehydo-D-xylose derivative initiated by SmI_2 led to compounds **85** (73%),[347] and likewise coupling of the protected glycosyl phenylsulfone derived from *N*-acetylneuraminic acid with the galactose-derived aldehyde using the same activating reagent gave dimers **86**.[348]



85



86

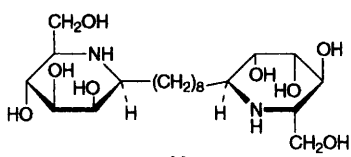


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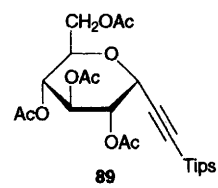
Several compounds having one carbon atom bridging two sugar units have been recorded. Dimerization of a C-1 methylene compound by treatment with BF_3 gave compound **87**,[301] and a related β-D-Gal dimer 1,1′-linked by a hydroxymethylene group was made by addition of a 1-lithiated glycal derivative to a 1-*C*-formylglycal analogue.[349] Two groups have prepared methylene-linked lactose analogues, the first by galactosyl radical additions to a 4-deoxy-4-methylene glucoside within a O-3–O-2′ tethered system,[350] while the second, which conducted conformational analysis on the products and produced compounds with CH_2 or C^2H_2 as the bridge, depended on adding the branched carbon centre of a 4-*C*-branched compound to a galactono-δ-lactone followed by radical removal of the extraneous SMe glycosidic group produced by the procedure.[351] Two other groups have reported β-(1→6) linked, methylene bridged galactobiose, the first paper leading to a trimer of the series,[352] and the second to a trimer and tetramer which had the same affinity for three monoclonal antigalactan antibodies as did the analogous *O*-linked oligosaccharides.[353] A 1,6-ethyne-linked compound is noted below.

Compounds with longer inter-unit bridges are a bis-α-D-galactopyranosyl compound linked 1,1′ by a but-2-en-1,4-diyl group[354] and the α,α- and β,β-bridged 1-deoxymannonojirimycins (**88** is the β,β-compound) which were made following ingenious elaborations of chiral 1-bromo-cyclohexa-4,6-diene-2,3-diol.[355]

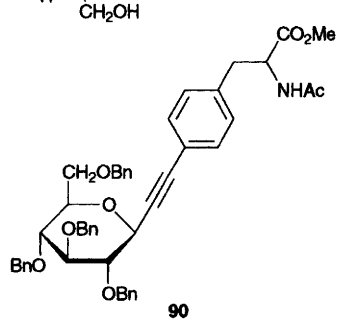
C-Acetylenic compounds have proved increasingly popular because of the second substitutions that can be effected on the alkyne functions. A modified approach to their synthesis involves treatment of *e.g.* tetra-*O*-acetyl-α-D-glucopyranosyl iodide with (trisopropyl)ethynyl trifluoromethylsulfone and hexabutylditin which gives compound **89** (65%, α:β 12:1).[356] The tetra-*O*-benzyl-trimethylsilyl β-analogue of **89** coupled with a *p*-iodophenylalanine derivative gave compound **90** which, with similar compounds, was used as building blocks for the combinatorial synthesis of *C*-linked glycopeptides.[357] Bis(trimethylsilylacetylene) coupled ($TiCl_4$) with diacetyl-D-xylal and -L-arabinal gave the enantiomeric *trans*-related 2,3-unsaturated *C*-glycosyl trimethyl-



88



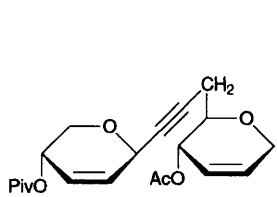
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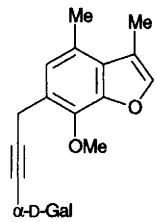
90

silylacetylenes and di-*O*-pivaloyl-D-xylal coupled with the appropriate 6-trimethylsilylacetylenic unsaturated sugar derivative produced the bis-unsaturated alkyne **91** in high efficiency and with 20:1 anomeric selectivity.[358]

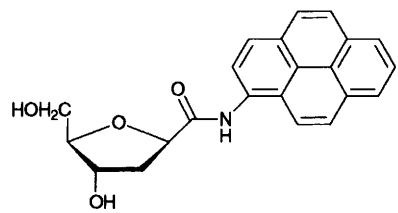
Coupling of tetra-*O*-benzyl-α-D-galactopyranosyl trifluoroacetate with the appropriate alkyne led to compound **92**.[359]



91



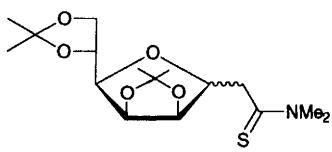
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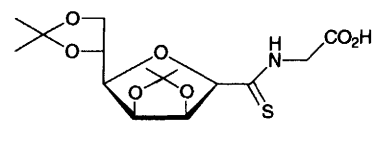
93

3.2 Furanoid Compounds. – 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl acetate gave the β-cyano *C*-glycoside in 70% yield with trimethylsilyl cyanide and $AlCl_3$.[360] A corresponding carboxylic acid was converted into compound **93** which was used as a pseudo-nucleoside and incorporated into oligodeoxynucleotides by solid phase methods.[361] An unusual synthesis of *C*-vinyl tri-*O*-benzyl-β-D-xylofuranoside involved Pd-catalysed ring closure of the appropriate 4,5,7-tri-*O*-benzyl-1,2,3-trideoxy-hept-2-enitol.[362]

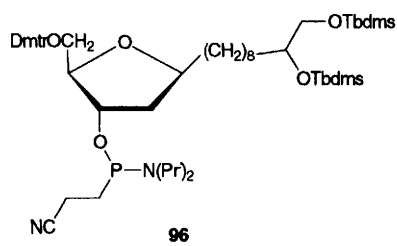
Compound **94**, made from the free sugar and the corresponding diethyl phosphonate, was converted (i, MeI; ii, H_2S,Py) into the corresponding dithioester and hence with glycine to **95** in a new way of *C*-linking glycopeptides.[363] *C*-Glycoside **96** was made from an *O*-protected glycosyl chloride and incorporated into an oligonucleotide; the derived α-diol was then cleaved, and biotin was bonded by way of the derived aldehyde function.[364]



94



95



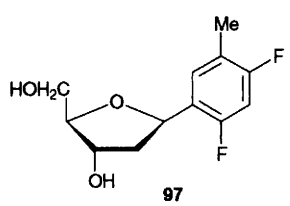
96

An improved route to 2-deoxy-β-D-ribofuranosylbenzene (27% overall) involved phenyllithium addition to a γ-lactone followed by reduction of the hydroxy group formed.[365] Otherwise for 2-deoxyribo- and ribo-aryl glycosides

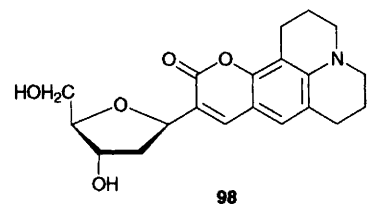
Grignard reactions applied to glycosyl fluorides have been used,[341] as have furanosyl aryltellurides which have the remarkable advantage of being convertible into their glycosyl free radicals, carbocations or carbanions (with Et_3B, BF_3 and BuLi, respectively) each of which can be used to generate *C*-glycosides, the first giving access to aryl compounds from electron-poor aromatic compounds, and the carbocations reacting well with electron-rich compounds. The anions react with electrophiles such as aldehydes.[366]

The difluorotolyl compound **97**, an isostere of thymidine, does not hydrogen bond to deoxyadenosine[369] and is unlikely to play a role in DNA replication (theoretical determinations).[367] Coumarin *2*-deoxy-*C*-riboside **98** was made by Pd-coupling of a glycal with a 3-triflate of the appropriate enone for incorporation into oligodeoxynucleotides as a photosensitive probe.[368]

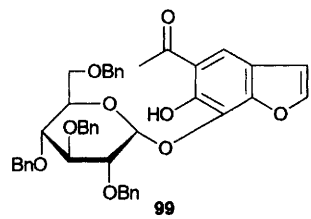
Reaction of an *O*-protected glucosyl trichloroacetimidate with a substituted benzofuran with TMSOTf as catalyst resulted in the flavone *C*-glycoside **99**.[369]



97



98



99

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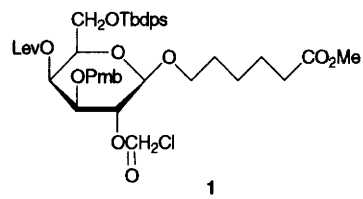
4
Oligosaccharides

1 General

As previously, this chapter deals with specific tri- and higher saccharides; disaccharides are dealt with in Chapter 3. Most references relate to chemical, enzymic or chemico-enzymic syntheses. Chemical features of the cyclodextrins are noted separately; their properties as complexing agents are not treated. With the increasing use of enzymic synthetic methods in the field, the rising importance of complex structures (as in glycoproteins) and rapid developments in the application of combinatorial procedures, more examples are appearing in the literature of oligosaccharide mixtures that are difficult to classify by the approach used in these reports. Work in glycobiology is revealing more and more the importance of the oligosaccharides in biology and medicine, and progress in synthetic work is advancing rapidly to meet the challenges offered.

Reviews in the field have appeared as follows: on progress in solid-phase synthesis;[1] on the synthesis of oligosaccharide and glycomimetic libraries,[2] one on the use of both solid phase and liquid phase strategies for making oligosaccharide and glycoconjugate libraries,[3] and a further (by the developers) on the preparation of complex oligosaccharide-based products by the 'glycal assembly' method;[4] on strategies involving the use of glycosyl fluorides, Tms ethers or acetates as glycosyl donors;[5] and on the introduction of thiosugars into oligomers and the behaviour of the products towards hydrolases.[6] Relevant reviews on enzymic synthesis have appeared,[7,8] and a further focused on the use of glycosyltransferases in syntheses.[9] The topic of the chemicoenzymic synthesis of Sia Le^x has also been surveyed.[10]

Several matters of general relevance have been reported. Compound **1**, which contains four selectively removable protecting groups, has been converted to the various mono-ols and then glycosylated, mono-deprotected, glycosylated *etc.* to give a library of 45 di-, tri- and tetra-saccharides of



1

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biological relevance.[11] In related work Boons and colleagues (*cf.* Vol. 30, p. 63, ref. 35), using but-1-en-2-yl glyosides of several fucosyl- or galactosyl-terminating disacharides bearing specific acetyl and *p*-methoxybenzyl groups, have selectively deprotected them, and by fucosylation have made a set of 16 trisaccharides.[12]

A novel method for coupling lactose or dextran to bovine serum albumin involves brief heating of the reactants to high temperature.[13]

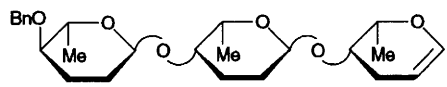
$Sc(OTf)_3/Ac_2O$ efficiently cleaves dioxyxylene (DOX) linkers to polyethylene glycol (PEG) polymer supports in oligosaccharide synthesis efficiently to give the product in the form sug-O-DOX-OAc.[14]

Production of gluco-oligosaccharides from maltose using two different types of glucansucrase from *Streptococcus sobrinus* has been described,[15] and in related work mutant dextran sucrases have been used to transfer glucose from sucrose to various oligosaccharide acceptors; for example, in the case of lactose, glucose was transferred to O-2 of the reducing unit.[16] Invertase has been used to link a second fructose unit to sucrose,[17] and a mutant β-glucosidase/β-galactosidase from *Agrobacterium* sp. was found to transfer these glycosyl residues from α-galactosyl or α-glucosyl fluorides to a wide range of mono- or di-saccharide aryl glycosides to give mainly β-(1→4)-linked di- and tri-saccharide glycosides.[18]

2 Trisaccharides

2.1 General. – Compounds in Sections 2.2–2.4 are treated according to their non-reducing end sugars. Unless otherwise specified, the sugar abbreviations (Glc *etc.*) imply the pyranosyl modifications.

2.2 Linear Homotrisaccharides. – Boons's '2-direction' approach was applied to the preparation of β-D-Glc-(1→4)-D-Glc-(1→4)-D-Glc, the central unit being initially introduced as the glycosylating agent ethyl 2,3,6-tri-*O*-benzyl-1-thio-4-*O*-triethylsilyl-β-D-glucopyranoside (activated with IDCP), and the resulting disaccharide being treated with tetra-*O*-benzoyl-D-glucopyranosyl fluoride. This reagent with $Cp_2ZrCl_2/AgOTf$ recognizes primary and secondary silyl ethers as acceptor groups.[19] Various glucotrioses have been made during the study of a cellobiose phosphorylase.[20] Aryl glycosides of β-D-Glc-(1→4)-β-D-Glc-(1→3)-β-D-Glc were made by the unusual process of converting the trisaccharide, obtained enzymically from barley β-glucan, into the acetobromo derivative which was coupled with phenols under phase transfer conditions.[21] β-D-Gal*f*-(1→3)-β-D-Gal*p*-(1→6)-β-D-Gal*f*-OMe, related to a streptococcal antigen, has been made.[22] α-D-Gal-(1→4)-β-D-Gal-(1→4)-β-D-Gal has been spacer group-linked to *m*-xylene-α,α-dithiol to give a potential inhibitor of bacterial adhesion,[23] α-D-Man-(1→2)-α-D-Man-(1→2)-D-Man has been made by trichloroacetimidate-coupling to a 2-unprotected mannose unit *S*-bonded to controlled pore glass,[24] and α-D-Man-(1→2)-α-D-Man-(1→6)-D-Man was spectacularly made and coupled to each of the hydroxyl groups of pentaerythritol



2

by way of spacer groups in a one-pot procedure.[25] An iterative approach using a 3,6-dideoxyglycal and 4-hydroxy-5-(Tbdmsoxy)hexyne was used to make compound **2**.[26]

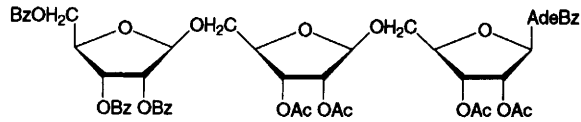
Condensation between 2′,3′-di-*O*-acetyl-*N*-benzoyladenosine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose ($SnCl_4$ catalyst) gives the trisaccharide nucleoside derivative **3** (17%) as well as the disaccharide analogue (29%), the nucleoside derivative acting as a ribosyl donor.[27] α-D-Ara*f*-(1→3)-α-D-Ara*f*-(1→5)-D-Ara*f*-OMe and the 1→5,1→5-linked isomer were made by formal chemical synthesis as mycobacterial transferase substrates,[28] and long-chain alkyl xylotriosides have been reported as potential antimicrobial agents.[29] Combinatorial libraries of trimers of 2,6-dideoxy-L-hexoses have been made by use of glycals.[30]

2.3 Linear Heterotrisaccharides. – The following glucose-terminating compounds have been made: α-D-Glc-(1→3)-α-D-Man-(1→2)-α-D-Man[31] and 3,6-di-OMe-β-D-Glc-(1→4)-2,3-di-OMe-α-L-Rha-(1→2)-3-OMe-L-Rha,[32] the latter by an improved method that permitted ^{13}C labelling of some or all of the methyl groups.

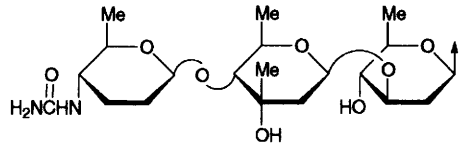
Three groups have made the lactose derivative α-D-Gal-(1→4)-β-D-Gal-(1→4)-β-D-Glc in the form of various glycosides that allow the development of bioactive glycoconjugates,[33-35] the last paper, which is based on enzymic methods, also describing the α-(1→3), β-(1→4)-linked compound.[35] β-D-Gal-(1→6)-β-D-Gal-(1→6)-D-GlcNAcNH_2 was produced by glycal technology.[36] Enzymic methods [recombinant α-(1→3)-galactosyl transferase] were used to make the lactosamine derivative α-D-Gal-(1→3)-β-D-Gal-(1→4)-D-GlcNHR (R = variable acyl),[37] and α-D-Gal-(1→4)-α-D-Gal-(1→3)-L-Rha, related to the repeating unit of a polysaccharide of *E. coli*, has been prepared with a pyruvate acetal at O-2, O-3 of the central sugar.[38] Enzymic methods have yielded β-D-Gal-(1→3)-β-D-Gal-(1(8)-NeuNAc and β-D-Gal-(1→4)-β-D-Gal-(1→3)-D-GlcA.[39] Other galactosyl-terminating trisaccharides to have been reported are α-D-Gal-(1→3)-α-D-Man-(1→2)-D-Man,[40] α-D-Gal-(1→3)-β-D-GlcNAc-(1→2)-D-Man[41] and β-D-Gal-(1→4)-β-D-GlcNAc-(1→3)-L-Fuc.[42]

Deoxyhexose compounds to have been described are α-L-Rha-(1→2)-β-D-Gal-(1→2)-D-GlcA (saponin component),[43] α-L-Rha-(1→6)-β-D-Glc-(1→3)-L-Rha (found in a new clerodane glycoside),[44] α-L-Fuc-(1→2)-β-D-Gal-(1→3)-S (S = D-Glc, D-Gal, D-GlcNAc, D-GalNAc),[45] α-L-Fuc-(1→2)-α-D-Glc-(1→6)-D-Glc and α-L-Fuc-(1→2)-α-D-Gal-(1→4)-D-GlcNAc.[46]

Amino-sugar-terminating trisaccharides to have been synthesized are β-D-GlcNAc-(1→7)-α-Hep-(1→6)-Glc (*E.coli* K-12 lipopolysaccharide core oligosaccharide),[47] β-D-GalNAc-(1→4)-β-D-GlcNAc-(1→3)-α-D-Gal (non-fucosylated backbone unit of a glycan of *Schistosoma manson*)[48] and β-D-ManNAc-



3



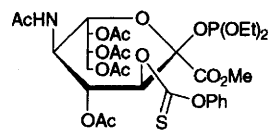
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(1→4)-α-D-Glc-(1→2)-L-Rha (capsular polysaccharide repeating unit of *Streptococcus pneumonia*).[49] A new anthraquinone *C*-glycoside from *Streptomyces sp.* P371 with gastric mucosal protective activity contains the trisaccharide **4**.[50]

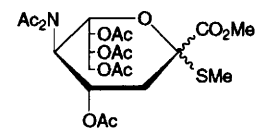
Compound **5** is an excellent α-sialylating agent, the thiocarbonate group anchimerically assisting the displacement and being removable by radical reduction. It was used to make α-NeuNAc-(2→3)-β-D-Gal-(1→4)-D-Glc.[51] See also an enzymic sialylation approach to a ceramide glycoside of this trisaccharide.[52] Others have made a ceramide glycoside (ganglioside GM_3) with a ^{13}C label at the NeuNAc carboxylate group.[53] GM_3 has also been coupled to a fluorescent tag and then to a polypeptide for studies of the flu virus.[54] Compound **6**, activated with NIS/TfOH, was used to make α-$NeuNAc_2$-(2→3)-β-D-Gal-(1→4)-D-$GlcNH_2$[55] and α-NeuNAc-(2→3)-β-D-Gal-(1→3)-D-GlcNHR (R widely varied) were produced by use of sialyl transferases.[56] The porcine liver enzyme was used to transfer Kdn to give α-Kdn-(2→3)-β-D-Gal-(1→3)-2-*O*-Ac-D-Gal.[57]

5-Deoxy-3-*O*-Me-L-Xyl*f*-(1→4)-β-D-Ara*p*-(1→2)-D-Xyl*p* is a component of sponges,[58] and β-D-Xyl-(1→2)-D-Man-(1→4)-D-Glc is found in the glycophospholipid of *Hyriopsis schlegelli*.[59]

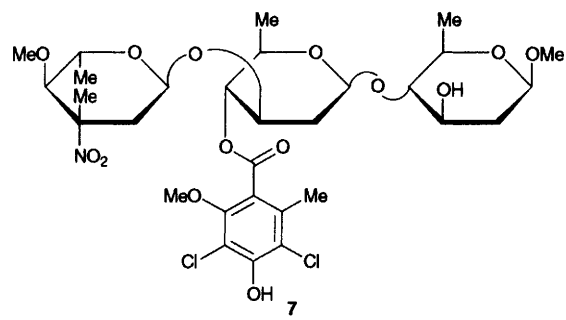
The deliconitrose-containing trimer **7** has been prepared by Nicolaou's group as part of everninomicin.[60]



5



6



7

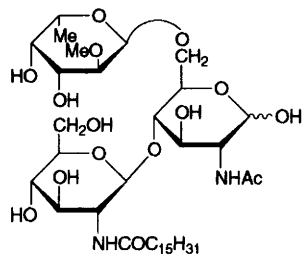
2.4 Branched Homotrisaccharides. – α-D-Glc-(1→3)-[α-D-Glc-(1→4)]-D-Glc and the α,β-, β,α- and β,β-isomers were synthesized chemically as their α-methyl glycosides as reference compounds for NMR and computational conformational analyses.[61]

1,2-*O*-[(1-Cyano)ethylidene]-3,6-di-*O*-[α-D-mannopyranosyl)-β-D-mannosyl nonaacetate has been used as a trisaccharide glycosyl donor,[62] and neoglycolipids based on 3,6-di-*O*-[α-D-mannopyranosyl]-D-mannose and analogues with β-D-Glc, β-D-Gal, β-D-Lac and α-L-Rha in both non-reducing positions have been reported.[63]

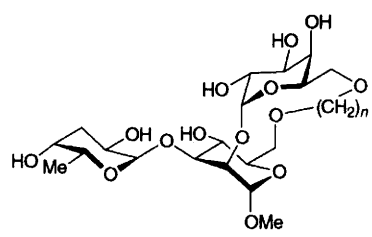
2.5 Branched Heterotrisaccharides. – Compounds in this section are categorized according to their reducing end sugars.

Highly selective chemical galactosylation of a 3′-*O*-benzyl-β-D-lactopyranoside occurred at O-6 to give access to 4,6-di-*O*-β-D-galactosyl-D-glucose.[64] Two α-galactosyl transferases were used to make α-D-Gal-(1→3)-[α-D-Man-(1→6)]-D-Man.[65]

β-D-GalNAc-(1→4)-[α-L-Fuc-(1→3)]-D-GlcNAc, the GalNAc for Gal analogue of Le^x trisaccharide, was made and coupled to BSA *via* a linker.[66] The Le^x trisaccharide itself has been converted to the mono-, di- and trisulfates (ester groups in the galactosyl moiety)[67] and a 3-*C*-methylglucosamine analogue has been described.[68] The structurally similar compound **8**, as well as derivatives with acetyl and sulfate groups on O-4 or O-3 respectively of the fucose moiety, were made as analogues of modulation factors of *Rhizobia*.[69] Enzymic procedures were used in the preparation of β-D-Gal-(1→3)-[β-D-GlcNAc-(1→6)]-D-GalNAc as a component of a mucin type 2 core.[70] β-D-Xyl-(1→3)-[β-D-Glc-(1→2)]-D-Fuc was made as a α-trichloroacetamidate derivative and used to make a saponin with strong anti-inflammatory activity.[71] 6-Deoxy-α-L-Tal-(1→2)-α-L-Rha-(1→5)-3-deoxy-D-*lyxo*-heptulosaric acid and the isomer with the rhamnopyranose replaced by β-L-Rha*f*, the former being the repeating unit of a rhizobial lipopolysaccharide, have been synthesized.[72]

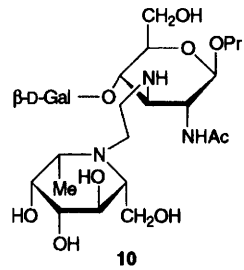


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9

2.6 Analogues of Trisaccharides and Compounds with Anomalous Linking. – Tethered trisaccharides **9** [α-D-Gal-(1→2)-[α-D-Abe-(1→3)]-α-D-Man derivatives] were designed on the basis of crystal structures to probe intersaccharide flexibility in carbohydrate–protein interactions.[73] A new class of Le and



10

LacNAc analogues exemplified by **10** were made as potential fucosyl transferase inhibitors.[74]

Amide bonding between the amino group of β-D-Gal-(1→3)-D-GlcNH$_2$ and hexuronic acids has been used to make 'saccharopeptides' to which α-NeuNAc and α-L-Fuc were enzymically bonded *via* O-3 and O-4 of the Gal and GlcNH$_2$ respectively, and thus Sia-Le^a-like products were obtained.[75] An analogous amido-linked compound, formed by solid phase condensation of three molecules of 6-amino-2,5-anhydro-6-deoxy-D-gluconic acid, has been reported.[76] Phosphodiester bonding is involved in the synthetic α-D-Man-(1-PO$_3$H-6)-β-D-Gal-(1→4)-α-D-Man which is present in the lipophosphoglycan of *Leishmania*.[77]

Trisaccharides with sulfur in place of oxygen as one of the inter-unit linkages to have been reported are: a chitotriose derivative (S between units 1 and 2),[78] and two analogues of Le^x trisaccharide {β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-D-GlcNAc} with one sulfur atom linking the α-L-Fuc[79] or β-D-Gal.[80]

See Chapter 19 for cyclitol-based trisaccharide analogues.

3 Tetrasaccharides

Compounds of this set and higher oligosaccharides are classified according to whether they have linear or branched structures and then by the nature of the sugars at the reducing ends.

3.1 Linear Homotetrasaccharides. – An *Actinomycetes* strain produces a very unusual type of non-reducing tetramer comprising two 1,1′-α-bonded sophorose [β-D-Glc-(1→2)-D-Glc] molecules each carrying tiglate (*Z*-2-methylbut-2-enoyl) ester group on O-6, O-2′ and O-3′.[81] Two + two coupling was used to produce the α-(1→4), α-(1→3), α-(1→4) and α-(1→3), α-(1→4), α-(1→4) linked glucotetraoses,[82] and a solid support method gave β-(1→4) linked compounds. The method involved the use of a 6-linked glucosylating agent on the polymer which was coupled to 3,6-di-benzyl-D-glucal to give a bound disaccharide glycal which was reconverted into a saturated *S*-ethyl thioglycoside for further coupling. The system can be iterated and the tetramer was made.[83]

3.2 Linear Heterotetrasaccharides. – Action of a β-galactosidase on lactose gave a set of novel non-reducing oligosaccharides containing the α-D-Glc-(1↔1)-β-D-Gal unit. Twelve were characterized; they conformed with the general structure β-D-Gal-(1→4)$_n$-α-D-Glc-(1↔1)-β-D-Gal- [(4←1)-β-D-Gal]$_m$ (*m*, *n* = 1, 2, 3, 4).[84] The lactose-containing β-D-Gal-(1→4)-β-D-GlcNAc-(1→3)-β-D-Gal-(1→4)-β-D-Glc has been made by chemical procedures,[85] and glycal technology has been used in the synthesis of β-D-Gal-(1→3)-β-D-GalNAc-(1→4)-β-D-Gal-(1→4)-β-D-Glc-O-Cer, which is asialo-GM$_1$.[86]

α-D-Kdo-(2→4)-α-D-Kdo-(2→6)-β-D-GlcNH$_2$-(1→6)-α-D-GlcNH$_2$ as its 1,4′-bisphosphate is a constituent of the lipopolysaccharide of a deep rough mutant of *E. coli*.[87]

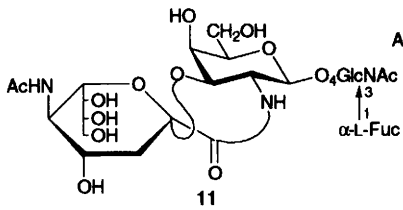
Ganglioside LM$_1$, α-Neu5Ac-(2→3)-β-D-Gal-(1→4)-β-D-GlcNAc-(1→3)-β-D-Gal, has been prepared with the aid of an α-Neu5Ac xanthate as glycosylating agent.[88]

3.3 Branched Heterotetrasaccharides. – The hydroxylamine glycoside α-Neu-(2→3)-β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-β-D-GlcONH$_2$ was made by enzymic sialylation and fucosylation of *N*-lactosyloxysuccinimide to give means of coupling the tetrasaccharide to peptides,[89] and the same Sia Le^x analogue was coupled to several complex long chain compounds *via* ethylene glycol spacers.[90] β-D-Glc-(1→3)-[α-L-Ara*f*-(1→4)]-α-L-Rha-(1→2)-D-Glc was isolated from cytotoxic triterpenoid glycosides of *Albizia julibrissin* and chemically coupled to diosgenin to give a product with some retained cytotoxicity.[91]

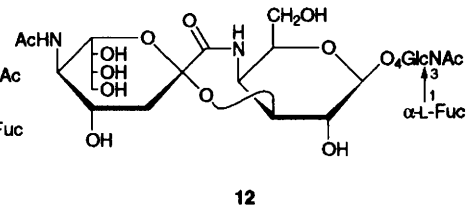
A most elegant 'one pot' synthesis of β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-β-D-Glc-(1→3)-D-Gal utilized a disarmed lactosyl thioglycoside derivative which was fucosylated with an armed fucosyl thioglycoside prior to coupling to galactose.[92] For the synthesis of the following repeating unit of an *E.coli* antigen the β-mannosyl link was made *via* a β-glucoside which was inverted at C-2 by an oxidation/reduction sequence: β-D-GlcNAc-(1→2)-β-D-Man-(1→3)-[β-L-Fuc-(1→2)]-D-Gal.[93] The tetrasaccharide repeating unit of the K-antigen of *Klebsiella* type 57 {α-D-Man-(1→3)-β-D-Gal-(1→3)-[α-D-Man-(1→4)]-D-Gal} has been made as the β-(2-trimethylsilyl)ethyl glycoside[94] and as a highly substituted derivative having the galactose unit present as a 1,6-anhydride.[95]

Appreciable work on Sia Le^x {α-NeuNAc-(2→3)-β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-D-GlcNAc} continues to be published. Three further chemical syntheses have been reported,[96–98] as well as two enzymic procedures.[99,100] The first report on enzymic work also described the analogue with glucose in place of GlcNAc,[99] and the second was conducted on a sepharose matrix.[100] Wong and colleagues have described the synthesis of Sia Le^x and analogues, and the nature of their binding with selectins in a major review.[101]

New derivatives of Sia Le^x to have been recorded are the 6-aminohexyl glycoside (byethods applicable on a large scale),[102] a range of compounds with various *N*-acyl groups and aglycons,[103] 9-deoxy-9-(methylmercuri)thio-NeuNAc (made enzymically)[104] and the cyclic amido compounds **11** and **12**.[105] Further compounds to have been described have Sia Le^x glycosidically bonded to polyamides (they inhibit binding of bound forms of Sia Le^a and selectins)[106]

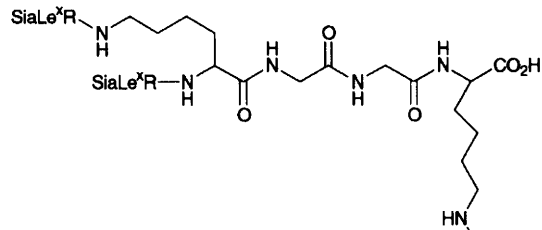


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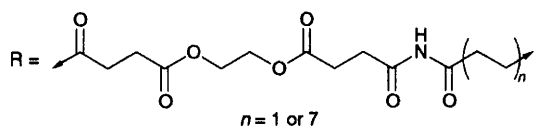


12

or to carboxymethyl derivatives of polysaccharides which showed enhanced accumulation in inflammatory lesions relative to Sia Le^x itself.[107] Compounds with structure **13** are trivalent inhibitors of E-selectin-mediated cell adhesion which show some bioactivity, but this is very greatly enhanced in derived lipsomes.[108] Variations of the sugars of Siae^x have given α-L-Fuc-(1→2)-β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-β-GlcNAc.[109]



13



n = 1 or 7

Enzymic procedures have led to Sia Le^a with variable acyl groups: α-NeuNAc-(2→3)-β-D-Gal-(1→3)-[α-L-Fuc-(1→4)]-GlcNAcyl,[110] and to analogues with the fucose moiety replaced by β-D-Ara*p*, 2-deoxy-2-F-α-L-Fuc or β-L-Gal.[111] Danishefsky and colleagues have elaborated related compounds using glycal technology and the solid phase approach.[112]

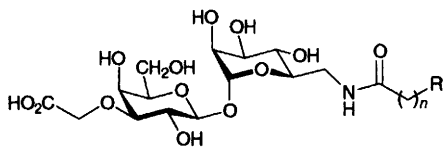
A further lactosamine-based compound to have been made by methods involving enzymes is β-D-Gal-(1→4)-β-D-Glc-(1→6)-[β-D-Gal-(1→4)]-β-D-GlcNAc.[113]

Compounds terminating in GalNAc to have been made are β-D-GlcA-(1→3)-β-D-GalNAc-(1→6)-[β-D-GlcA-(1→3)]-D-GalNAc, part of an antigen of *Schistosoma mansoni*,[114] and β-D-Gal-(1→4)-β-D-GlcNAc-(1→6)-[β-D-Gal-(1→3)]-D-GalNAc with a sulfate ester on either of the galactose units,[115] while α-D-GlcNAc-(1→4)-β-D-Gal-(1→3)-[α-NeuNAc-(2→6)]-D-GalNAc and the isomer having GalNAc instead of GlcNAc were characterized as their alditol derivatives during the structural analysis of oviducal mucins of *Rana dalmatina*,[116]

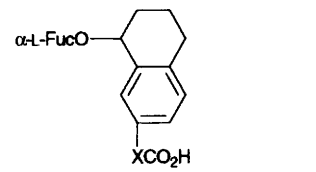
The synthesis of α-L-Rha-(1→3)-[2,4-di-*O*-(2*S*-2-methylbutanoyl)-α-L-Rha

(1→2)]-3-*O*-Ac-β-D-Glc-(1→2)-D-Fuc has also been reported,[117] and β-D-Glc-(1→4)-[α-Hep-(1→3)]-α-Hep-(1→5)-3-deoxy-D-*manno*-octulose, the tetrasaccharide of the core of the lipopolysaccharide of *Haemophilus influenzae,* has been made.[117a]

3.4 Analogues of Tetrasaccharides and Compounds with Anomalous Linkings. The non-reducing galactosyl mannoside compound **14** has been made as a Sia Le^x mimetic,[118] likewise compounds **15**.[119] Transglycosylations with an amylase have replaced the terminal glucose residue of acarbose (**16**) with such sugars as 6-Glc, 6′-maltose, 3′-maltose, 6-Man (35 examples).[120] Vasella's work on acetylene-linked carbohydrates has led to the series **18** (n = 1, 3, 7) from **17** as starting material.[121]

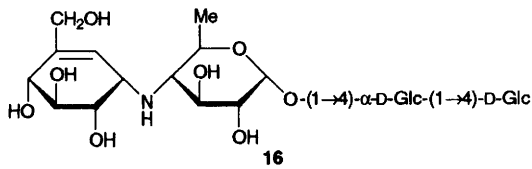


14 n = 9, R = Me, CH_2CO_2H, CH_2NH_2, CH_2OSO_3H
n = 4, R = CH_2OSO_3H

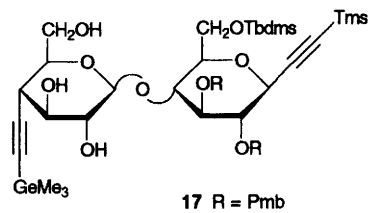


15 X = CH_2NHCO, $CH_2CH_2CH_2$, $C(Me)_2C{\equiv}C$, $C(Me)_2CH_2CH_2$

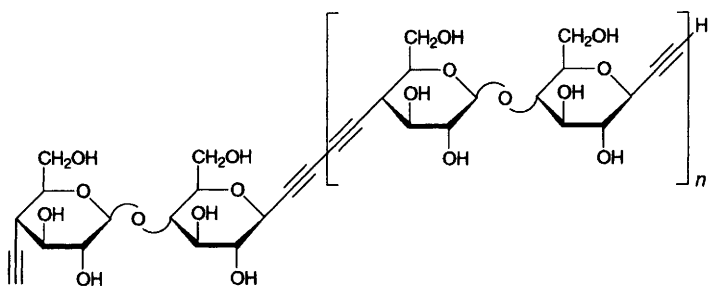
The *C*-linked β-(1→6) galactobiose, -triose and -tetraose and the *O*-linked analogues bind similarly to monoclonal anti-galactan antibodies.[122]



16



17 R = Pmb

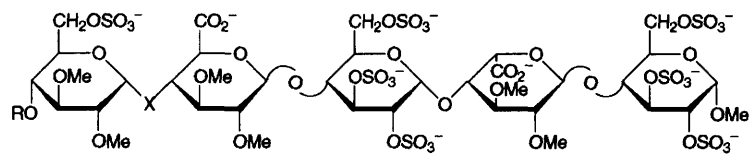


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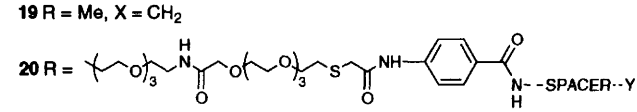
4 Pentasaccharides

4.1 Linear Homopentasaccharides. – The series of β-D-Gal-(1→6)-linked oligomers with the inter-unit O-atoms replaced by methylene groups has been made up to the pentamer.[122] Enzymic methods have been used to make maltotrioses, -tetraoses and -pentaoses with the third glucose moiety modified to 6-deoxy and 6-amino-6-deoxy-D-glucose.[123] Studies have been reported on the inhibitory effects on the AIDS virus of azidothymidine bound to sulfated laminaripentaose or alkyl laminaripentaosides.[124] Enzymic methods are used to prepare *p*-nitrophenyl *N*-acetyl-β-chitopentaoside from the *N*-acetylpentaose.[125]

4.2 Linear Heteropentasaccharides. – α-D-Gal-(1→3)-β-D-Gal-(1→4)-β-D-GlcNAc-(1→3)-β-D-Gal-(1→4)-β-D-Glc-OMe was made as an analogue of the ceramide glycoside involved in xenotransplantation rejection response. The synthesis is notable in that it assembles simple building-blocks without the need for protecting group manipulations.[126] Compound **19**, with one *C*-inter-unit linkage, was found to have almost the same biological properties and affinity for antithrombin III as did its *O*-linked analogue,[127] and the closely related conjugates **20** were designed to bind antithrombin III and thrombin binding domains.[128] The analogue of the heparin pentasaccharide with a 3-deoxy modification in the L-iduronic acid moiety has been made.[129]



19 R = Me, X = CH_2



20 R =

X = O, Y = dermatan sulfate, cellobiose, maltobiose

In related work α-D-Gal-(1→3)-β-D-Gal-(1→4)-β-D-Glc-(1→3)-β-D-Gal-(1→4)-β-D-GlcNAcN_3, which represents epitopes found in pig organs used in xenotransplantation, was made chemo-enzymically to study the binding of epitopes with human anti-Gal antibodies.[130] The pentasaccharide of hyaluronic acid with β-D-GlcA-(1→3)-β-D-GlcNAc at the reducing end was made as the *p*-methoxyphenyl glycoside (see also hexasaccharide section).[131]

α-L-Rha-(1→3)-α-L-Rha-(1→2)-α-D-Gal-(1→3)-α-D-GlcNAc-(1→3)-α-L-Rha was made with ^{13}C labelling in the galactosyl residue and used to reveal that α-D-Gal-(1→3)-α-D-GlcNAc-(1→3)-α-L-Rha is conformationally different from related higher saccharides.[132] Glycosylating agent **21** was used to link the branched-chain sugar *via* O-3 to the terminating L-Rha moiety of 2-*O*-Me-α-D-Rha-(1→3)-2-*O*-Me-α-L-Fuc-(1→3)-α-L-Rha-(1→2)-6-deoxy-L-Tal.[133]

4.3 Branched Homopentasaccharides. – The branched arabinofuranosyl pentasaccharide β-D-Ara*f*-(1→2)-α-D-Ara*f*-(1→3)-[β-D-Ara*f*-(1→2)-α-D-Ara*f*-(1→5)]-D-Ara*f*, corresponding to a structural unit of the arabinogalactan of the cell wall of *Mycobacterium tuberculosis*, has been synthesized.[134]

4.4 Branched Heteropentasaccharides. – Sia Le^x pentasaccharide with a $(CH_2)_3CH(C_{13}H_{27})_2$ aglycon attached to the Gal moiety at the reducing end is a useful ligand for *in vitro* ELISA screening of selectin blockers. It is easier to make than the natural compound with a ceramide aglycon.[135] Schmidt and colleagues have synthesized the Le^a and Le^x pentasaccharides by chemical methods,[136] and enzymic procedures were used to obtain Sia Le^x having β-D-Glc, α-D-Gal, β-D-Gal, α-L-Gal and β-L-Gal all in the form of their uronic acids *N*-amide linked to the D-$GlcNH_2$ unit in place of the normal *N*-Ac group.[137] In related work β-D-GalNAc-(1→4)-[α-L-Fuc-(1→3)]-β-D-GlcNAc-(1→6)-[3-O-sulfo-β-D-Gal-(1→3)]-D-GalNAcOMe was shown to be five-fold better than Sia Le^xOMe at inhibiting L- and P-selectin.[138]

Using solid-phase methods Schmidt and colleagues have prepared β-D-$GlcNH_2$-(1→2)-α-D-Man-(1→3)-[β-D-$GlcNH_2$-(1→2)-α-D-Man-(1→6)]-D-Man, a branched pentasaccharide common to many complex *N*-glycans.[139] Also in the area of mannose-containing compounds T. Ogawa and colleagues have reported the synthesis of α-D-Man-(1→3)-[α-D-Man-(1→6)]-β-D-Man-(1→4)-[β-D-GlcNAc-(1→6)]-D-GlcNAc.[140]

The branched pentamer 3-O-Me-β-D-Glc-(1→3)-β-D-Glc-(1→4)-[β-D-Xyl-(1→2)]-6-deoxy-β-D-Glc-(1→2)-D-Xyl as a trisulfate is the carbohydrate constituent of a steroidal glycoside from the sea cucumber *Cucumaria frondosa*.[141]

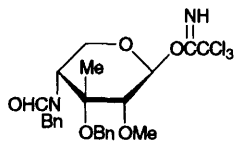
4.5 Pentasaccharides with Anomalous Linking. – Compound **19** is a pentamer with one *C*-glycosidic linkage.[127]

5 Hexasaccharides

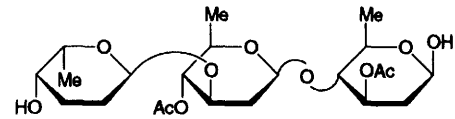
As has become customary in these volumes, an abbreviated method is now used for representing higher saccharides. Sugars will be numbered as follows, and linkages will be indicated in the usual way:

1 D-Glc*p*	**2** D-Man*p*	**3** D-Gal*p*
4 D-Glc*p*NAc	**5** D-Gal*p*NAc	**6** Neu*p*NAc
7 L-Rha*p*	**8** L-Fuc*p*	**9** D-Xyl*p*
10 D-Glc*p*NH_2	**11** D-Glc*p*A	**12** D-Qui (6-deoxy-D-glucopyranose)
13 L-*Glycero*-D-*manno*-heptose	**14** L-Ara*f*	**15** Kdn

5.1 Linear Hexasaccharides. – Enzymic partial hydrolysis of barley (1→3), (1→4) glucan gave β-D-Glc-(1→4)-β-D-Glc-(1→3)-D-Glc, which was isolated as its peracetate in 49% yield. The derived deacetylated glycosyl fluoride on exposure to a 4-glucanohydrodase gave the alternately (1→4), (1→3)-linked



21



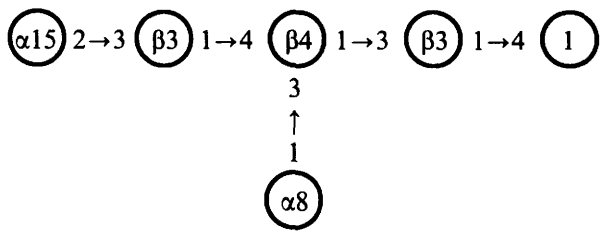
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hexamer in 20% yield.[142] By use of egg-white lysozyme di-*N*-acetylchitobiose was efficiently converted into *N*-acetylchitohexaose.[125]

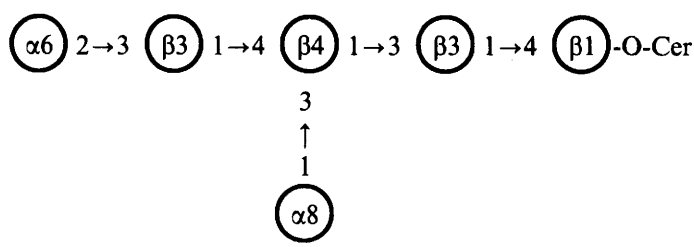
Activation of compound **22** as the glycosyl phosphite ester and coupling to a glycosidic analogue with free hydroxyl group on the non-reducing unit allowed access to the hexasaccharide fragment of landomycin A, an antitumour antibiotic.[143] The syntheses of the β-(1→4)-linked trimer of β-D-GlcA-(1→3)-D-GlcNAc (a hyaluronic acid repeating unit), an analogue with a 4,5-double bond in the non-reducing unit and one carrying sulfate groups at O-6 of the Glc in the position of the initial GlcA units, have been described.[131]

5.2 Branched Hexasaccharides. – A convergent syntheses of the phytoelicitor hexasaccharide consisting of four β-(1→6)-linked glucose units bearing β-(1→3)-linked glucose substituents at units 1 and 4 has been reported.[144]

Compound **23**, KDN-Le^x ganglioside, and analogues with L-Rha in place of L-Fuc and 1,5-anhydroglucitol at the 'reducing' end have been described,[145] as have the Sia Le^x ganglioside **24** together with analogues with modifications (OMe, NHAc, NH_2) for 6-OH of the Gal bonded to NeuNAc.[146]



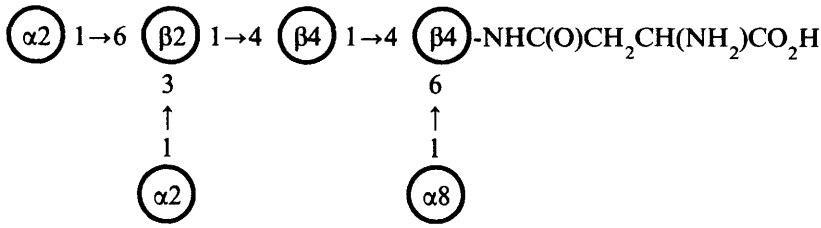
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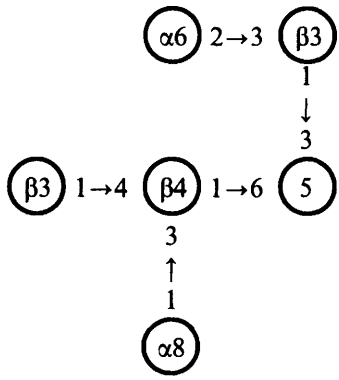
An β-(1→6)-linked mannobiose with β-lactose units joined at O-2 and O-6 of the non-reducing group has been reported.[147]

A specific dimer of Le^x has been made comprising two β-(1→3)-linked *N*-acetyllactosamine units with L-fucose bonded to O-3 of each of the *N*-acetylglucosamines.[148] (See heptasaccharides for a related Le^a dimeric moiety). T. Ogawa and colleagues have reported compound **25**, which is the core hexasaccharide of *N*-linked glycoproteins which are linked to asparagine. The β-mannosyl linkage was made by their intramolecular acceptor-delivery method.[149]



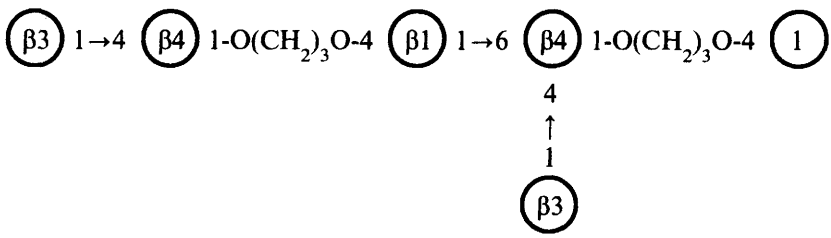
25

The synthesis of the doubly branched **26** has also been reported.[150]



26

5.3 Hexasaccharides with Anamolous Linking. – Chemoenzymic methods were adopted to prepare **27** which is a hexasaccharide mimic of fragments of the *Streptococcus pneumoniae* type 14 polysaccharide.[151]



27

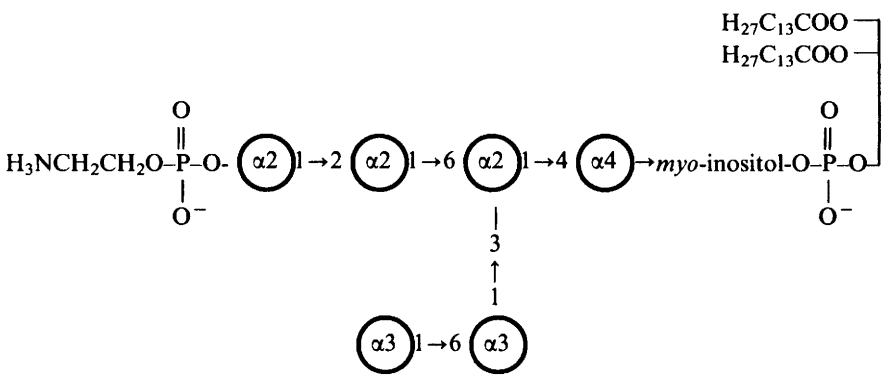
6 Heptasaccharides

The branched glucoheptaose phytoalexin elicitor has been prepared by solid phase procedures,[152] and a simplified mimetic has been described with all the important glycosyl units linked covalently by an appropriate spacer.[153] The highly branched wedge-like glucoheptaose having 3,6-di-*O*-β-D-glucopyranosyl-β-D-glucose bonded at C-3 and C-6 of D-glucose has been combined in dendrimer fashion to C-1, -3 and -5 of benzene tricarboxylic acid *via* spacer groups.[154]

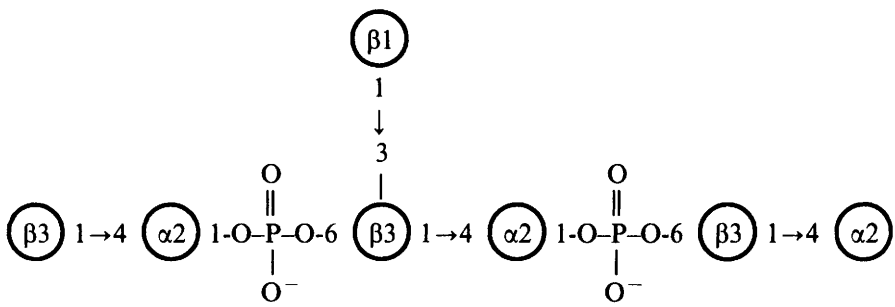
Mainly by judicious choice of their cyclic acetal protecting groups and of glycosylating agents Ley and colleagues very impressively have synthesized the branched mannoheptaose **28** in a one-pot procedure.[155] Related work has led to the total synthesis of the heptaose mimetic **29** carrying choline phosphate on the terminal mannose unit and a phosphoglyceride on the inositol, this being the anchor compound of *T.- brucei*.[156] The further 'anomalous heptaose' **30,** which is a constituent of *Leishmania mexicana* lipophosphoglycan, has also been synthesized.[77]



28



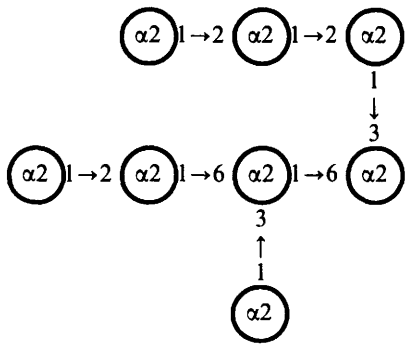
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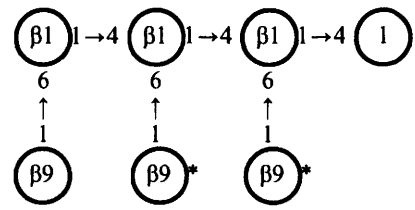
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7 Octasaccharides

A chemico-enzymic approach, using just a few synthetic steps, was employed in the preparation of the branched mannooctaose **31**.[157] The xyloglucan fragment **32**, having a β-D-Gal moiety (1→2)-linked at one of the indicated xylose units, has been characterized by MALDI-TOF mass spectrometry, illustrating the power of this method for structural analysis of branched oligosaccharides.[158]



31

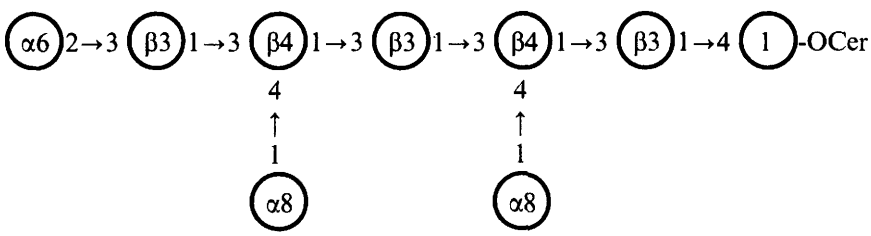


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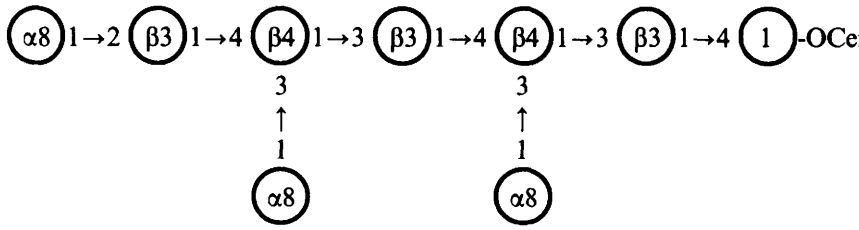
8 Nonasaccharides

The trimeric -[O-4-β-D-ManNAc-(1→4)-α-D-Glc-(1→2)-α-L-Rha-O-P(O)-OH-]$_3$, a fragment of the capsular polysaccharide of *Streptococcus pneumoniae*, has been synthesized.[159]

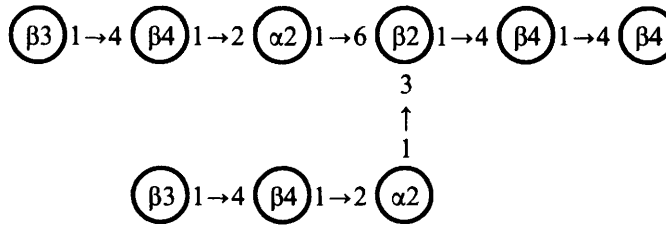
Most compounds of this size to have been described have branched structures. Polymer-supported methods have led to a nonasaccharide with the phytoalexin elicitor structure, *i.e.* it is the β-(1→6)-linked glucose hexamer having β-(1→3) glucose substituents on alternate residues.[160] In the sialylated oligomeric series the trimer of NeuNAc-(2→3)-LacNAc trisaccharide has been made as have the related sialylated antigenic **33**[161,161a] and **34**[162] and the *N*-glycopeptide core compound **35**.[163]



33



34



35

9 Higher Saccharides

The decasaccharide corresponding to compound **35** with GlcNAc β-(1→4) linked to the branching mannose residue has also been made,[163] as has a glycopeptide analogue having a mannononaose (1→4)-linked to β-glucosyl-amine amide bonded to a peptide.[164]

At the 16-mer level a heparin-like polymethylated, polysulfated compound which contains the antithrombin binding pentamer, a polyglucose spacer and a sulfated tetrasaccharide for thrombin binding has been constructed,[165] as have a series of oligomers, containing 10, 12, 14, 16, 18 and 20 sugar units, which are based on the heparin structure and show anticoagulant properties up to half of that of the natural polymer.[166] A compound corresponding to four repeating units of the *Shigella dysenteriae* O-specific polysaccharide antigen α-L-Rha-(1→2)-α-D-Gal-(1→3)-α-D-GlcNAc-(1→3)-α-L-Rha-(1→3) has been made by chemical methods.[167,168]

The discovery of heptadecasaccharide glycosidic antibiotics, which contain a range of modified sugars and show activity against multi-drug resistant Gram +ve bacteria, is noted in Chapter 19.

The oxazoline analogue of 2-acetamido-2-deoxy-6-*O*-tosyl glucose was used in self condensation reactions to make 'hyperbranched' aminopolysaccharides with average degree of polymerization 17.6.[169] In a similar approach glycals derived from cellobiose with free hydroxyl groups at O-6′ or O-4′ have been polymerized by use of IDCP to give products containing up to 24 sugar moieties.[170] Glucose itself has been polymerized under ultrasonic irradiation in suspension in dodecanol in the presence of acid, and compounds containing up to 23-monosaccharide units were produced. Structural studies were carried out.[171]

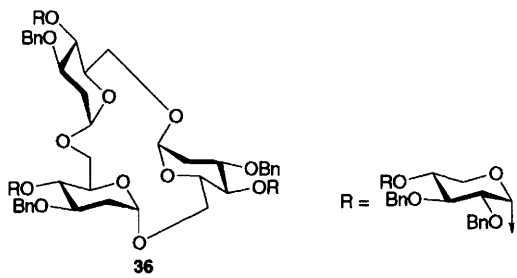
The specific 22-sugar compound consisting of three β-(1→3′)-linked LacNAc units having Sia Le^x tetrasaccharide moieties bonded to O-6 of each of the three galactoses and to O-3′ of the terminal galactose is a highly potent L-selectin antagonist.[172]

10 Cyclodextrins

10.1 General Matters and Synthesis of Cyclodextrins. – Interest in the cyclodextrins continues to expand in several directions, but only matters relating to their synthesis and their derivatives are dealt with here. New work relating to their associating properties or to their complexes or their activity as catalysts is not covered.

Indicating their current high profile in chemistry, *Chemical Reviews* has devoted an entire issue to the cyclodextrins,[173] particularly relevant papers being on the chemical, enzymic and chemo-enzymic methods used in their synthesis[174] and on methods employed for their selective substitution.[175]

Cycloinulohexaose, involving six 1,2-linked D-fructofuranose units has been reported together with some mono 6-*O*-alkyl and small acyl derivatives.[176] The very unusual cyclic trimer **36** was produced in 89% yield when 1,6-anhydro-



36

1,2′,3′,4′,6′-penta-*O*-benzoyl-2-deoxymaltose, made from 1,6:2,3-dianhydro-D-mannose by glucosylation followed by reductive epoxide ring opening and benzylation, was treated with PF_5 in CH_2Cl_2 at −40 °C. The reaction appears to depend on the presence of the glucosyl moiety and may occur by way of a polysaccharide intermediate.[177] Large ring cyclodextrins formed enzymically from starch together with the α-, β- and γ-compounds have previously been shown to contain up to 17 anhydroglucose units. Now larger analogues with 18–21 units have been reported.[178]

α-Cyclodextrin labelled with ^{14}C has been made enzymically from labelled maltose. Intermediate maltodextrins were cyclized using a bacterial cyclodextrin-glucosyl transferase.[179] α-, β- and γ-Cyclodextrins have been oxidized with TEMPO/NaOCl/NaBr to convert the primary centres into carboxylate groups, controlled reaction giving mono- or hexa-oxidation or intermediate products.[180]

The thermal properties and stability of the glassy form of per(tri-*O*-methyl)-β-cyclodextrin have been examined in detail and show it to be highly stable.[181] Conformation analysis has been conducted on per-(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin using annealed molecular dynamics calculations.[182]

10.2 Branched Cyclodextrins. – Three positional isomers of 6^A,6^x-di-*O*-α-D-glucopyranosyl β-cyclodextrin, made by enzymic methods, have been examined.[183] In related work several positional isomers of 6^A,6^X-di-*O*-[α-D-Man]-γ-CD and mono-*O*-[α-D-Man*p*-(1→6)-α-D-Man*p*]-γ-CD have been described,[184] and the same workers have reported di- and tri- mannosyl-β-CD.[185]

10.3 Cyclodextrin Ethers and Anhydrides. – Procedures have been described for making per-(2,6-di-*O*-alkyl-, 2-*O*-alkyl- and 6-*O*-alkyl)-β-CD (usually methyl and benzyl derivatives).[186] Mono-6-*O*-Tbdms-β-CD was used to make peralkyl derivatives having one 6-*O*-pent-4-enyl ether substituent,[187] mono-2-*O*-ocetenyl-β-CD has been characterized,[188] and β-CD with four isopropyl ether groups at primary centres has been used to encapsulate anti-inflammatory non-steroidal drugs.[189] Condensation of β-CD with propylene oxide in aqueous NaOH has afforded 6-hydroxypropyl-β-CD,[190] and a related family of compounds was made by polymeric coupling of ethylene oxide with the primary hydroxyl groups of β-CD.[191]

Fluorescent probes for organic analytes are based on β-CD carrying a calix[4]arene linked through an aromatic spacer to O-3,[192] and a novel photoswitchable host is based on azobenzene carrying two β-CD rings ether linked through the 4- and 4′-positions.[193]

Per-(2,6-*O*-Tms)-α- and β-CD are reported to be formed in high yield by use of *N*-(trimethylsilyl)acetamide in DMF,[194] and per-(6-*O*-Tbdms)-β-CD with NaH/DMF and tosylimidazole gives the per-(2,3-anhydro)-derivative, and the same product is obtainable *via* the heptakis-2-mesylates.[195]

10.4 Cyclodextrin Esters. – Benzoylation of β-CD with 1-benzoyloxy-1*H*-benzotriazole gave the heptakis 2-*O*-benzoate,[195] while the preparations of the mono-6-benzoate, -methyl phthalate and -2-naphthoate have also been described.[196] Other workers have reported a simple route to the hexakis 6-benzoate of α-CD from the 2,3-dibenzyl analogue,[197] 6-monoethyl phosphates and 6-monodiphenyl phosphates of α-, β- and γ-CD,[198] and 6-tosyl and 6-pivaloyl esters of β-CD, which were converted into the corresponding 3,6-anhydro derivative.[199] A study of the chloroacetylation of α-, β- and γ-cyclodextrins has been reported.[200]

Further work on arylsulfonates reported several mono-2-esters of γ-CD[201] and an improved preparation (61%) of the 6-monotosylate of β-CD.[202]

10.5 Amino Derivatives. – Heptakis[6-deoxy-6-(2-hydroxyethylamino)]-β-CD has been made as a binder for nucleotides,[203] and mono-6-deoxy-6-(2-hydroxyethylamino)-β-CD has been condensed with 1,3,5-tri(bromomethyl)benzene

to lead to a benzene derivative having three benzyl substituents carrying 2-*N*-hydroxyethyl-2-CD-amino groups.[204] Other 6-amino-6-deoxy-α- and β-CD compounds to have been described have 2-(benzoylamino)ethyl-*N*-substituents, and this paper also reported mono 6-benzoates, methyl phthalates and 2-naphthoates.[196] Otherwise, β-CD bearing 6-bis(diphenylphosphinylmethyl)-amino-6-deoxy groups has been made as a ligand for supramolecular rhodium catalysts,[205] and β-CD with ω-(*t*-butoxycarbonylamino)-alkylamino substituents have been made for study of 'cup and ball' molecules.[206] In related work zinc complexes have been made of β-CD carrying imidazole and 6-(bis-2-aminoethyl)-2-aminoethylamino-6-deoxy groups which showed bifunctional catalysis in phosphate hydrolysis.[207]

Two research groups have made compounds having 1,4,7,10-tetraazacyclododecanes with attached cyclodextrins. In both cases the attachments were by way of linkages from the macrocyclic ring nitrogen atoms to 6-amino-6-deoxy-β-CD.[208,209]

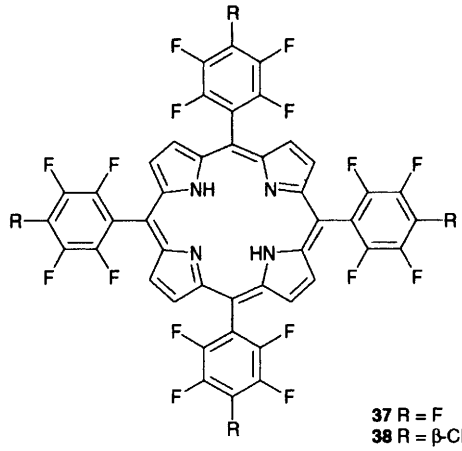
Reaction of per-(6-azido-6-deoxy-2,3-di-*O*-methyl)-α- and β-CD with dimethyl acetylenedicarboxylate afforded the analogous per-[6-deoxy-6-(4,5-dicarboxy-1,2,3-triazol-1-yl)] compounds by 1,3-dipolar cycloaddition reactions.[210]

Several reports have appeared on 6-acylamino-6-deoxy derivatives or analogues thereof, a β-CD derivative having a 6-deoxy-6-guanidinium substituent belonging to the latter class.[211] An α-CD compound made of alternating tri-*O*-methyl-D-glucose and 6-amino-6-deoxyglucose having a $COCH_2CH_2CO$-$N(OH)CH_3$ acyl group on the amino function has been reported,[212] and a set of cyclodextrin derivatives produced as mimics of class I aldolases include compounds with (2-aminoethyl)amino groups at C-3 or C-6 and one with (2-aminoethyl)amino and imidazole functions in the same molecule. In the course of the work 6-amino compounds carrying amide-linked proline and histidine were produced.[213] Other 6-amido compounds to have been made are β-CD with benzyloxycarbonylamino,[199] *t*-butoxycarbonylamino[199] and amide *N*-linked phenolphthalein[214] functions.

Dimeric β-CD compounds have been described with 3-amino groups linked by α,ω-dicarboxylic acids, the amino functions having been introduced by use of 2,3-anhydromannose intermediates,[215] and reaction of heptakis(6-amino-6-deoxy)-β-CD with β-D-glucosyl isothiocyanate gave a product with glucose attached by thiourea bridges to the cyclodextrin.[216]

10.6 Thio Derivatives. – Mono-6-*O*-tosyl-β-CD treated with 6,6′-dithio-α,α-trehalose has given a dimer consisting of two 6-thio-cyclodextrin molecules linked by a trehalose bridge.[217] In related work 6,6′-di-(2-aminoethyl)thiotrehalose was treated with $6^A,6^D$-dideoxy-6^A6^D-diiodo-β-CD to give a trehalose-capped CD as product.[218]

Reaction of the tetrakis(pentafluoro)phenylporphyrin **37** with 6-thio-β-CD gave the cyclodextrin-porphyrin **38** which bound Mn(II) to give a complex that catalytically hydroxylated an androstanediol derivative with complete regioselectivity and with 187 turnovers.[219]



37 R = F
38 R = β-CD-6-S-

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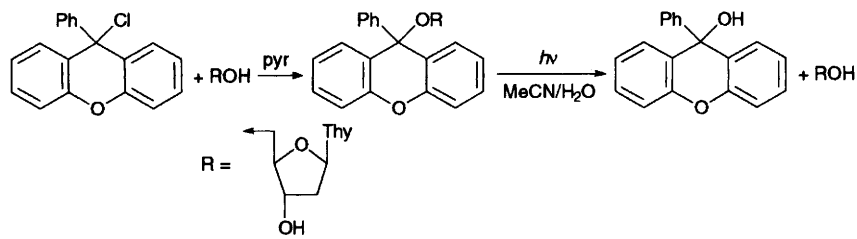
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5
Ethers and Anhydro-sugars

1 Ethers

1.1 Methyl Ethers. – The plant *Nepeta grandiflora* has yielded 1,5,9-epideoxyloganic acid analogues each containing a 2-, 4- or 6-*O*-methyl-β-D-glucopyranosyl moiety,[1] and the sugar components of new insecticidal alkaloids from amarylidaceae contained 4-*O*-methyl- and 2,3,4-tri-*O*-methyl-D-glucose constituents.[2] A Sia Le^x analogue containing a 6-*O*-methyl-D-galactose residue has been reported.[3]

1.2 Other Alkyl and Aryl Ethers. – Sugar alcohols, including secondary alcohols, can be bound efficiently to resins by reaction with resin-bound benzyl trichloroacetimidates to give the corresponding resin-bound benzyl ethers.[4] The 9-phenylxanthen-9-yl ether group has been proposed as a photolabile protecting group for primary alcohols (Scheme 1).[5] Selective alkylation of the



Scheme 1

bis-dibutylstannylene derivative of xylitol has afforded 1,5-di-*O*-benzyl-(and -*n*-butyl-)xylitol.[6] 4-Methoxybenzyl 2,3,4-tri-*O*-(4-methoxybenzyl)-α-D-glucopyranoside has been described as an oligosaccharide building block.[7]

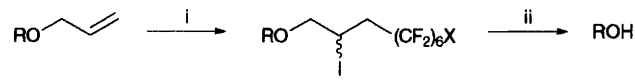
The selective removal of trityl and dimethoxytrityl ethers using 1% I_2 in MeOH has been reported, with glycosidic bonds and esters being stable to these conditions.[8]

2-Naphthylmethyl ethers undergo hydrogenolysis selectively in the presence of *O*-benzyl ethers.[9]

A new two-stage cleavage of allyl ethers employs iodinated intermediates with subsequent treatment with zinc dust (Scheme 2).[10]

Stannic chloride has been used for the selective deprotection of 4-methoxy-

Carbohydrate Chemistry, Volume 32
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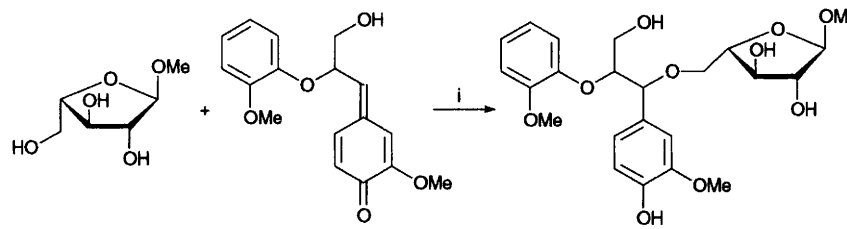
Reagents: i, $I(CF_2)_6X$, $Na_2S_2O_4$, $NaHCO_3$, aq. MeCN, (X = Cl, F); ii, Zn, NH_4Cl, EtOH, reflux

Scheme 2

benzyl ethers in the presence of acetals, esters and benzyl ethers,[11] whereas other workers have utilized clay-supported ammonium nitrate under dry conditions with microwave activation to effect the same deprotection.[12] A comparison of the stability of 4- and 3-methoxybenzyl ethers has concluded that the former are much more acid labile and are cleaved more readily by DDQ.[13]

Scaffolding for carbohydrate-centred dendrimers has been prepared from allyl 2,3,4,6-tetra-*O*-allyl-α-D-glucopyranoside by ozonolysis followed by reductive amination (or reduction) to give the per-*O*-[2-amino-(or 2-hydroxy-) ethyl] ether derivatives.[14,15] Similar methodology has been used in the synthesis of 4-*O*- and 6-*O*-(2-iodoethyl)-D-glucose from the corresponding allyl ethers.[16]

Lignin-bound carbohydrates have been prepared by the acid-catalysed reaction of sugar alcohols with quinone methides (Scheme 3).[17]

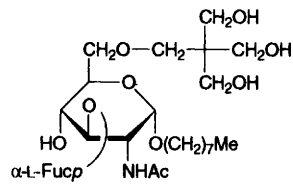


Reagents: i, TsOH

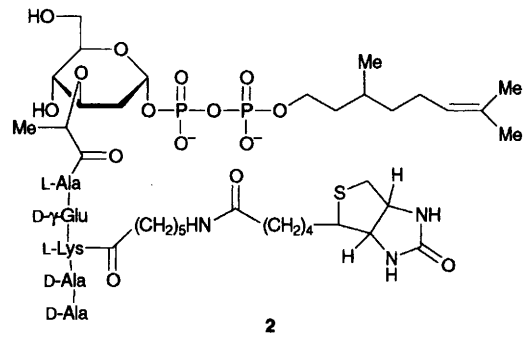
Scheme 3

Carbohydrate aryl ethers have been prepared by the Mitsunobu reaction of sugar primary alcohols with phenols.[18] The triflate ester of 5-azidopentan-1-ol has been allowed to react with carbohydrate primary alcohols to give *O*-(5′-azidopentyl) ethers.[19] Poly(ethyleneglycol) derivatives with a reducing sugar at one end have been prepared by the reaction of potassium alkoxides of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose or 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with excess ethylene oxide.[20]

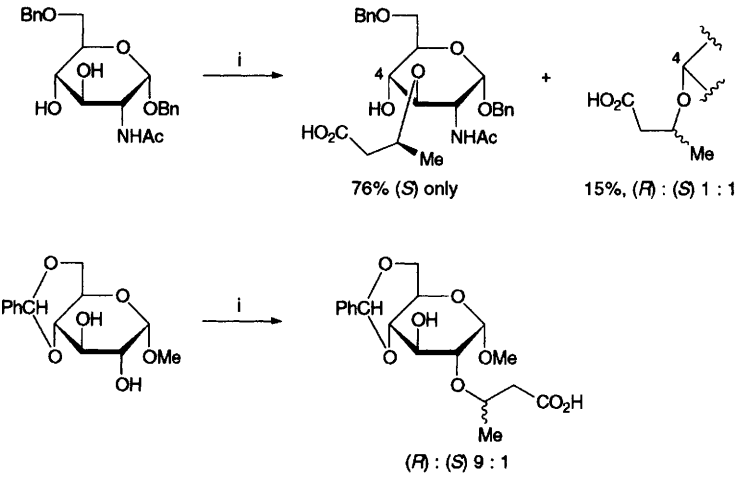
Some polyhydroxylated alkyl ether carbohydrate derivatives (*e.g.* **1**) have been described.[21] The epimeric 4-*O*-[1-(*S*)- and (*R*)-carboxyethyl]-D-mannose have been synthesized and used as standards in determining that there is no 4-*O*-(1-carboxyethyl)-D-mannose in the capsular polysaccharide of *Rhodococcus equi* serotype 3.[22] The synthesis of biotinylated glycopeptide **2** has been described. It is an acceptor substrate analogue of a bacterial glycosyl transferase involved in peptidoglycan biosynthesis.[23] The conjugate addition of sugar alcohols to ethyl crotonate affords products with, in some cases, excellent stereoselectivity. Some examples are shown in Scheme 4.[24]



1

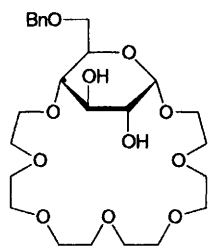


2



Scheme 4

The glucose-derived crown ether **3** has been prepared[25] and some aza-crown ethers derived from D-glucose have been synthesized and their application as catalysts in asymmetric synthesis has been tested.[26]



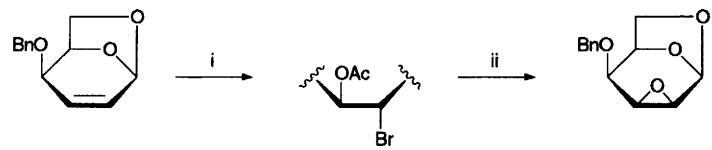
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1.3 Silyl Ethers. – Use of the 1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl (Tipds) protecting group for 1,2- and 1,3-diols has been reviewed. Methods for

introduction and removal of the group are described as well as its application in the synthetic modifications of nucleosides and mono- and oligosaccharides.[27] Both primary and secondary silyl ethers are compatible with glycosylation conditions using glycosyl fluorides with Cp_2ZrCl_2/AgOTf as promoters.[28]

2 Intramolecular Ethers (Anhydro-sugars)

2.1 Oxirans. – The stereoselective epoxidation of *O*-acetylated glycals has been achieved using a new ruthenium(II) catalyst,[29] and other 1,2-anhydrosugars have been prepared as glycosyl donors using standard methods.[30] An improvement in the conversion of methyl 4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside into the corresponding 2,3-*manno*-epoxide by the use of ultrasound has been claimed.[31] Alkene **4** has been stereoselectively epoxidized to **5** in a two-step process (Scheme 5).[32]

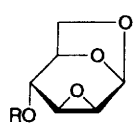


4 **5**

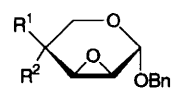
Reagents: i, AcOBr, CCl_4; ii, K_2CO_3, MeOH

Scheme 5

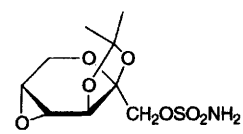
The opening of epoxide **6** with *O*- *N*- and *S*-nucleophiles to give 2-replaced 1,6-anhydro-β-D-glucopyranose derivatives has been studied,[33] and the utility of epoxysulfonates such as **7** and **8** in the synthesis of aminodeoxy, halodeoxy, branched-chain, aziridino and thiazoline sugar derivatives has been reviewed.[34] The epoxysulfamate **9** has been prepared as an analogue of topiramate.[35] Base treatment (NaOMe, MeOH) of **10** has afforded a mixture of **11** and **12** by way of benzoyl and silyl migrations prior to epoxide formation.[36]



6 R = alkyl or aryl

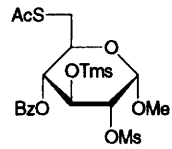


7 R^1 = H, R^2 = OTf
8 R^1 = OTf, R^2 = H

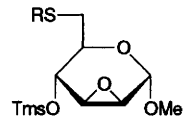


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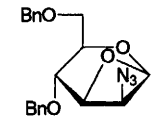
2.2 Other Anhydrides. – A new method for the preparation of 1,6-anhydrohexopyranoses has been developed which involves the treatment of 1,6-*O*-unprotected hexopyranoses with *N*,*N*'-sulfuryldiimidazole and sodium hydride.[37] Another approach has been to treat acetylated glycosyl halides with pyridine and then the intermediate glycosyl pyridinium salts formed with



10



11 R = Bz
12 R = H



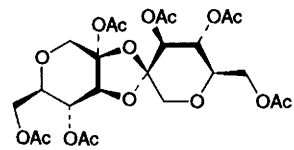
13

NaOMe/MeOH to afford the 1,6-anhydrohexopyranoses.[38] Iodocyclization of D-xylal followed by radical reduction has given 1,5-anhydro-2-deoxy-β-D-*threo*-pentofuranose.[39]

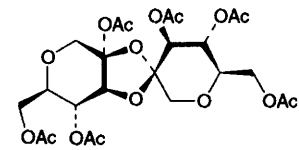
The synthesis of 1,3-anhydro-sugar derivative **13** and its use as a glycosyl donor have been described,[40] while the enzymic oxidation of 1,5-anhydro-D-glucitol has afforded 1,5-anhydro-D-fructose by specific oxidation of the hydroxyl group at C-2.[41]

2-*O*-Acyl-1,5-anhydro-3-*O*-benzyl-β-D-xylofuranose compounds have been prepared and used for the synthesis of β-(1→5)-xylofuranans by ring-opening polymerization.[42,43] Similarly, some new 1,6-anhydro-3,4-di-*O*-benzyl-D-glucosamine derivatives have been prepared with different protecting groups on the amino function to investigate their effects on the acid-catalysed ring-opening polymerisation of these compounds.[44]

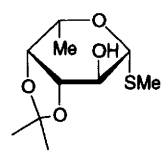
Acid catalysed acetylation of 1,5-anhydro-D-fructose has generated the two epimeric structures **14** and **15**,[45] while self condensation of fucose thioglycoside **16** has afforded the symmetric difucopyranose dianhydride **17**.[46]



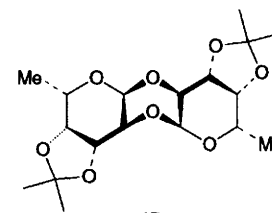
14



15



16



17

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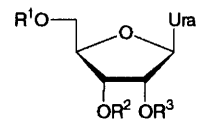
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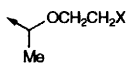
6
Acetals

1 Acyclic Acetals

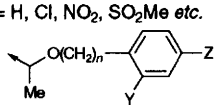
In search of an ideal protecting group for OH-2′ of nucleosides, to be used in the machine-assisted assembly of oligonucleotide chains by the phosphoramidite approach, a series of 35 new uridine 2′-acetals, such as compounds **2** and **3**, have been synthesized by reaction of the 3′,5′-*O*-Tipds-protected nucleoside **1** with the appropriate vinyl ethers under acidic conditions, followed by desilylation. The half-life ($T_{1/2}$) of these derivatives in 80% aq. HOAc varied between 70 and > 4000 s^{-1}.[1] Formation of acyclic acetals was also observed in the acetonation of methyl 5-*C*-methoxy-β-D-galactopyranoside with 2,2-dimethoxypropane/TsOH (see ref. 3 below).



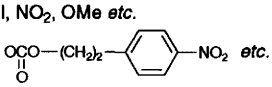
1 R^1, R^2 = Tips, R^3 = H

2 $R^1 = R^2 = H$, R^3 = 

X = H, Cl, NO_2, SO_2Me *etc.*

3 $R^1 = R^2 = H$, R^3 = 

n = 0–2, Y = H, Cl, NO_2, OMe *etc.*

Z = H, OH, OMe, 

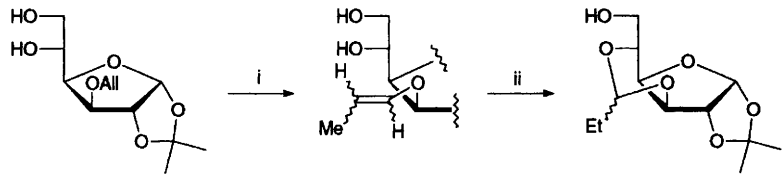
etc.

2 Ethylidene, Isopropylidene and Benzylidene Acetals

A novel method for preparing ethylidene acetals intramolecularly from diol monoallyl ethers is illustrated in Scheme 1.[2]

The acetonation of methyl 5-*C*-methoxy-β-D-galactopyranoside **4** with a large excess of 2,2-dimethoxypropane/TsOH, which gives **6** as the main product in 44% yield, has been examined in detail and compared with the

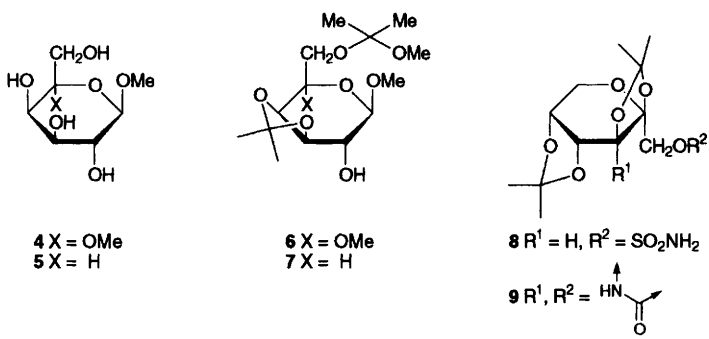
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Reagents: i, KOH, DMSO; ii, HCl, CH_2Cl_2

Scheme 1

analogous reaction of the parent compound **5**, which furnished **7** in 70% yield (see Vol. 20, p. 62, ref. 6).[3] A comprehensive structure-activity relationship study on the anticonvulsant topiramate [2,3:4,5-di-*O*-isopropylidene-D-fructopyranose 1-sulfamate (**8**), see Vol. 27, pp. 102–103, ref. 100; Vol. 31, p. 98, ref. 8] has been published; *inter alia*, the replacement of the 4,5-*O*-isopropylidene group by methylidene or hexafluoroisopropylidene is described.[4] The homochiral 1,3-oxazine derivative **9** of 2,3:4,5-di-*O*-isopropylidene-D-fructopyranose, synthesized in four easy steps from D-fructose, has been used as a chiral auxiliary in reactions such as aldol condensations, Diels–Alder cycloadditions and α-brominations.[5]



4 X = OMe
5 X = H

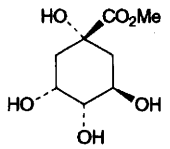
6 X = OMe
7 X = H

8 R^1 = H, R^2 = SO_2NH_2

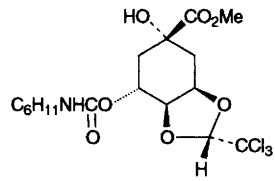
9 R^1, R^2 = HN

3 Other Acetals

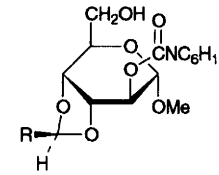
The procedure developed by Miethchen for the concomitant acetalization and carbamoylation of *cis,trans*-configured 1,2,3-triols with inversion at the central position by treatment with chloral/DCC (see Vol. 28, p. 97, Scheme 3) has been applied to the epimerization of methyl quinate (**10**→**11**) and methyl shikimate.[8] It has also been shown that the reaction proceeds just as readily if



10



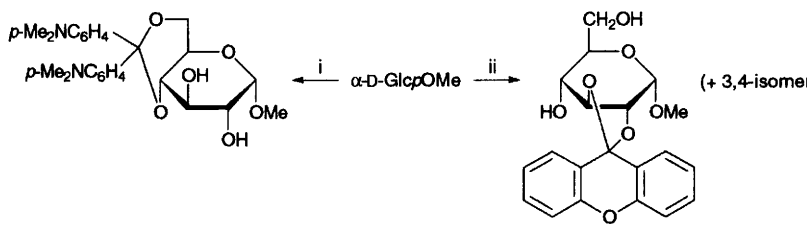
11



12 R = C_4F_9, C_8F_{13} *etc.*

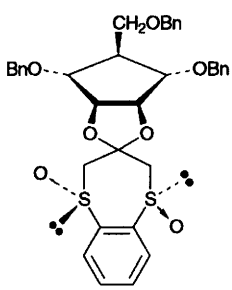
chloral is replaced by higher perfluorinated aldehydes (*e.g.*, α-D-Man*p*OMe→**12**).[9]

In a new method for acetal formation under non-acidic conditions, carbohydrate diols were exposed to thioketones in the presence of silver triflate and triethylamine; 4,4′-bis(dimethylamino)thiobenzophenone and xanthene-9-thione tended to give predominantly dioxane and dioxolane products, respectively. Examples are shown in Scheme 2.[10] A novel, C_2-symmetric bis-sulfoxide has been used in the desymmetrization of a *meso*-cyclopentitol *via* its acetal derivative **13**.[11]

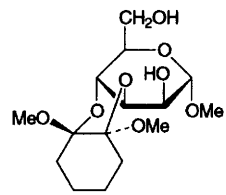


Reagents: i, $(p\text{-Me}_2NC_6H_4)_2C{=}S$, AgOTf, Et_3N; ii, xanthene-9-thione, AgOTf, Et_3N

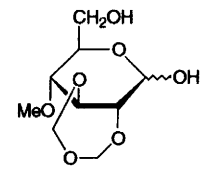
Scheme 2



13



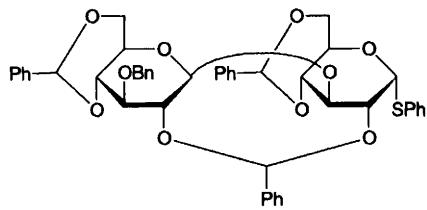
14



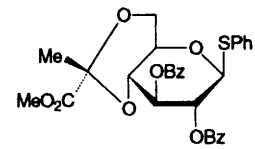
15

A detailed procedure for the preparation of the methyl α-D-mannoside-derived dispiroketal **14** (see Vol. 28, p. 98, Scheme 5) has been published.[12] The glucose derivative **15** was one of two sugar components found in a new group of insecticidal alkaloids from amaryllidicaeae.[13]

Monoacetalizations of sucrose at O-4/O-6 with α- or β-ionone or citral were achieved in satisfactory yields by acetal-transfers from the dimethyl acetals of the corresponding aldehydes under acid catalysis in DMF.[14] In Part IV of a



16

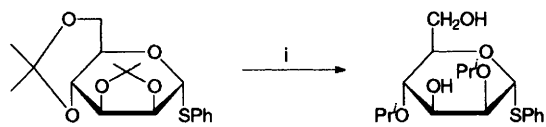


17

series on inter-unit acetals, the preparation of disaccharide derivative **16** has been described (Part III, see Vol. 30, pp. 79/80, ref. 201).[15] The known 4,6-*O*-[(1-ethoxycarbonyl)ethylidene]-derivative **17** (see Vol. 28, p. 96, ref. 10) has been used as glycosyl donor in the synthesis of a naturally occurring pyruvated trisaccharide, found in a marine sponge.[16]

4 Reactions of Acetals

Sugar isopropylidene acetals have been efficiently deprotected by use of ozone in aq. MeOH[17] or $CuCl_2.2H_2O$ in MeCN,[18] and ceric ammonium nitrate in aq. MeCN caused rapid hydrolysis of sugar benzylidene acetals.[19] Mild reductive opening of sugar isopropylidene- and benzylidene-acetals has been effected with dibutylboron triflate in conjunction with BF_3.THF, as exemplified in Scheme 3.[20]



Reagents: i, Bu_2BOTf, BH_3•THF

Scheme 3

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7
Esters

1 Carboxylic Esters and Related Compounds

1.1 Synthesis. – The range of methods available for making carboxylic acid esters, particularly by selective processes, is well illustrated this year – especially by the tin-mediated method and by the use of enzymes.

1.1.1 Enzymic Methods. A commercially available cellulase has been used to give 1-*O*-benzoyl-β-D-glucopyranose,[1] and 2- and 3-substituted esters have been obtained from various glycosides of 4,6-*O*-benzylidene-α- and β-glucose by use of a lipase,[2] but much more common are substitutions at O-6 of glucose,[3–7] and its pyranosides[8,9] and its naturally occurring aryl *C*-glycoside bergenin.[10] In this last work 4- as well as 6- esters and 4,6-diesters were made by use of selective acylating and deacylating lipases in work that led to a combinatorial library of selectively substituted products.

Used hydrolytically, lipases have released hydroxyl groups selectively at C-4 and C-6 of α[11]- and β[12]-D-hexose and -hexoside peracetates.

In the D-galactose series the sugar itself has been converted to the 6-*O*-perfluorooctanoate by use of a lipase,[13] and highly selective acylation of ethyl 4,6-*O*-benzylidene -1-thio-β-D-galactopyranoside occurred at O-3.[2]

An enzyme was used to transfer acyl groups (C >10) from vinyl esters to O-1 of fructose in pyridine,[14] while another afforded access to 1,6-di-*O*-acylfructoses.[15] Fructose-containing di- and oligosaccharides accepted butanoyl groups at the primary positions when treated in DMF containing 2,2,2-trifluoroethyl butanoate with subtilisin as catalyst.[16]

Isobutyl 2,3,6-trideoxy-β-D,L-*erythro*-hexopyranoside was resolved following selective lipase-promoted acylation at O-4 of the L-enantiomer.[17] Similar acetylation was applied to the 1,6-anhydro-β-D- and L-hexopyranoses (of glucose, galactose, mannose and allose). In the case of the D-galactose anhydride preferential reaction occurred at the equatorial O-4 whereas its enantiomer reacted at the axial O-2.[18] In the cases of the anomeric methyl 2,3-di-*O*-acetyl-6-deoxy-α- and β-D-arabinofuranosides pig liver esterase cleaved the 2-ester selectively and quantitatively in the case of the former glycoside, but the latter reacted unselectively.[19]

1.1.2 Chemical Methods of General Significance. A microwave-assisted phase transfer *trans*benzoylation procedure uses methyl benzoate in DMF in the

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presence of a base; high yields were produced in short reaction times from several partially *O*-protected compounds.[20] Benzoates having ^{17}O enrichment in the sugar ester atoms have been prepared by use of $PhCO^{17}OH$ and Mitsunobu chemistry or triflate displacement. Inversion occurs at secondary centres and gentiobiose was made with the inter-unit atom labelled.[21]

A series of known monohydroxy sugar derivatives were converted into esters with the enantiomers of α-methoxy-α-trifluoromethyl phenylacetic acid (Mosher reagent), and study of the ^1H NMR chemical shifts in the vicinity of the esters revealed that this approach can be used to determine sugar absolute configurations.[22] Methacrylate derivatives of *e.g.* 1,2:5,6-di-*O*-isopropylidene-α-D-glucose undergo additions (*e.g.* Michael) with enantioselectivity (See Chapter 24).

1.1.3 Carboxylic Esters at the Anomeric Centres. Montmorillonite K-10 catalyses the peracetylation of mono- and oligo-saccharides to give pyranoid and furanoid products in approximately equilibrium proportions.[23] Peracetylated hexofuranoses, on the other hand, are available from the octyl furanosides by acetylation followed by acetolysis.[24] Glycosyl acetates are the products of BF_3-catalysed acetolysis of sugars glycosidically linked *via* tethers to resins so they can be manipulated during solid-phase synthesis.[25] Bile acids have been linked through the carboxylate groups to O-1 of benzyl 2,3,4-tri-*O*-benzyl-D-glucuronate by the Mitsunobu method,[26] while acetobromo-glucose and -galactose have been coupled with carboxylic acids in the presence of a phase-transfer catalyst in another approach to glycosyl esters.[27] Specifically, the glucose derivative was used in the preparation of 1-*O*-(2-naphthyloxy)acetyl-β-D-glucose and related esters in the course of studies of plant growth regulating compounds.[28] Ring opening of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucose with carboxylic acids followed by benzoylation has given the expected 1-*O*-acyl-β-D-glucoses; several compounds were made in this way, including the uronic acid ester **1**.[29]

1.1.4 Carboxylic Esters at Non-anomeric Centres. Several studies of selective acylations of glycosides and similar compounds incorporating dibutyltin oxide as an activating agent have been reported. They are summarized as follows: methyl 6-*O*-trityl-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (ester, pivaloate; site of selectivity, O-2);[30] 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (benzoate; O-6);[31] methyl 4,6-*O*-benzylidene-α-D-galactopyranoside and methyl α-L-rhamnopyranoside (benzoates);[32] benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (benzoates; O-6[33,34]; pivaloates; O-6[35]); methyl α-D-mannopyranoside (benzoates, O-3)[36–38] (the first using polymer-supported tin reagent); methyl α-D-mannopyranoside (long-chain fatty acid esters; O-6);[39] methyl 6-*O*-trityl-α-D-mannopyranoside O-3;[40] and benzyl α-L-lyxopyranoside (pivaloates, O-3).[35]

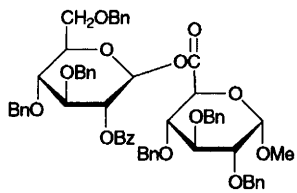
Related work on selective pivaloylation indicated methods for making high yields of methyl α-D-glucoside, methyl α-D-mannoside, phenyl 1-thio-β-D-galactopyranoside and -glucoside monoesters at O-2, O-3, O-3 and O-3,

respectively. These procedures used 4,6-*O*-benzylidene derivatives of the starting materials. Without this protecting group high yields of the following esters were obtainable: 2,6-, 3,6-, 3,6-diesters and the 6-ester, respectively.[41] Similar studies on glucose led directly to the 1,3,6-(β, 33%) and 1,2,6-tripivaloates (β, 48%).[42]

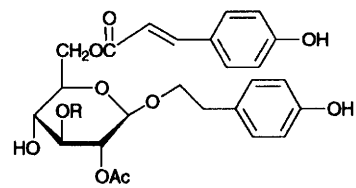
A large number of reactions were applied to tetra-*O*-lauroyl-1-thio-β-D-galactopyranose – notably following addition to Michael acceptors – to generate libraries of products.[43]

Several esters based on aromatic carboxylic acids have been studied: alkoxylated derivatives, *e.g.* 4-octyloxybenzoates of glucose as potential liquid crystals;[44] 2-*O*-acetyl-osmanthuside (**2**) was made in a seven-step synthesis,[45] and some 'glycophanes' based on disaccharides have been described, *e.g.* *p*-carboxybenzyl 4'-*O*-*p*-(hydroxymethyl)benzoyl-α-D-maltoside cyclized in symmetrical fashion with another maltose molecule to give a cyclic product, the properties of which were compared with those of α-cyclodextrin.[46]

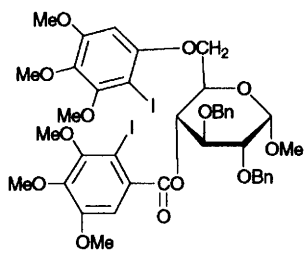
In work related to the ellagitannins the di-iodo compound **3** was cyclized to **4** by treatment with nickel chloride. Because of restriction of rotation within



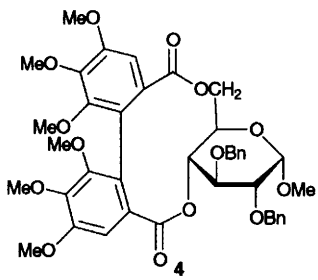
1



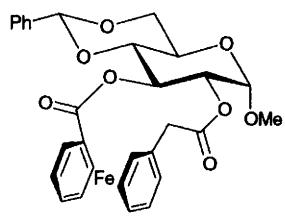
2 R = α-L-Rha



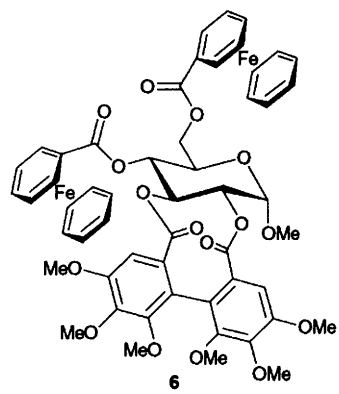
3



4



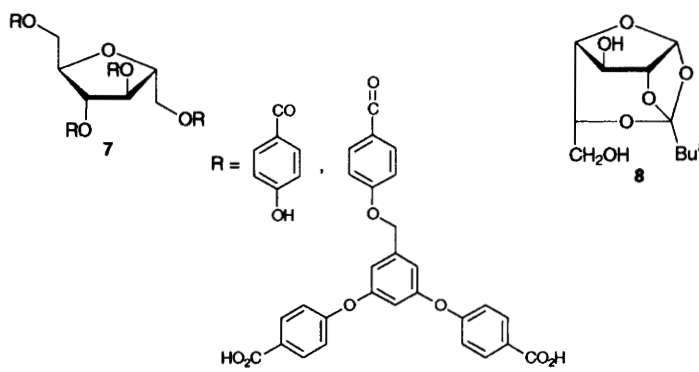
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6

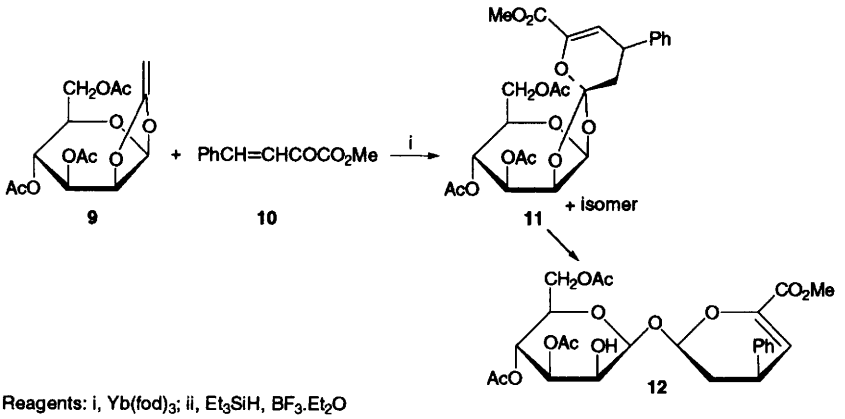
the new ring, diastereomeric products are possible. In the case of **4** and its analogue with 2,3-substituted large ring the *S*-diastereomer was formed. Likewise in the case of a galactoside with the ring fused at positions 3 and 4, but the *R*-product was made with the 2,3-system derived from a mannopyranoside.[47] Other workers have synthesized mahtabin A, which has a similar but 2,3-ring fused structure to **4**, by use of a racemic substituted diphenyl diacid and separation of the diastereomeric products.[48] Related Japanese research has led to compounds having ferrocenyl-based diacyl substituents in place of the large dilactone rings, *e.g.* compound **5**, which was made using ferrocene dicarboxylic acid. Ferrocene monocarboxylic acid gave compound **6**.[49]

1.1.5 Alditol Carboxylic Esters. (Refer also to Chapter Monoesters of glucitol and aromatic acids have been made by transesterification from methyl esters.[50] Xylitol has been esterified (benzoate and octanoate) at the primary positions in almost quantitative yield by way of the bis-dibutylstannylene derivative.[51] 1,4:3,6-Dianhydro-D-glucitol has been converted into long chain fatty acid esters,[52] and 2,5-anhydro-D-mannitol, a tetrafunctional compound with C_2 symmetry, has been converted into dendrimers by elaboration of ester **7**.[53]



1.1.6 Orthoesters, Carbonates, Carbamates. Treatment of 5-*O* chloroacetyl-2,3,6-tri-*O*-pivaloyl-D-galactofuranosyl chloride with thiourea in pyridine afforded access to the 1,2,5-orthoester **8**,[54] and condensation of aldonolactones with methyl 2,6-di-*O*-benzyl-D-galactopyranoside affords inter-unit orthoesters involving the carbonyl group of the lactones and the 3,4-diol of the galactoside.[55] As shown in Scheme 1, ketene acetal **9** and α-ketoester **10**, underwent facially selective inverse electron demand hetero-Diels–Alder reactions to give orthoester adduct **11** which could be reductively cleaved to β-mannoside **12** resembling a non-reducing branched-chain disaccharide.[56]

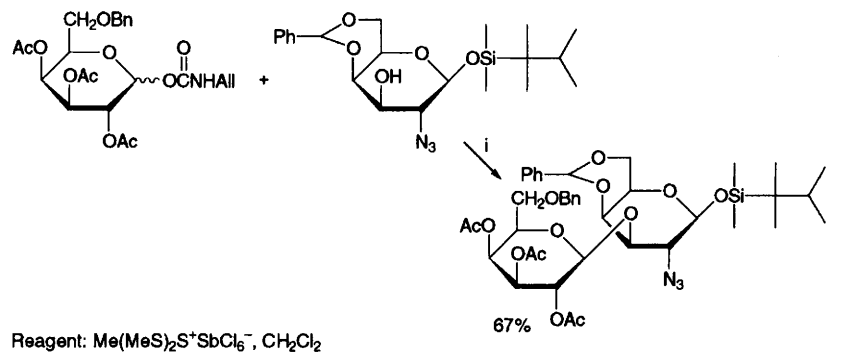
A 'one-pot' regioselective synthesis of mixed carbonates involving the use of alcohols and 1,1-carbonyldiimidazole produces, for example compound **13**, from methyl α-D-glucopyranoside.[57] The 4,6-cyclic carbonate and corresponding methyl orthoester of the β-D-glucopyranosyl unit of a benzofuran analogue of the natural glycoside phlorizin were employed in the synthesis of



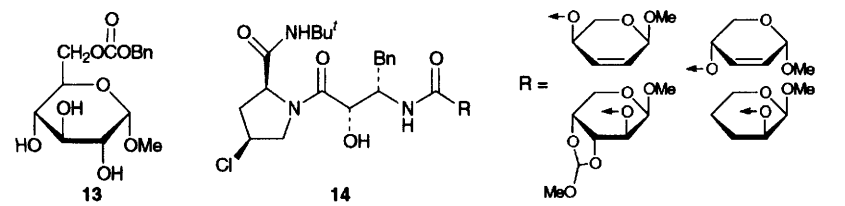
Scheme 1

various 4- and 6-esters.[58] Various polysubstituted sucrose carbamates have been made by use of different chloroformates.[59]

Glycosyl *N*-allyl carbamates, made using allyl isocyanate and compounds with free anomeric hydroxyl groups, have been used as glycosyl donors[60] (see Scheme 2). The urethanes **14** have been made as potential HIV protease inhibitors,[61] and several mono-, di- and tri-*N*-2-fluorophenyl carbamates of spirostanyl β-cellobioside have been made for use as possible cholesterol absorption inhibitors.[62]

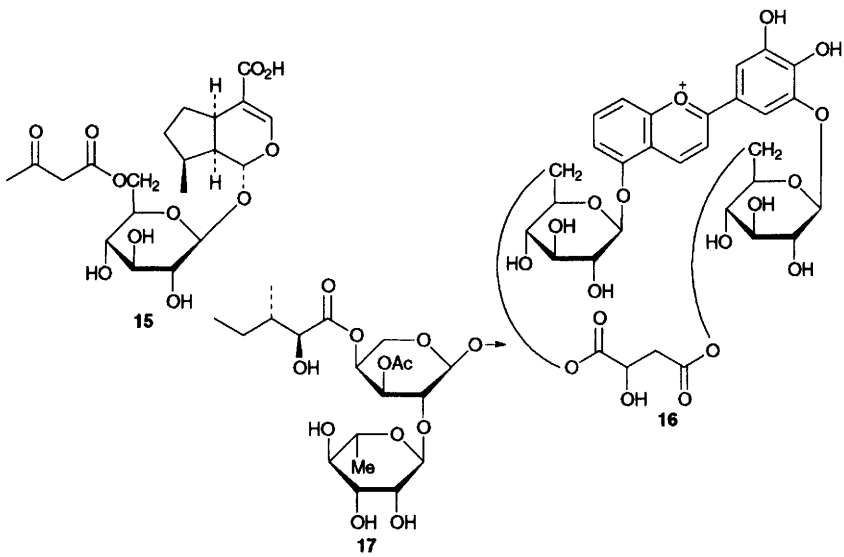


Scheme 2



1.2 Natural Products. – An unusual acetoacetyl group has been found in the iridoid glycoside **15** of the plant *Nepeta grandiflora*.[63] The major pigment in

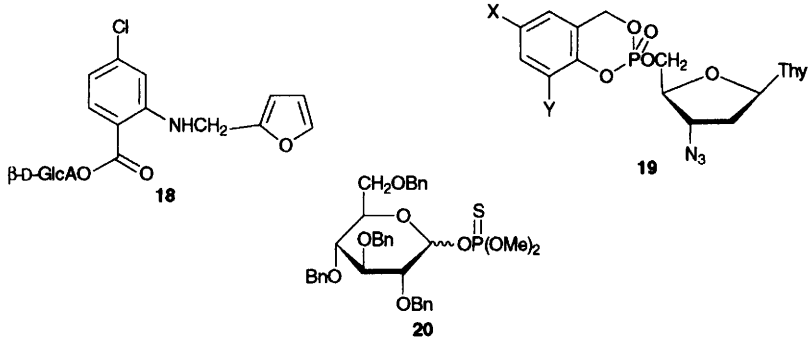
the flowers of a cultivar of the mauve carnation is the macrocyclic anthocyanin **16**, and is the first such macrocyclic malate lactone to have been reported.[64] The 2-*O*-L-rhamnopyranosyl-L-arabinose **17**, bearing a 2-hydroxy-3-methylpentanoyl ester group, is the carbohydrate unit of a steroidal saponin, and has potent anti-leukemic activity.[65] Actinotetraose hexatiglate [tiglic acid is (*E*) MeCH=CMeCO$_2$H] has two units of sophorose [β-D-Glc*p*-(1→2)-D-Glc] carrying the ester group at O-6, O-3′ and O-4′α-1→α-1 linked as in trehalose.[66] Compound **18** is the product of photodegradation of the major glucuronide metabolite of furosemide.[67]



2 Phosphates and Related Esters

Considerable reference is made to phosphate derivatives of nucleosides in Chapter 20. A further synthesis of UDP-Gal and its monodeoxygalactose analogues has utilized the unusual donor 2,3,4,6-tetra-*O*-trimethylsilyl-α-D-galactosyl iodide, and the products were used in conjunction with methoxycarbonyloctyl *N*-acetylglucosaminide to afford *N*-acetyllactosamine and deoxy analogues as their spacer group-linked β-glycosides.[68] Compounds **19** (X = H, NO_2, Cl, Me, OMe; Y = H, Me,Me) have been made as prodrugs for the delivery of AZT monophosphate.[69]

3-Methoxypyridin-2-yl β-D-glucopyranoside with phosphoric acid in DMF gives α-D-glucose 1-phosphate (66%), and this method, which uses donors with *O*-unprotected sugar rings, has also been used to make the 1-phosphates of α-D-Gal, α-L-Fuc and also UDPG and UDPGal (enzymic coupling in the last case). With the 2-azido-2-deoxy-β-glucoside, dibenzyl phosphate led to a preferred synthesis of the α-glycosaminyl phosphate.[70] The same compound

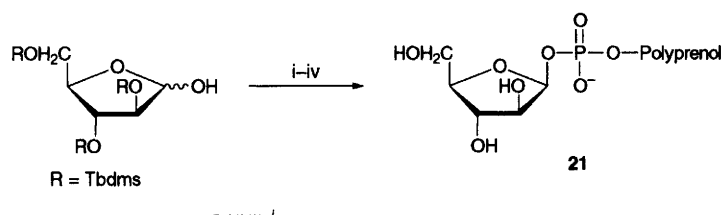


can be made by use of the same nucleophile and the α-oxazoline derived from GlcNAc, and β-glucosaminyl phosphate is obtainable in like fashion by use of the analogues trifluoromethyl analogue of the oxazoline.[71] β-D-Glucopyranosyl trisphosphate is obtainable (yields up to 47%) by reaction of the free sugar with sodium cyclo-trisphosphate.[72]

Tetrabenzyl-D-glucosyl diethylphosphite has again been used as a glycoyl donor, and disaccharides have been made in 30–95% yield, the α,β-ratios being > 1 when ether or dichloromethane were the solvents and < 1 with acetonitrile.[73]

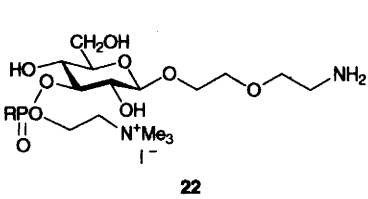
Tetra-*O*-benzyl-β-D-glucopyranosyl *S*-phosphorothioates, *S*-phosphorodithioates and *Se*-phosphoroselenates have been synthesized,[74] and the dimethylthionophosphates **20**, activated by NIS/AgOTf, have afforded 82% of the 4-linked glucobiosides (α,β 3:1).[75]

In the area of glycosyl phosphate diesters the β-D-arabinofuranosyl compound **21** was made as indicated in Scheme 3[76] and in related work glycosyl *H*-phosphonates were used to couple monosaccharides glycosidically with sterols by way of phosphate diester bridges.[77] The stability to alkali of phosphoethanolamine L-*glycero*-D-*manno*-heptoside derivatives has been studied.[78]

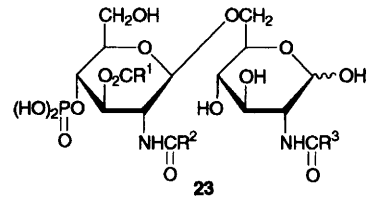


Scheme 3

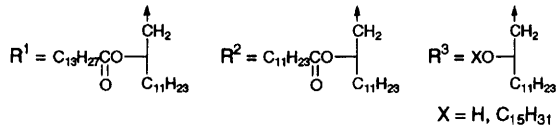
As always, several phosphates with the ester groups at the non-anomeric position have been examined. 5,6-*O*-Isopropylidene-L-ascorbic acid reacts with diphenylphosphinyl chloride in the presence of triethylamine to give the 3-ester which rearranges in the presence of a proton donor to the 2-isomer.[79] 3-(*S*)-Phosphinates of 1,2:5,6-di-*O*-isopropylidene-α-D-glucose have been described,[80] and the β-glucoside phosphonates **22** (R = Me, Ph) have been made



22



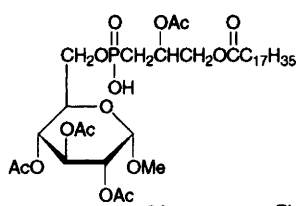
23



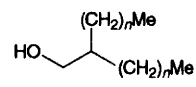
as transition state analogues of acylation reactions for conjugation to proteins.[81]

4-Phosphate **23**, a monophosphate analogue of the repeating unit of *Salmonella* lipid, has been made by chemical methods.[82] Micelles made from the α- and β-$C_{14}H_{29}$ D-glucopyranoside 4,6-cyclic phosphates are structurally very different, the β-isomer being the better chiral selector,[83] and the cyclic diester **24** has been made as a platelet aggregation inducer.[84] 6-Phosphofructokinase was used in the synthesis of carba-β-D-fructofuranose 6-phosphate,[85] and likewise a kinase was used to phosphorylate D-*altro*-heptulose (sedoheptulose). Instead of occurring at a primary position, esterification unexpectedly produced the 6-phosphate.[86] Selective chemical substitution was used to make *N*-acetylneuraminic acid 9-*H*-phosphonate from the benzyl glycoside or the methyl ester methyl glycoside.[87]

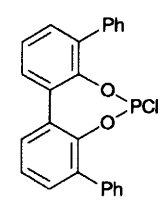
All of the O-2,-3,-4,-6 and -7 monophosphates of methyl β-L-*glycero*-D-*manno*-heptopyranoside have been made following chain extension from C-6 of methyl α-D-mannopyranoside and then standard, selective protection methods. Under the acid conditions used for the hydrolysis of lipopolysaccharides the esters migrated and hydrolysed. Under basic conditions they were



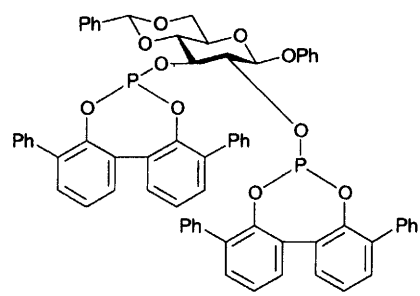
24



25



26

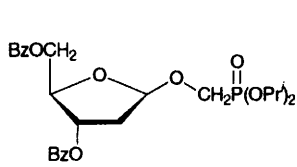


27

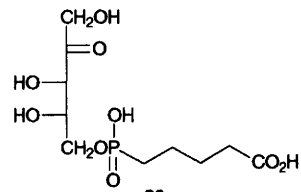
stable.[88] Eight 3,4-bis-phosphates of β-galactosides and β-lactosides of the branched fatty alkyl alcohols **25** (n = 0, 2, 13) were tested as selectin mimics.[89]

Several bidentate chiral ligands for effecting rhodium (I)-catalysed asymmetric reactions have been made by condensing reagents such as **26** with carbohydrate α-diols to give bisphosphites such as **27**.[90]

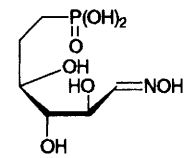
Phosphonates to have been described are the 2-deoxyribose derivative **28** and related compounds (including the analogue with C-1 of the sugar bonded to phosphorus),[91] and the L-*erythro*-pentulose ester **29**.[92] The sugar-*C*-bonded phosphonate **30** is an analogue of D-arabinose 5-phosphate oxime which is a potent inhibitor of glucosamine 6-phosphate synthase. It was made from the corresponding D-arabinofuranoside by Wittig-like extension from the derived C-5 aldehyde.[93] Other such phosphonates are described in Chapter 17.



28

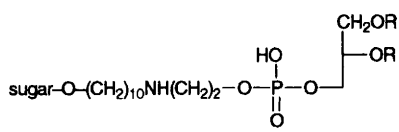


29



30

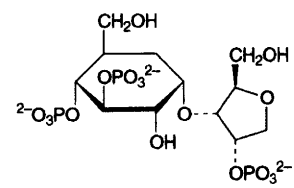
Compounds **31**[94] and **32**[95] represent compounds with phosphate esters in the aglycons; several other such phosphates are reported in the glycoside chapter (Chapter 3).



sugar = β-Gal, β-GlcA, β-GlcNAc, β-Lac

R = stearoyl, oleoyl, palmitoyl

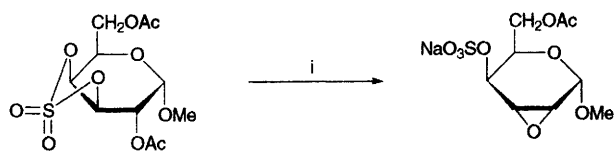
31



32

3 Sulfates and Related Esters

Hexopyranoside 4,6-cyclic sulfates are attacked at the primary position by nucleophiles and ring opened. Cyanide therefore allows chain extension from C-6, and a neighbouring acyloxy group can participate in cyclic sulfate ring opening as indicated in Scheme 4.[96] A detailed paper has given extensive



Reagent: i, NaCN, DMF

Scheme 4

description of the structure/activity relationships of the anticonvulsant topiramate (**33**) and related compounds, *e.g.* the cyclic sulfate analogue **34** (See Vol. 27, p. 102–103 for earlier work). Over 100 related compounds were described.[97]

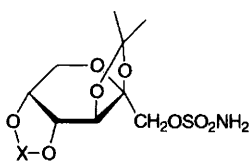
2-Sulfo-β-D-glucose has been found in the fruit of *Foeniculum vulgare* (fennel) as its *p*-methoxybenzyl and 2-(*p*-methoxyphenyl)ethyl glycosides.[98]

Glycolipid work has led to the synthesis of several compounds having sulfates at: O-3 of galactosides of ten branched alkane ols, diols and triols;[99] at O-3′ of the β-lactoside of **35** and of ring-substituted phenylalanines;[100] at O-3 of the galactose unit of β-D-Gal-(1→4)-[α-L-Fuc-(1→3)]-deoxynojirimycin;[101] the O-3′ of α-L-Fuc-(1→2)-β-D-Gal of a glycolipid.[102]

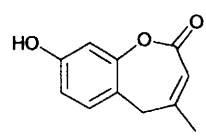
Glucosamine 4-sulfate was present as a component of the toxin wedeloside present in *Wedelia asperrina,*[103] and the galactose moiety of the Le^x trisaccharide was sulfated at O-4. In the course of the work di- and tri-sulfates were also obtained.[104]

Use of a sulfatase offers a useful approach to the preparation of specific esters, β-glucoside 3,6-disulfates being partially cleaved to the 6-esters by an abalone enzyme.[105] A neuraminic acid 8-sulfate derivative has been isolated from a sphingolipid of a sea cucumber.[106]

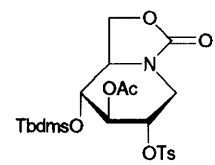
Several di- or oligosaccharide sulfates have been described. 4′- and 1′-sulfates have been obtained from a 6-*O*-acyl sucrose and 6- and 6′-sulfates from a 1-O-acyl ester. Otherwise sucrose 4,6-cyclic sulfate with acyl nucleophiles gave the 6-O-acyl-4-sulfates.[107] Several sulfates of β-D-galactosyl and



33 X = $C(Me)_2$
34 X = SO_2



35



36

lactosyl long-chain alkyl glycosides have been made,[89] and β-D-Gal-(1→4)-β-D-GlcNAc-(1→6)-[β-D-Gal-(1→3)]-α-D-GalNAcOBn has been made with a single sulfate at either of the two Gal units.[108] Several sulfates of other oligosaccharides are noted in Chapter 4.

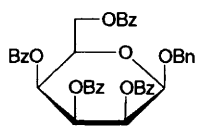
An MM3 force-field parametrization for sulfate group was applied on eight sulfated derivatives of α-D-Gal-(1→3)-β-D-Gal, *i.e.* the repeating unit of the carrageenans.[109]

4 Sulfonates

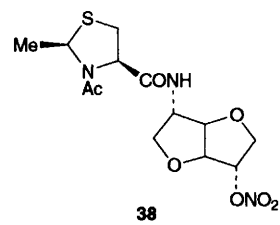
Sulfonates are of such great value in carbohydrate chemistry that their use is referred to extensively throughout this Report; the following are additional references which highlight the esters rather than products of their reactions. Voelter and colleagues have reviewed the synthetic utility of 2,3-anhydropentopyranoside 4-triflates for the preparation of aminodeoxy, halodeoxy,

branched-chain, cyclopropanated, aziridino, epithio and thiazoline sugars.[110] Nucleophilic displacement of the tosyloxy group with caesium acetate from compound **36** gave access to 1-deoxmannojirimycin, and in the same paper a method, involving a 4-chloromethylsulfonate, was described for the preparation of 1-deoxygalactojirimycin.[111] In related work β-talopyranoside tetrabenzoate **37** was produced from benzyl 3-O-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside 2-triflate which, on treatment with *tert*-butanol, gave three mannosides: the 2,3-orthoester and the two monobenzoates. This method applied to a substituted galactosylmannose gave a 4-talosylmannose derivative and β-mannosides from β-glucosides were made using displacements at C-2.[112] Use of the dibutyltin oxide selective activation method with methyl 6-*O*-trityl-α-D-mannopyranoside gives access to the 3-mesylate, 3-tosylate and 3-benzenesulfonate.[113] *O*-Acetylated α,α-trehalose 6,6′-ditriflate has been used to make derivatives with long-chain acyl esters at the primary positions.[114]

Monotosylation at O-2 of cyclodextrins has been described;[115] other sulfonates are reported in Chapter 4. Negative ion chemical ionization mass spectrometry of different sulfonates is referred to in Chapter 22.



37



38

5 Other Esters

1,4:3,6-Dianhydro-D-glucitol 5-nitrate and related compounds have been used for DCC-promoted coupling with sulfur amino acids *en route* to many compounds, *e.g.* **38**, some of which have vasorelaxing properties.[116]

Boronic acid-containing polymers have been used to condense methyl α-D-glucopyranoside at O-4, O-6 and hence afford access to 2,3-*O*- and 2-*O*-substituted derivatives.[117]

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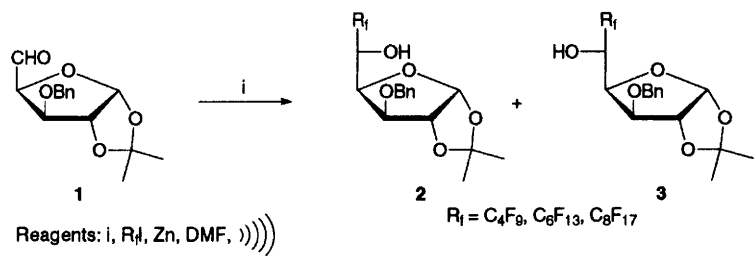
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8
Halogeno-sugars

1 Fluoro-sugars

The chemistry of glycosyl fluorides has been reviewed.[1] The electrolysis of 1-*O*-unprotected hexo-pyranose or -furanose derivatives in the presence of Ph_3P and Bu_4NF has afforded the corresponding glycosyl fluorides,[2] and the conversion of glycosyl bromides and thioglycosides into the corresponding glycosyl fluorides is covered in a review of organic halides.[3]

A sonochemically-induced Barbier-type reaction applied to aldehyde **1** has afforded the fluorinated sugars **2** and **3** in a ratio of ~2:1 (Scheme 1).[4] By use of Grignard methodology the same products have been prepared from **1**, but in a ratio of ~95:5.[5] A dithionite initiated addition of perfluoroalkyl iodides to unsaturated sugars has been exploited (Scheme 2).[6] An achiral synthesis of 2,6-dideoxy-6,6,6-trifluoro-D, L-*arabino*-hexose has been described,[7] and the synthesis of trifluoromethylthio ether sugar derivatives is covered in Chapter 11.

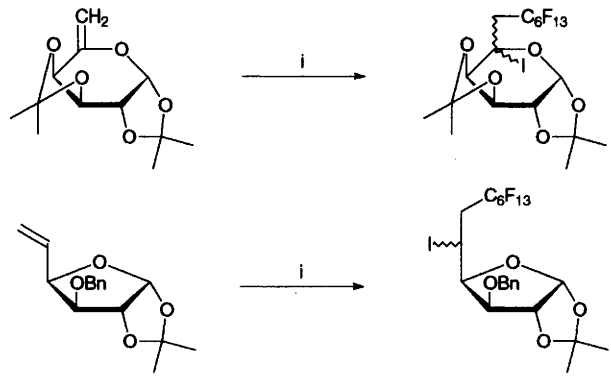


Scheme 1

A generalized Karplus-like equation for vicinal $^3J_{H,F}$ couplings has been proposed based on some monodeoxy-monofluoro nucleosides and 2′,2′-difluoro-nucleosides.[8]

Syntheses of 3,5-di-*O*-benzoyl-2-deoxy-2,2-difluoro-D-ribose have been achieved *via* DAST treatment of appropriate hexos-3-ulose derivatives followed by either periodate oxidation of a 1,2-diol, or ozonolysis of a glycal moiety.[9] 4-*O*-Benzoyl-2,2-difluoro-L-oleandrose (4-*O*-benzoyl-2,6-dideoxy-3-*O*-methyl-L-*arabino*-hexose) has been prepared by way of DAST treatment of a rhamnos-2-ulose derivative.[10]

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Reagents: i, $C_6F_{13}I$, $Na_2S_2O_4$, $NaHCO_3$, aq. MeCN

Scheme 2

Some fluorinated 4-thiofuranose derivatives and the corresponding nucleosides have been covered in Chapters 11 and 20.

The hydrogenation of **4** has provided new access to **5**, an intermediate for the synthesis of fluorinated nucleosides.[11]

Fluoride ion displacement reactions applied to glucofuranose 3,5-*O*-, or 5,6-*O*-cyclic sulfate derivatives has afforded regiospecifically the corresponding 5-deoxy-5-fluoro-L-*ido*-and the 6-deoxy-6-fluoro-D-*gluco*-compounds respectively.[12] 1-Fluoroglycopyranosyl cyanides have been prepared from the corresponding 1-bromo- or 1-chloro-glycosyl cyanides by reaction with AgF in MeCN or $AgBF_4$ in toluene.[13] The 3-, 4-, and 6-deoxyfluoro-GlcNAc-β-(1→3)-Gal-β-1-*O*Me disaccharides have been prepared in order to explore the substrate specificities of a β-(1→4)-galactosyl transferase.[14]



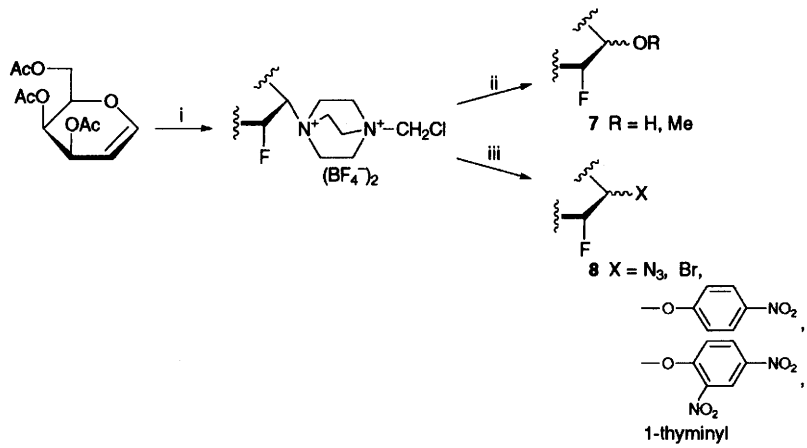
4 **5** **6**

In a further example of the application of Selectfluor® **6** as an electrophilic source of fluorine, D-galactal triacetate has afforded the 2-deoxy-2-fluoro derivatives **7** and **8** (Scheme 3).[15]

A synthesis of 2-deoxy-2-[^{18}F]-fluoro-D-glucose on a quaternary ammonium salt polymer support has been described.[16]

2 Chloro-, Bromo- and Iodo-sugars

The use of glycosyl iodides in organic synthesis has been reviewed.[17] Treatment of a number of *O*-protected glycosyl trichoroacetimidates with SmI_2 in THF has afforded the corresponding 4-iodobutyl glycosides by a reaction incorporating the solvent. However, mannose trichloroacetimidates gave the respective

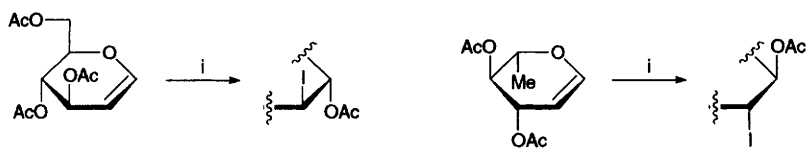


Reagents: i, **6**; ii, ROH; iii, NaN_3, or $MgBr_2$, or KOPNP, or KODNP, or bis(TMS)thymine

Scheme 3

glycosyl iodides, as did tetra-*O*-benzyl-D-glucosyl trichloroacetimidate.[18] The electrochemical reduction on a silver electrode of acetylated glycosyl bromides has given 1,1′-linked *C*-disaccharides.[19]

The iodoacetoxylation of glycals (Scheme 4) has afforded preferentially the 1,2-*trans*-diaxial products.[20] Similar results have been obtained using a $NaIO_4$/NaI mixture in a phosphate or acetate buffer.[21] The large-scale synthesis, and radiolabelling, of 6-deoxy-6-iodo-D-glucose has been described.[22]

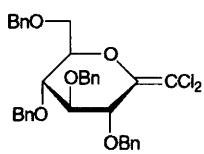


Reagents: i, I_2, $Cu(OAc)_2$, HOAc

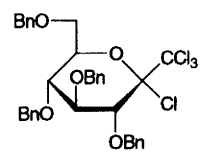
Scheme 4

A variation of the conventional halogenation of carbohydrates using Ph_3P and halocarbon solvents in highly concentrated solutions under microwave activation has been reported.[23]

Attempts to epoxidize poorly reactive olefins such as **9** using *m*CPBA/CH_2Cl_2 has resulted in chlorinated products, *e.g.* **10**.[24]



9



10

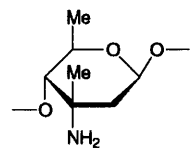
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9
Amino-sugars

1 Natural Products

Vicenisamine, 2,4,6-trideoxy-4-*N*-methylamino-D-*ribo*-hexopyranose, has been found as a sugar residue in the macrocyclic lactam anti-tumour antibiotic Vicenistatin.[1] The branched-chain amino-sugar residue **1**, named saccharosamine, was present in saccharomicins A and B, two heptadecasaccharide glycoside antibiotics isolated from a *Saccharothrix* sp.[2]



1

2 Syntheses

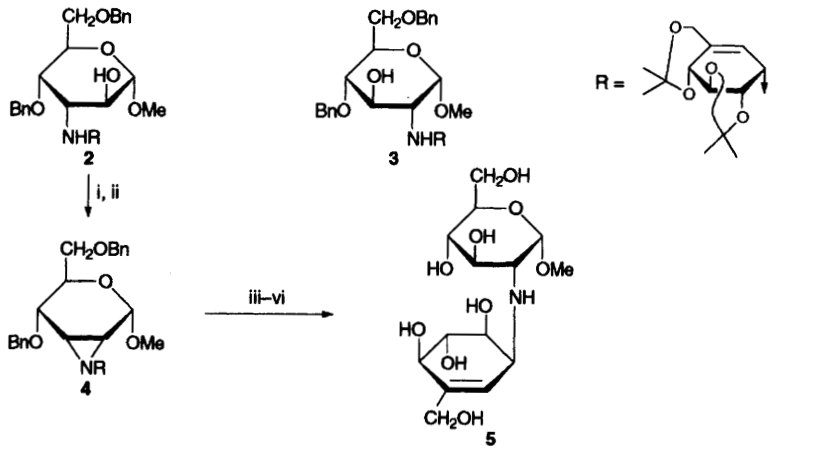
Syntheses covered in this section are grouped according to the method used for introducing the amino-functionality.

2.1 By Chain Extension. – Syntheses of C-4 epimeric 4-amino-4-deoxy-nonulosonic and -neuraminic acids, by chain extension of 1-deoxynitromannitol and 2-acetamido-1,2-dideoxy-1-nitromannitol derivatives, respectively, are detailed in Chapter 16.[3]

2.2 By Epoxide Ring Opening. – 1,6-Anhydro-2-, 3- and 4-benzylamino-2-, 3- and 4-deoxy-β-D-glucopyranoses have been synthesized by reactions of 1,6;2,3- and 1,6;3,4-dianhydro-β-D-hexopyranoses with benzylamine, and converted into 1,6-anhydro-2,3-(*N*-benzylepimino)-2,3-dideoxy- and 3,4-(*N*-benzylepimino)-3,4-dideoxy-β-D-hexopyranoses with the D-*allo*-, D-*galacto*- and D-*talo*-configurations by application of the Mitsunobu reaction.[4] The isomeric products **2** and **3** (Scheme 1) were obtained in 33 and 6% yields, respectively, on condensation of a 2,3-anhydro-α-D-mannoside with a cyclitolamine derivative (RNH_2). The desired 2-amino-D-glucoside derivative **5** could be obtained

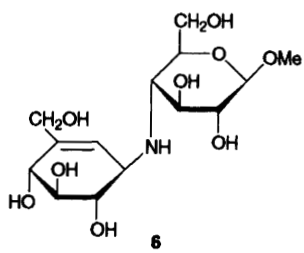
Carbohydrate Chemistry, Volume 32
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from **3** directly, or from **2** by formation and ring opening of epimine **4**, which led to a more favourable 5:4 ratio of the 2- and 3-amino-D-glucosides. Compound **5** was an inhibitor of α-glucosidase (Bakers' yeast), with an IC_{50} of 3 (M, but not sucrase, isomaltase or glycan processing α-glucosidase (rat liver).[5]

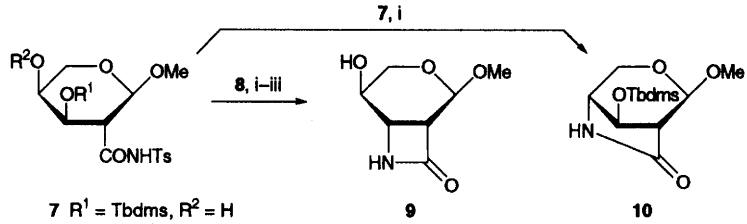


Reagents: i, MsCl, Py; ii, DBU; iii, NaOAc, HOAc, H_2O; iv, Ac_2O, Py; v, NaOMe, MeOH; vi, Na, NH_3

Scheme 1



2.3 By Nucleophilic Displacement. – The methyl acarviosin diastereomer **6** was synthesized by condensation of an *O*-benzyl protected cyclitolamine with methyl 2-*O*-benzyl-3-*O*-benzoyl-β-D-galactopyranoside 4-triflate, which gave much better yields than the corresponding 2,3-di-*O*-benzyl analogue.[6] 2-*C*-(*N*-Tosyl-carboxamido)-derivatives such as **7** and **8**, derived from glycals by [2+2]-cycloaddition of tosylisocyanate followed by methanolysis, underwent intramolecular displacements under Mitsunobu conditions to give the β- and γ-lactams **9** and **10**, respectively (Scheme 2).[7] 5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-idofuranose or 6-amino-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose derivatives were obtained by stereo- and regio-specific reactions of the corresponding 6-*O*-acetylated 3,5-cyclic sulfate or the 3-*O*-protected (Ac, Bn or Ms) 5,6-cyclic sulfates of 1,2-*O*-isopropylidene-α-D-glucofuranose, respectively, with azide ion followed by reduction (H_2, Pd/C) .[8] Azide displace-



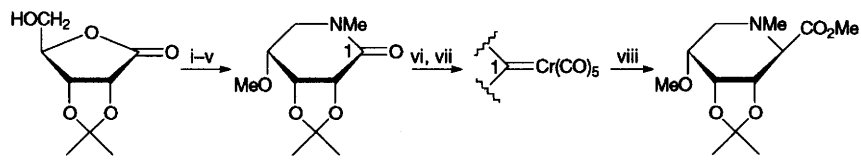
7 R^1 = Tbdms, R^2 = H
8 R^1 = H, R^2 = Bn

9 **10**

Reagents: i, DEAD, Ph_3P; ii, Na–naphthalene; iii, H_2, Pd/C

Scheme 2

ments were also employed in the synthesis of (a) 6^C-amino-6^C-deoxy-maltotetra- and pentaoses from mono-*O*-tosyl-β-cyclodextrin following treatment with cyclodextrin glycosyltransferase and maltose then with α-amylase,[9] and (b) sialyl-Lewis^x ganglioside analogues having a 6-NH_2 or 6-NHAc group on the galactose moiety, which involved treatment of an *O*-protected sialyl-(2→3)-galactoside 6-triflate with azide ion.[10] The 2,6-dideoxy-2,6-imino-D-allonate **14** was synthesized from the D-ribonolactone derivative **11**, by way of lactam **12**, and involved photolysis in methanol of the metal-stabilized carbene **13** (Scheme 3).[11] Several sugar derivatives with N-linked imidazole and pyrimidine moieties are covered in Chapter 10, Section 6. The preparation of 1,4-anhydro-2,3-dideoxy-pentitol 5-phosphates with *N*-linked heterocyclic bases attached at C-2, is covered in Chapter 18.



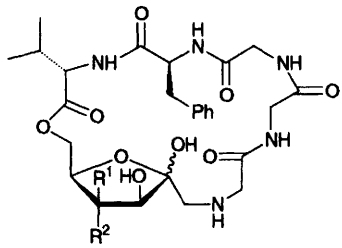
11 **12** **13** **14**

Reagents: i, TsCl, Py; ii, NaN_3, DMF; iii, H_2, Pd/C; iv, NaH, DMF; v, MeI; vi, $K_2Cr(CO)_5$; vii, TmsCl; viii, *hν*, MeOH

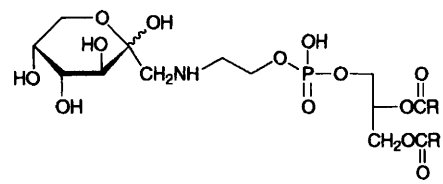
Scheme 3

2.4 By Amadori Reaction. – The cyclic 1-amino-1-deoxy-D-fructose and -D-tagatose derivatives **15** and **16** were obtained, respectively, by intramolecular Amadori reactions (in Py, HOAc) of D-glucose (or D-mannose) or D-galactose 6-*O*-acylated with a pentapeptide moiety.[12] Reaction of egg yolk phosphatidyl-ethanolamine with D-glucose in methanol gave the Amadori rearrangement product **17**, which is also found in blood plasma and red cells.[13]

2.5 From Azido-sugars. – 2′-Amino- and 6-amino-analogues of 2-(trimethylsilyl)ethyl 4-*O*-(α-D-galactopyranosyl)-β-D-galactopyranoside were prepared for evaluation as inhibitors of the binding of *E. coli* pilus protein to glycolipids. 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl bromide was used as a glycosyl donor in the synthesis of the former.[14] Various 2-azido-2-deoxy-D-



15 R^1 = H, R^2 = OH
16 R^1 = OH, R^2 = H

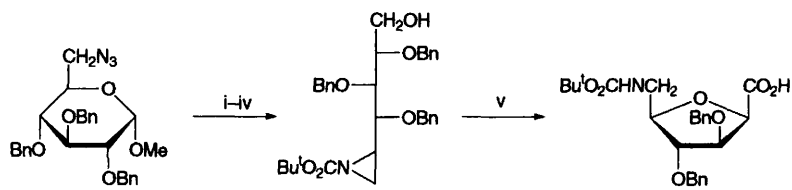


17 RCO = fatty acyl

fucopyranose derivatives with 1-OAc, 1-SEt and 1-OC(N=H)CCl_3 groups were prepared from a D-fucoside by double inversion at C-2 by an oxidation–reduction sequence followed by displacement of a 2-triflate group with azide ion. Their use in the stereoselective α-glycosylation of cyclopentanol and conversion to the *N*-methylamino-derivative, involving methylation of a 2-$NHCOCF_3$ group, was studied as a model for the synthesis of the neocarzinostatin chromophore.[15] Methyl 2-azido-2-deoxy-1-thio-α,β-L-fucopyranoside was synthesized from L-fucal diacetate, starting with an azido-nitration reaction, and was used as a glycosyl donor in the construction of benzyl 2-*O*-(2-acetamido-2-deoxy-α-L-fucopyranosyl)-α-L-fucopyranoside.[16] Other applications of azido-sugars derivatives as glycosyl donors in the construction of amino-sugar glycosides are covered in Chapter 3.

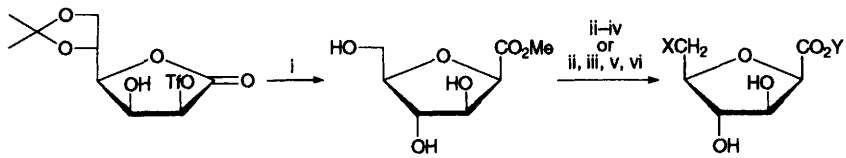
3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gluco- and allo-furanose could be converted into the corresponding 3-(*tert*-butoxycarbonylamino)-derivatives on treatment with Me_3P and 'Boc-ON' [2-(*tert*-butoxycarbonyloximino)-2-phenylacetonitrile], either stepwise or in one pot.[17]

The 'furanoid sugar amino acid' **20** was synthesized from the 6-azido-D-glucoside **18** by way of the epimine **19**, which on reaction with PDC in DMF underwent cycloetherification with simultaneous debenzylation and oxidation of the primary hydroxy group (Scheme 4). The C-2 epimer of **20** was available in the same way from the corresponding 6-azido-D-mannoside.[18] Related monomers **23** and **24**, prepared from D-mannose by way of acid-catalysed cyclization of 2-triflate **21** to β-C-arabinofuranoside **22** (Scheme 5), were used in the construction by solution and solid-phase techniques, of oligomers (*e.g.* **25**) that displayed a repeating β-type turn secondary structure in solution.[19–21]



Reagents: i, H_3O^+; ii, $NaBH_4$; iii, Ph_3P; iv, $(Bu^tO_2C)_2O$; v, PDC, DMF

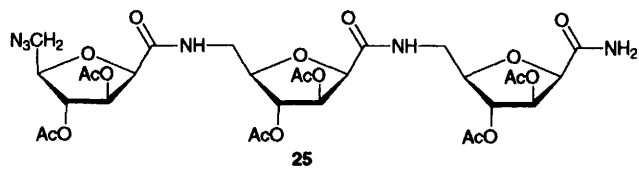
Scheme 4



21 **22** **23** X = N_3, Y = H; **24** X = NH_2, Y = Pr^i

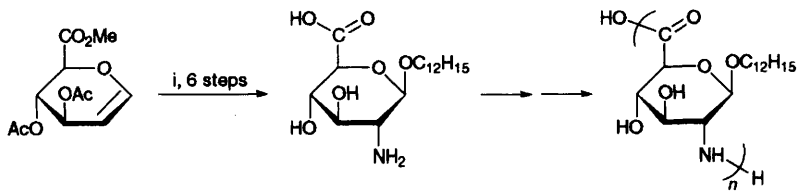
Reagents: i, HCl, MeOH; ii, TsCl, Py; iii, NaN_3; iv, NaOH, H_2O; v, K_2CO_3, Pr^{i}OH; vi, H_2, Pd/C, Pr^{i}OH

Scheme 5



25

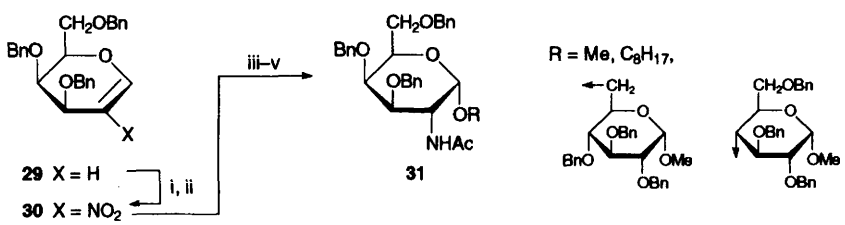
2.6 From Unsaturated Sugars. – The dodecyl 2-amino-2-deoxy-β-D-glucuronoside **27** was synthesized from D-glucofuranurono-6,3-lactone, a key step being the azido-nitration reaction of the glycal **26** (Scheme 6). It was polymerized to give the poly(sugar amino acids) **28**, which have self-assembling properties.[22] 3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal **30**, prepared from the corresponding galactal **29**, yielded α-linked 2-acetamido-2-deoxy-galactosides **31** in good yield when a strong base [*e.g.* MeONa, ^{t}BuOK or $(Tms)_2NK$] was used to catalyse the addition of the alcohol (Scheme 7), but mainly β-linked



26 **27** **28** *n* = 2–13

Reagents: i, NaN_3, $Ce(NO_3)_6(NH_4)_2$, MeCN

Scheme 6



29 X = H; **30** X = NO_2 **31**

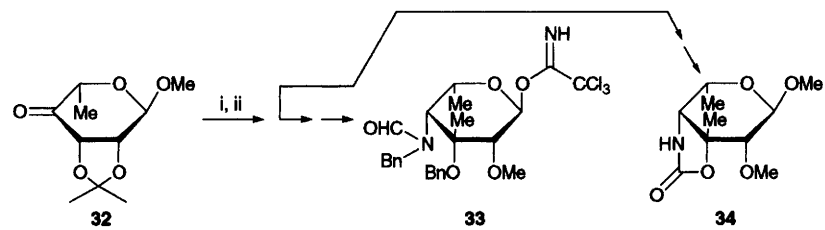
Reagents: i, HNO_3, Ac_2O; ii, Et_3N, CH_2Cl_2; iii, ROH, Strong base; iv, Raney Ni, H_2(80–90 atm), MeOH; v, Ac_2O, Py

Scheme 7

galactosides when a weak base (*e.g.* Et_3N) was used.[23] The synthesis of protected and *N*-methylated 2-amino-2,6-dideoxy-D-galactose (D-fucosamine) from D-galactal, involving amination with a nitrido manganese reagent, has been reviewed.[24] The construction of a β-D-NeuAc-(2→3)-β-GalNH$_2$-OC$_{12}$H$_{25}$ analogue bearing an inter-residue N-2,C-1′ lactam bridge and four contiguous ^{13}C and ^{15}N labels, is covered in Chapter 16.

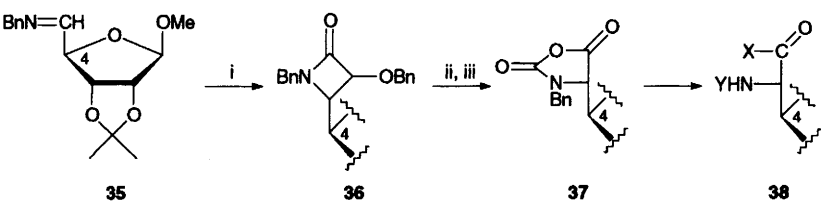
2.7 From Aldosuloses, Dialdoses and Ulosonic Acids. – Mechanistic studies have demonstrated that in the biosynthesis of desosamine (3-amino-3,4,6-trideoxy-D-hexose), which is found in several macrolide antibiotics, a 6-deoxy-D-hexos-3-ulosyl thymidine diphosphate is enzymically 4-deoxygenated then reductively aminated at C-3 by a transaminase, rather than the other way around.[25] The *N*-formyl-kanosamine donor **33** was synthesized from the L-rhamnose-derived hexosid-4-ulose derivative **32**, the key steps involving *C*-methylation α- to the ketone and oximation-reduction (Scheme 8). This donor was used in the construction of a pentasaccharide with a terminal *N*-formyl-α-L-Kan*p* moiety.[26] Methyl α-L-callipeltoside **34**, the free sugar of which was a biologically active component isolated from a marine sponge, was obtained from **32** in a similar way.[27] Application of the Strecker reaction to **32**, to yield 4-amino-4-*C*-cyano-derivatives, is covered in Chapter 14. Conversion of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside to its 4-acetamido-4-deoxy-1,5-dithio-L-arabinoside analogue, by way of a 4-oxime, is covered in Chapter 11.

New α-amino acid systems based on the general structure **38** have been constructed from the benzylimine **35**, by formation and cycloexpansion of the β-lactam **36** to give **37** (Scheme 9). Alcoholysis of **37** gave esters **38** (*e.g.* X = OMe, Y = Bn) which could then be *N*-acylated with a peptide. Alternatively,



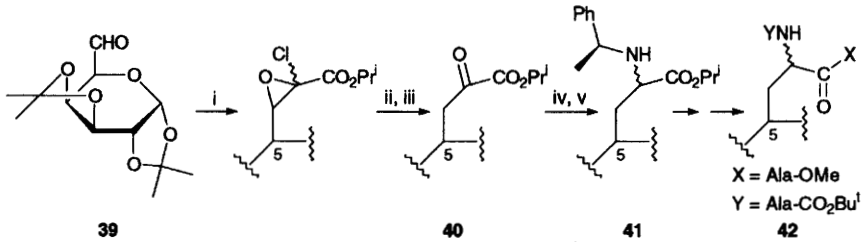
Reagents: i, LiNPr$^i_2$, MeI, HMPA; ii, NH_2OH

Scheme 8



Reagents: i, $BnOCH_2COCl$, Et_3N; ii, H_2, Pd/C; iii, NaOCl, KBr, TEMPO

Scheme 9

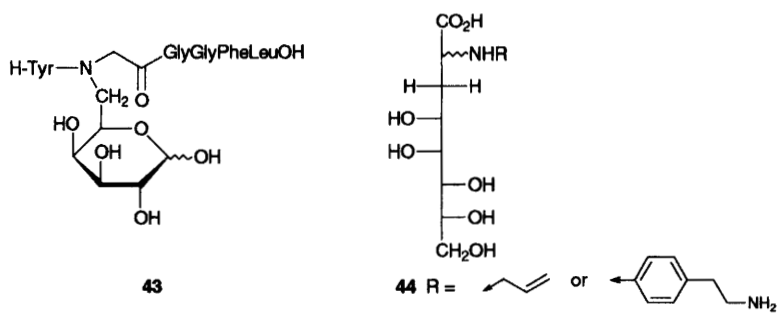


Reagents: i, $Cl_2CHCO_2Pr^j$, $KOPr^j$; ii, MgI_2; iii, $NaHCO_3$, H_2O; iv, Ph(H)C(NH$_2$)Me ; v, H_2, Pd/C

Scheme 10

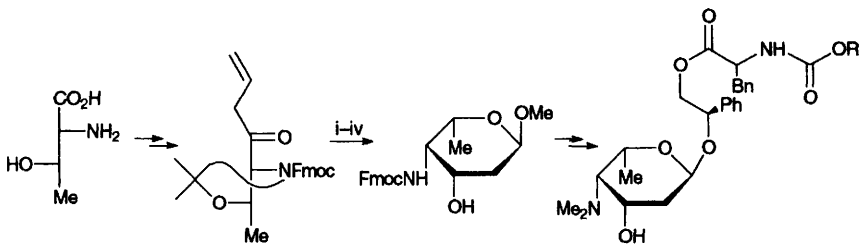
reaction of **37** with amino acid benzyl ester derivatives, gave amides **38** [*e.g.* X = NHCH(Pr^i)CO_2Bn, Y = Bn].[28] In a similar way, the representative α-amino acid **42** was constructed from 6-*aldehydo*-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **39**, by chain extension to ketoacid **40**, imine formation and reduction to give the separable epimers **41** and subsequent coupling to two alanine residues (Scheme 10).[29] The dialdehydo-derivative **39** was also used to make novel sugar-based peptidomimetics related to the enkephalins, such as **43**, by reductive amination ($NaBH_3CN$) with ethyl glycinate then peptide chain extension and *O*-deprotection.[30]

The epimeric 2-amino-2,3-dideoxy-octonic acids **44** were prepared by reductive amination of the octulosonic acid Kdo, along with the corresponding 2-hydroxy-compounds as by-products.[31]



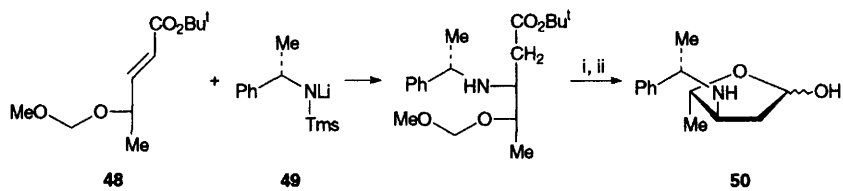
2.8 From Amino Acids. – The kedarosamine derivative **47**, an analogue of the enediyne natural product kedarcidin, was synthesized from D-threonine **45**, *via* the allyl-ketone **46** (Scheme 11).[32]

2.9 From Chiral Non-carbohydrates. – The 3-amino-2,3,5-trideoxy-pentose derivative **50** has been synthesized by 1,4-addition of the chiral nitrogen nucleophile **49** to the chiral 4-alkoxy-enoate **48** derived from lactic acid (Scheme 12). Reactions of related glyceraldehyde-derived enoates and the influence of differing chirality on the stereochemical outcomes were also studied.[33,34]



Reagents: i, H_3O^+; ii, $Me_4NBH(OAc)_3$; iii, O_3 then Me_2S; iv, MeOH, H^+

Scheme 11

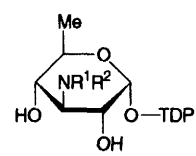


Reagents: i, H_3O^+; ii, Bu^i_2AlH

Scheme 12

3 Reactions and Derivatives

3.1 Interconversion and Degradation Reactions. – A method for the preparation of 2-amino-2-deoxy-D-glucose hydrochloride from chitin has been published.[35] $Ca(OH)_2$-catalysed epimerisation was used to introduce *ca.* 30% of ManNAc reducing terminal residues into chito-oligosaccharides; these ManNAc-containing compounds bind more strongly to NKR-P1 protein.[36] The thymidine diphospho (TDP) 3-amino-3,6-dideoxy-α-D-glucopyranoses **51** have been prepared from 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose by standard methods, and used as substrates in the characterization of a *N*,*N*-dimethyltransferase involved in the biosynthesis of mycaminose.[37]



51 R^1, R^2 = H or Me

The kinetics and mechanism of the oxidation of hexosamines with sodium *N*-chlorobenzenesulfonamide have been investigated. 2-Amino-2-deoxy-D-glucose and -mannose both gave arabinonic, ribonic and erythronic acids along with small amounts of hexonic and glyceric acids.[38] Allyl 2-acetamido-2-deoxy-α-D-glucopyranoside was isolated from an α,β-mixture by hydrolysis of the β-anomer with Jack bean β-*N*-acetyl-glucosaminidase and degradation of the released GlcNAc by incubation with cells of a *Rhodococcus rhodochrous* sp.

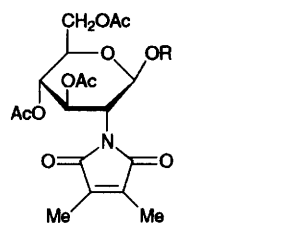
The susceptibility of variously substituted GlcNAc derivatives and analogues to degradation in this way was also reported.[39]

Syntheses of aminosugar *C*-glycosides are covered in Chapter 3, and of 2-acetamido-2-deoxy-α- and β-D-glucopyranose 1-phosphate in Chapter 7. A study of the FAB-MS fragmentation of amino-sugar-containing trisaccharides is covered in Chapter 22.

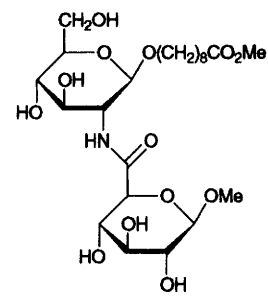
3.2 *N*-Acyl and *N*-Carbamoyl Derivatives. – Zinc powder has been found to promote the rapid, mild and efficient *N*-benzoylation or -pivaloylation by the corresponding acid chlorides of amines, *e.g.* 3-amino-3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose in toluene at room temperature.[40]

The dimethylmaleate (DMM) group has been introduced as a new amine-protecting group that is easier to remove than the phthalimido group. Thus the derivative **52** could be produced in 60% yield over two steps from 2-amino-2-deoxy-D-glucose hydrochloride, converted into a β-imidate glycosyl donor and thence into various β-glycosides **53**, and *N*-deprotected with aqueous NaOH prior to *N*-acetylation.[41] In studies on the construction of glycoprotein oligosaccharides, the 4,5-dichlorophthaloyl (DCPhth) group was used for *N*-protection of 2-amino-2-deoxy-D-glucose. This group proved to be stable during various protecting group manipulations, and under Lewis acid-, silver salt- and iodonium ion-promoted glycosylation conditions. It retained the 1,2-*trans*-directing nature of the phthaloyl protecting group, but could be removed under substantially milder conditions with ethylenediamine in alcoholic solvent.[42] Pent-4-enyl 2-deoxy-2-(pent-4-enamido)- and 2-tetrachlorophthalimido-β-D-glucopyranoside derivatives have been converted into related pent-4-enyl 2-azido-sugar building blocks for oligosaccharide synthesis by *N*-deprotection (with ethylenediamine or iodine, respectively) and diazotransfer (with TfN_3).[43]

The *N*-(*tert*-butoxycarbonyl) group can be removed during solid phase construction of oligonucleotides by the use of $AlCl_3$.[44]



52 R = Ac
53 R = *e.g.* Bn,  , sugar

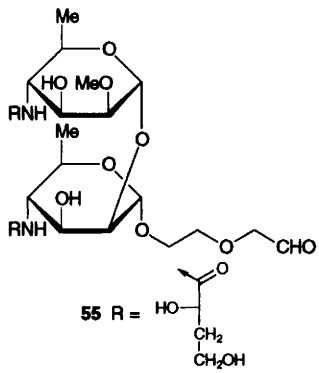


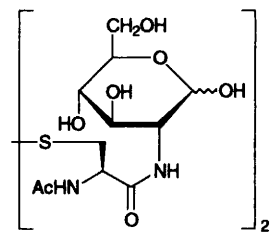
54

The amide-linked disaccharide analogue **54** and isomers containing methyl α- and β-D- and L-galactopyranosiduronoyl residues, were synthesized by *N*-acylation of a 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucoside with a hexuronic acid derivative, and were shown to be very good substrates for the

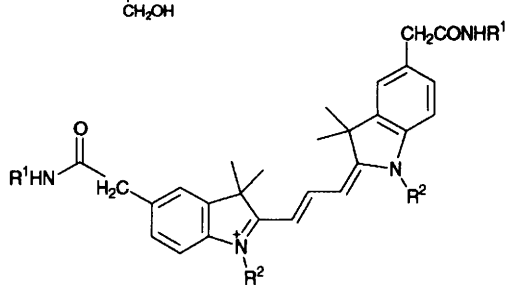
sequential action of β-galactosyltransferase, α-(2→3)-sialyltransferase and fucosyltransferase VI, in the construction of sialyl-Lewis^x analogues.[45] Further analogues of the presumed antigenic sugar residue of the O-specific polysaccharide of *Vibrio cholerae*, methyl 4,6-dideoxy-4-(3-deoxy-L-*glycero*-tetronamido)-α-D-mannopyranoside (*cf.* Vol. 30, p. 133) have been prepared by *N*-acylation of methyl 4-amino-6-deoxy-2-*O*-methyl-3-*O*-benzyl-α-D-mannopyranoside with isomeric and mono-deoxygenated tetronolactones. The products were subsequently converted to 3-deoxy-analogues.[46] The 1,2-linked disaccharide glycoside **55** containing two such residues has been synthesized and coupled to BSA by reductive amination.[47]

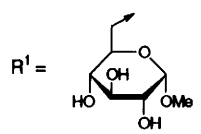
The cystine derivative **56**, the synthesis of which involved *N*-acylation of 2-amino-2-deoxy-D-glucose, was shown to be a substrate of *M. tuberculosis* mycothione reductase.[48] Synthesis of water-soluble cyanine dyes such as **57** involved *N*-acylation of methyl 6-amino-6-deoxy-α-D-glucoside.[49] Trimannosyl cluster compounds were prepared by condensation of derivatives of 6-amino-6-deoxy-mannopyranoside with nitro-tri-(2-carboxyethyl)methane, or of 6-deoxy-6-isothiocyanato-D-mannopyranoside with tri-(2-aminoethyl)amine, and their binding to *E. coli* α-mannoside receptors was evaluated.[50] The one-pot, Lewis acid catalysed formation of a β-glycoside from a 2-acylamino-1,6-anhydro-2-deoxy-β-D-glucopyranose derivative is covered in Chapter 3.





56

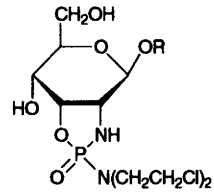




R^2 = Et or $(CH_2)_2CO_2H$

57

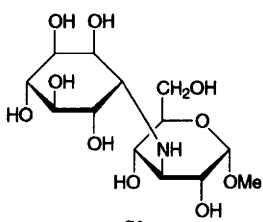
3.3 Cyclophosphamide. – Sugar-based analogues **58** of cyclophosphamide were synthesized as potential anti-cancer agents by reaction of the corresponding 4,6-*O*-benzylidene-2-amino-2-deoxy-sugar with $Cl_2P(O)N(CH_2CH_2Cl)_2$ followed by hydrogenolysis (H_2, Pd/C).[51]



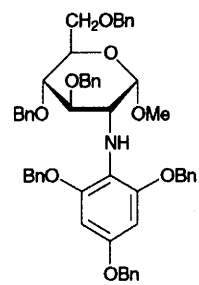
58 R = *e.g.* cyclohexyl

3.4 Imine, Urea and Isothiourea Derivatives. – Schiff bases have been formed by condensing various substituted benzaldehydes with 2-amino-2-deoxy-D-glucose in refluxing methanol.[52] Condensation of tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose with various alkyl or aryl-iso(thio)cyanates was used to prepare a number of *N*-(glucos-2-yl)-urea and -thiourea derivatives. *N*-(1-Deoxy-D-glucitol-1-yl)-derivatives were formed in a similar fashion. The products were evaluated as inhibitors of *Trichomonas vaginalis* *N*-acetyl-β-hexosaminidase.[53]

3.5 *N*-Alkyl and *N*-Alkenyl Derivatives. – Synthesis of the *N*-linked pseudodisaccharide **59** involved reductive amination ($NaBH_3CN$) between *O*-benzylated inosose and methyl 3-amino-3-deoxy-D-glucopyranoside derivatives. Compound **59** proved to be a poorer inhibitor of yeast α-glucosidase than deoxynojirimycin. An attempt to affect a similar condensation with the corresponding 2-amino-sugar led instead to the *N*-aryl-derivative **60**, following aromatization of the inosose moiety.[54] Syntheses of methyl 2-deoxy-2-*N*-(5-thiomannosyl)amino-D-glucopyranoside and the corresponding 3-amino-3-deoxy-isomer are covered in Chapter 9.

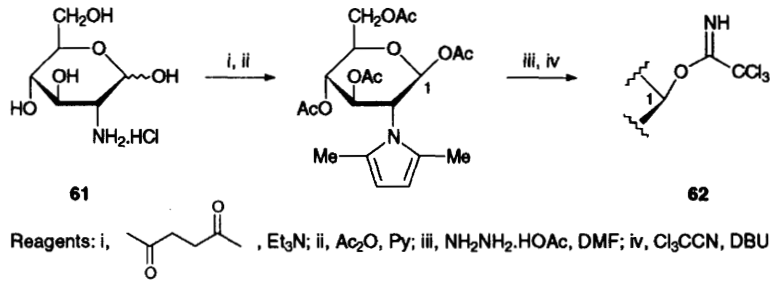


59



60

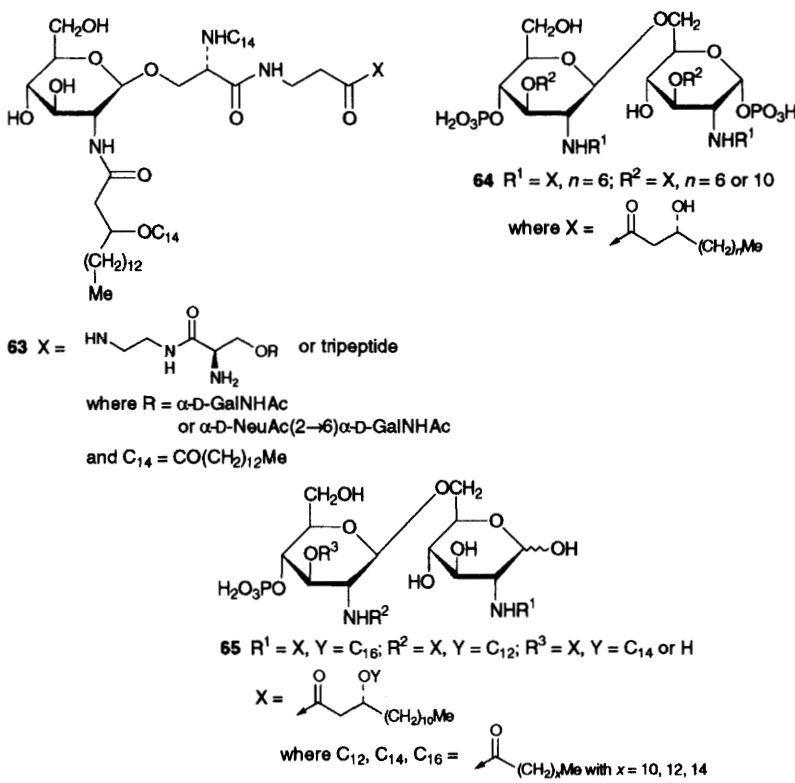
The 2,5-dimethylpyrrole moiety has been introduced as an amine-protecting group in oligosaccharide synthesis. It is compatible with many protecting group manipulations and can be cleaved with hydroxylamine, but is stable under conditions that cleave the *N*-phthalimido group. Thus the glycosyl



Scheme 13

donor **62**, prepared from 2-amino-2-deoxy-D-glucose **61** as shown in Scheme 13, was used in the preparation of a variety of disaccharides.[55] Synthesis of a 2-alkylamino-1,5-anhydro-hexitol by reduction of the corresponding 2-acylamino-derivative is covered in Chapter 18.

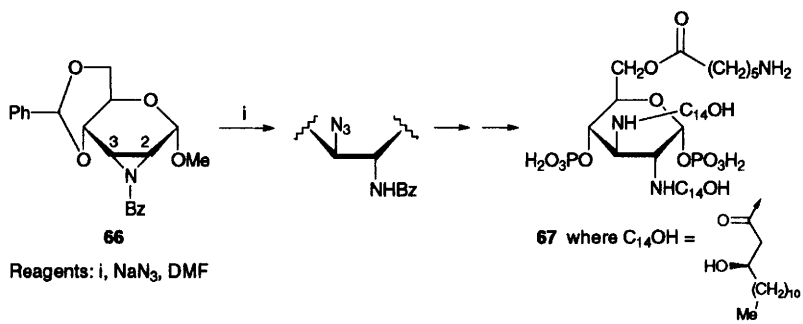
3.6 Lipid A Analogues. – In studies aimed at the development of a totally synthetic vaccine against cancer or HIV, conjugates **63** containing both a Lipid A analogue and a Tn or sialyl-Tn moiety, or an HIV-1-derived peptide antigen, have been synthesized and shown to have potent mitogenic activity.[56] The critical importance of acyl chain length to the biological activity of Lipid



A has been demonstrated by synthesis and testing of two analogues **64** with shorter than usual (*R*)-3-hydroxylacyl moieties. These compounds were 10 to 100-fold less active in inhibiting immune stimulation by IL-6 than the homologue **64** with $R^1 = R^2$ and $n = 10$.[57] Syntheses of monophosphorylated analogues **65** of *Salmonella minnesota* Lipid A have been reported.[58]

4 Diamino-sugars

trans-Diequatorial ring opening of the 2,3-aziridine **66** with azide (Scheme 14) was the key step in the synthesis from 2-amino-2-deoxy-D-glucose of the 2,3-diamino-D-glucose derivative **67**, which was evaluated for effects on murine macrophages.[59] A synthesis of benzyl 2-benzyloxcarbonylamino-4-dichloroacetamido-2,4-dideoxy-α-D-xylopyranoside from L-arabinose has been reported.[60]



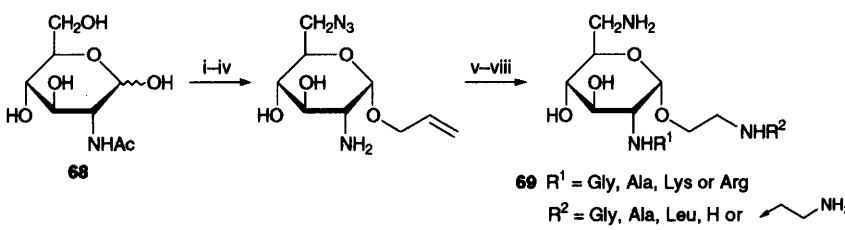
66

Reagents: i, NaN_3, DMF

67 where $C_{14}OH$ =

Scheme 14

The small library of aminoglycoside mimics **69** was prepared from 2-acetamido-2-deoxy-D-glucose **68** as shown in Scheme 15, and screened for interaction with RNA fragments.[61] The 2,6-dideoxy-6-guanidino-2-*N*-arylsulfonyamido-sugar derivatives **70** (as well as the corresponding 2-*O*-β-naphthalenesulfonate) were synthesized as arginine mimetics and shown to be thrombin inhibitors ($K_i \sim 1$ μM).[62]



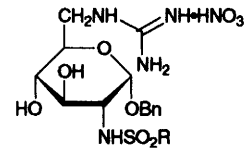
68

69 R^1 = Gly, Ala, Lys or Arg

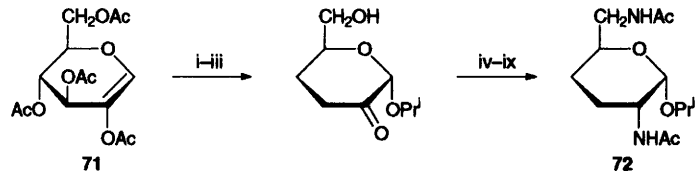
R^2 = Gly, Ala, Leu, H or

Reagents: i, , H^+; ii, TsCl, Py; iii, NaN_3; iv, $Ba(OH)_2$; v, amino acid succinimide ester, Et_3N, DMF; vi, O_3, MeOH then Me_2S; vii, $NaBH_3CN$, HOAc, amine; viii, H_2, Pd/C

Scheme 15



70 R = *e.g.* α-naphthyl

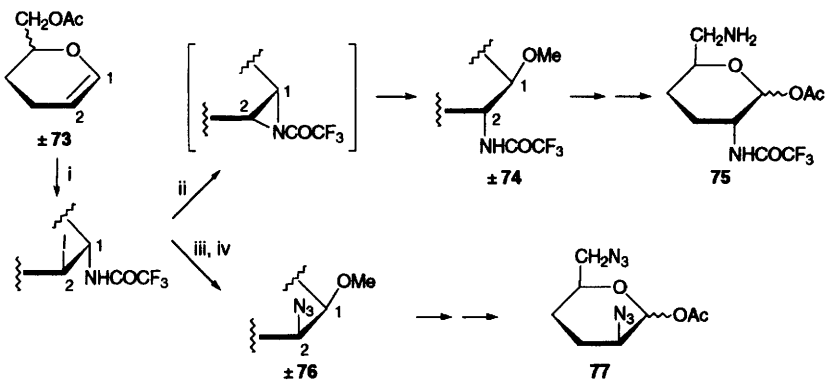


71 **72**

Reagents: i, PrⁱOH, $SnCl_4$; ii, H_2, Pd/C; iii, NaOMe, MeOH; iv, TsCl, Py; v, NaN_3; vi, NH_2OH; vii, Ac_2O, Py; viii, BH_3.THF; ix, Ac_2O, Py

Scheme 16

Purpurosamine C was synthesized as its di-*N*-acetylated isopropyl glycoside **72** from hydroxyglucal tetraacetate **71** (Scheme 16), the nitrogen functionality being introduced at C-6 by sulfonate displacement with azide and at C-2 by reduction of an oxime.[63] Improved routes to D- and L-purpurosamine derivatives suitable as glycosyl donors (*cf.* Vol. 28, p. 133) are outlined in Scheme 17. The racemic dihydropyran **73**, derived from acrolein dimer, was converted to the racemic glycosides **74** and **76**, which were subjected to lipase-catalysed resolution. The 6-amino-groups were introduced by way of mesylate displacement with azide, leading eventually to the D-enantiomers **75** and **77**, and their L-isomers.[64]



Reagents: i, NIS, CF_3CONH_2; ii, Et_3N, MeOH, DMF; iii, $Ce(NH_4)_2(NO_3)_6$, NaN_3; iv, MeOH

Scheme 17

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10
Miscellaneous Nitrogen-containing Derivatives

1 Glycosylamines and Related Glycosyl-*N*-bonded Compounds

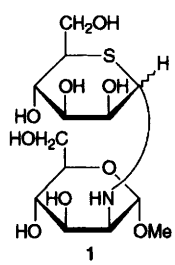
1.1 Glycosylamines. – An *N*-β-D-galactopyranosyl-imidazole has been identified as a bridging unit in a cyclic peptide isolated from a bacterium that is symbiotic with a marine sponge.[1]

The pK_a values of various *N*-aryl-glucopyranosylamines in methanol have been determined.[2]

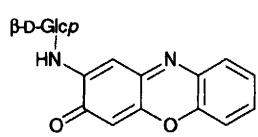
Formation of D-glucosylamines by reaction of D-glucose with *o*-, *m*- and *p*-aminobenzoic acid under mild conditions has been reported,[3] and reaction of D-glucose, D-xylose or L-arabinose with 3-amino-5*H*-3,4-dihydropyrimido[5,4-*b*]indol-4-one in methanol gave the corresponding glycosylamines.[4] Oxidative cyclizations of the aglycon moieties of *N*-glycosides of 3,4-bis(indol-3-yl)-furano- and -pyrrolo-2,5-diones have been reported.[5] Acid-catalysed condensation of 5-thio-D-mannose with methyl 2-amino-2-deoxy- or 3-amino-3-deoxy-D-glucopyranoside gave heteromannosyl disaccharides such as **1**.[6]

N-Glucosyl-questiomycin A (**2**), isolated as a *Microspora* sp. fermentation product, has been shown have a β-D-glucopyranosyl moiety by synthesis of both enantiomers through Mitsunobu coupling (Ph_3P, DEAD) of 2,3,4,6-tetra-*O*-acetyl-L- or D-glucose with *N*-(trichloroethoxycarbonyl)-questiomycin A and deprotection (MeONa, MeOH).[7] 2,3,5-Tri-*O*-benzyl-*N*-(*p*-methoxybenzyl)-α,β-D-xylofuranosylamine featured as an intermediate in the synthesis of the alkaloid (+)-lengtiginosine, covered in Chapter 24.[8]

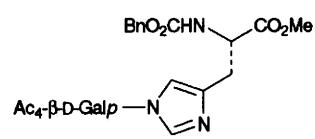
The first glycosylated histidine **3**, glycosylated on the τ- rather than the π-nitrogen atom of the imidazole ring, has been obtained in 15% yield by condensation of the corresponding histidine derivative with tetra-*O*-acetyl-α-D-galactopyranosyl bromide.[9] *N*-Glycosyl-indoles with antibacterial activity



1

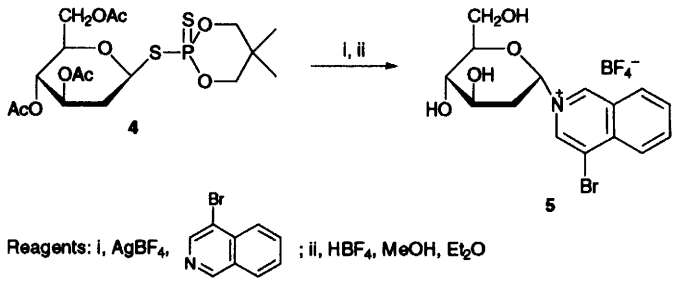


2



3

Carbohydrate Chemistry, Volume 32
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Scheme 1

were similarly obtained by Ag_2O-induced condensation of indoles with the acetobromosugars.[10]

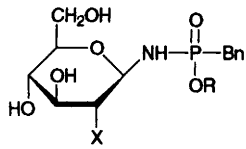
Various *N*-(2-deoxy-α-D-*arabino*-hexopyranosyl)-pyridinium and -quinolinium salts such as **5** were synthesized by condensation of the pyridine with β-glycosyl donor **4** (Scheme 1). A kinetic study of the hydrolysis of such salts in the presence of azide ion indicated that the 2-deoxyglycosyloxocarbenium ion is not solvent-equilibrated in water.[11] The 3:1 mixture of *N*-(tetra-*O*-acetyl-β- and α-D-glucopyranosyl)-pyridinium bromides formed on reaction of the corresponding α-bromide with pyridine, on treatment with MeONa in MeOH at 85 °C, gave 1,6-anhydro-D-glucopyranose which was isolated as its triacetate in 66% yield. In the mannose series, only the β-pyridinium salt is formed, and this does not cyclize but instead yields methyl α-D-mannopyranoside.[12]

N-Glycosyl-phosphoramidates **6** were synthesized as potential transition state analogue inhibitors of glycopeptidases, by phosphoramidation of the corresponding *O*-acetyl protected glucopyranosylamine. The phosphoramidate ester could be cleaved using TmsBr.[13]

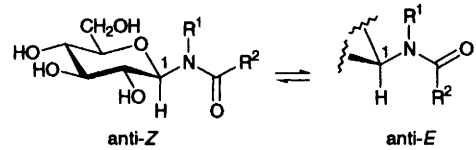
Maillard reaction products formed from lactose and the lysine residues of β-lactoglobulin have been identified by capillary electrophoresis and electrospray MS.[14]

1.2 Glycosylamides Including *N*-Glycopeptides. – The anti-periplanar conformation around the glycosidic bond is adopted preferentially by *N*-formyl-, *N*-acetyl- and *N*-acetyl-*N*-methyl-β-D-glycosylamines, as shown by NMR spectroscopy, X-ray crystallography and semi-empirical calculations, although mixtures of the *E*- and *Z*-isomers, *e.g.* **7**, are present in solution in some cases.[15] New surfactants **8a** have been synthesized by sequential condensation of glucose with a long-chain amine and then *N*-acylation with acryloyl or methacryloyl chloride, and their rotamer population studied by NMR spectroscopy.[16] New glycolipids, *e.g.* **8b**, were similarly obtained in two steps by condensation of various free sugars with a variety of long chain alkylamines and then treatment with mixed anhydride derivatives of various fatty acids. Some were strong stimulators of a specific immune response against antigens.[17]

Sialyllactosamine attached to a polystyrene backbone was prepared and examined for interaction with influenza virus. Sialyllactose was isolated as a 6.5:1 mixture of α-(2→6)- and α-(2→3)-linked isomers from bovine milk,

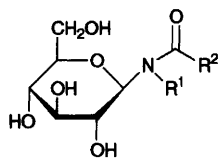


6 X = OH or NHAc
R = H, Et

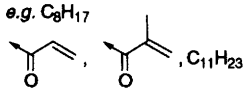


anti-*Z* anti-*E*

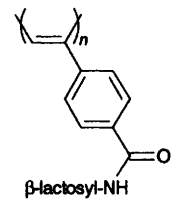
7 $R^1 = R^2$ = Me or H



8a R^1 = *e.g.* C_8H_{17}

R^2 = 

8b $R^1 = C_{12}H_{25}$
$R^2 = C_{11}H_{23}$

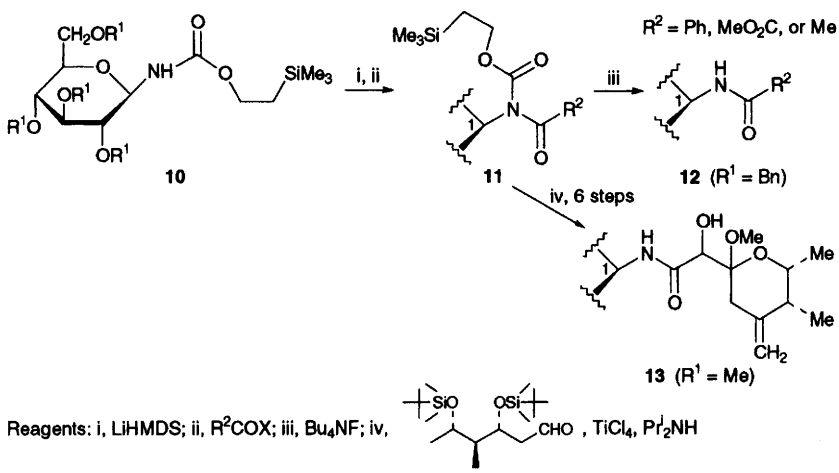


β-lactosyl-NH

9

converted to the corresponding β-glycosylamines with $(NH_4)_2CO_3$, *N*-acylated with 4-vinylbenzoyl chloride and polymerized (with ammonium peroxodisulfate as catalyst).[18] Lactosylamine and cellobiosylamine were similarly incorporated into polymers, *e.g.* **9**, by *N*-acylation with 4-ethynyl-benzoyl chloride and rhodium-catalysed polymerization. The backbone of the lactosylated polymer possessed alternating *cis-trans*-double bonds and a helical conformation. It bound with less avidity to a galactose-specific lectin than did the corresponding polystyrene analogue.[19]

N-(2-Trimethylsilylethoxycarbonyl)-β-glucosylamine **10** (R^1 = Bn) was *N*-acylated to give **11**, then *N*-deprotected by treatment with fluoride ion to give **12** (Scheme 2).[20] This temporary protecting group strategy was also employed

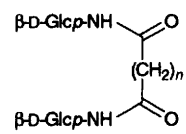


Reagents: i, LiHMDS; ii, R^2COX; iii, Bu_4NF; iv, , $TiCl_4$, Pr^i_2NH

Scheme 2

in the synthesis of the model *N*-glucosylpederamide **13**. Thus, compound **10** (R^1 = Me) was converted to the corresponding di-*N*-acylated **11** (R^2 = CH_2OBn) then subjected to an aldol condensation before being further modified.[21]

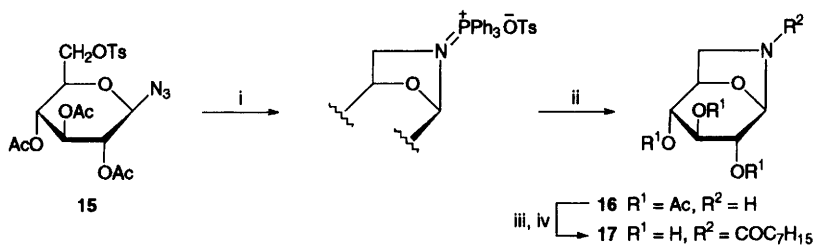
Per-*O*-acetyl-*N*-(chloroacetyl)-β-D-glycosylamines (of Glc, Gal, GlcNHAc and Lac) have been prepared from the corresponding per-*O*-acetyl-β-glycosyl azides by reduction (*n*-Bu_3P or propane-1,3-dithiol) and *N*-acylation with chloroacetic anhydride. Reactions of the products with thioacetic acid and triethylamine gave the corresponding *N*-(*S*-acetylmercaptoacetyl) derivatives.[22] Glycoconjugates of piperazine, 2-phenylethylamine, tryptamine, norephedrine, octopamine and dopamine were prepared by efficient mono-*N*-alkylation of these primary and secondary amines with *N*-chloroacetyl-glycosylamines (of Glc, Gal, Man, GlcNHAc and Lac).[23] New bolaamphiphiles, *e.g.* **14**, have



14 *n* = 6–18

been obtained by condensation of tetra-*O*-acetyl-β-D-gluco- or galactosylamine, freshly prepared from the corresponding azide, with a dicarboxylic acid dichloride, followed by de-*O*-acetylation.[24]

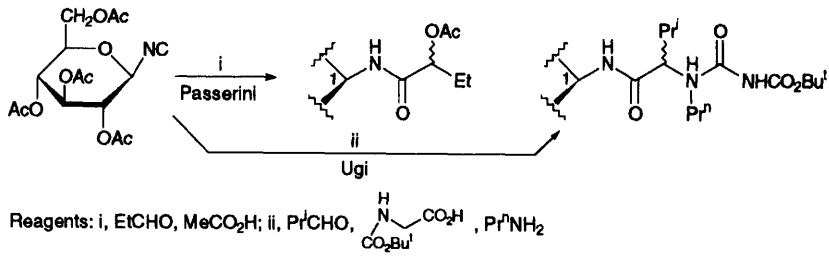
The 6-amino-1,6-anhydro-6-deoxy-β-D-glucopyranose derivative **16**, characterized as its stable *N*-acetate, was obtained by intramolecular displacement of the 6-tosylate group by the C-1 iminophosphorane produced by Staudinger reaction at the C-1 azide in **15** on treatment with triphenylphosphine (Scheme 3). The corresponding *galacto*- and *manno*-isomers were obtained in the same way. Amine **16** was converted to novel surfactants such as **17**.[25]



Reagents: i, Ph_3P; ii, Resin (OH^-); iii, $C_7H_{15}COCl$, py; iv, MeONa, MeOH

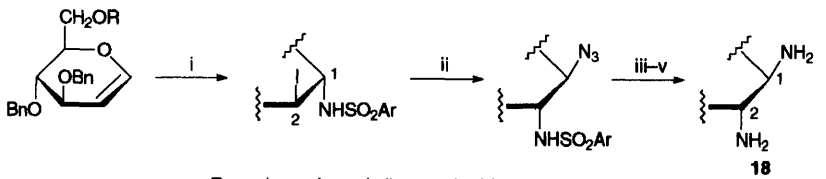
Scheme 3

Recent literature on the occurrence in nature of *N*- and *O*-linked glycopeptides and glycoproteins and on their chemical synthesis, as well as that of *S*- and *C*-linked analogues, has been reviewed.[26] Various *N*-linked glycosyl α-hydroxyamides and peptides have been synthesized by application of the Passerini and Ugi reactions, respectively, to glycosyl isonitriles as exemplified



Scheme 4

in Scheme 4.[27] In the synthesis of *N*-linked glycopeptides on a solid support, Danishefsky and co-workers have applied iodosulfonamidation chemistry (Scheme 5) to a previously described polymer-bound glycal (Vol. 29, p. 71, ref. 91; *Science* 1995, **269**, 202) to make the corresponding polymer bound β-D-Gal-(1→6)-β-D-Gal-(1→6)-β-D-GlcNHAc-1-NH_2 derivative **18** which was then coupled to a peptide moiety at the anomeric centre.[28] The synthesis of the *O*-

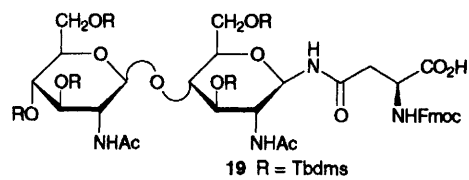


R = polymer-bound oligosaccharide, Ar = anthracen-9-yl

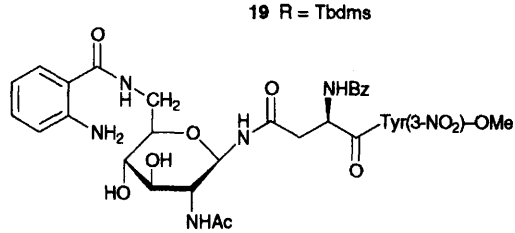
Reagents: i, I(collidine)$_2$ClO$_4$, $ArSO_2NH_2$; ii, $Bu_4N.N_3$; iii, Ac_2O, DMAP; iv, PhSH, Pr^i_2NEt, MeOH; v, Al(Hg), PriOH, THF, H_2O

Scheme 5

Tbdms protected *N*-chitobiosyl-asparagine derivative **19** and its use in the solid-phase synthesis of a glycopeptide fragment corresponding to Vitamin K-dependent protein S has been described.[29]



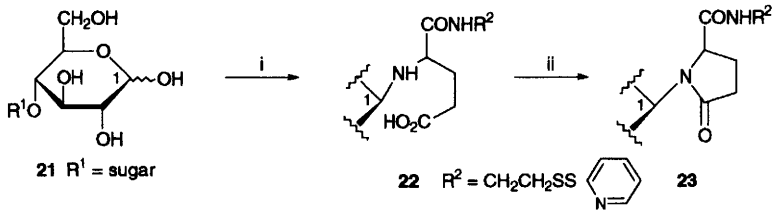
19 R = Tbdms

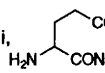


20

A fluorescence-quenched glycopeptide substrate **20**, which contains an anthranilate/nitrotyrosine donor/acceptor pair to provide fluorescence

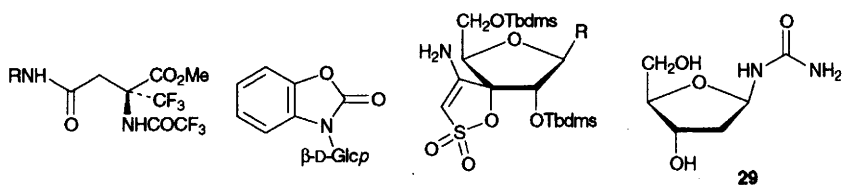
quenching by resonance energy transfer, has been synthesized as a first step towards the development of a more convenient assay for PNGase activity.[30] Oligoglycosylpyroglutamyl derivatives can be prepared in a one-pot, two-step reaction in high yield (Scheme 6). Thus lactose, α-Fuc-(1→3)-Lac or α-Gal-(1→3)-Lac (**21**) was condensed with a glutamic acid derivative in DMF containing imidazole to give **22** which was then stabilized by intramolecular acylation to give **23**.[31] Glycopeptides with a new peptide motif, **24** and their diastereomers, have been prepared.[32]



Reagents: i,  , DMF, imidazole; ii, BOP [benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate]

Scheme 6

1.3 *N*-Glycosyl-carbamates, -isothiocyanates, -thioureas and Related Compounds. – The structure of *N*-β-D-glucopyranoside **25**, a detoxification product formed by oats (*Avena sativa*) when incubated with the natural phytotoxin benzoxazin-2(3*H*)-one, was confirmed by chemical synthesis using an imidate donor and an *N*-silylated acceptor.[33] Analogues **26** of the HIV-1 reverse transcriptase inhibitor TSAO-T **27**, in which the thymine is replaced by an acyclic moiety, were synthesized from the corresponding azide **28**. The best activity was found for the *N*-acyl urea derivative **26** (R = NHCONHCOMe) in which the aglycon adopts an H-bonded structure resembling that of thymine.[34] Hydrolysis of 5-bromo-2′-deoxyuridine in aqueous solution has been investigated. *N*-Ureido-2-deoxy-β-D-ribose **29** was detected for the first time and was the major product under basic conditions.[35]



24 R = Ac_4-β-D-Glc- or Ac_3-β-D-GlcNHAc

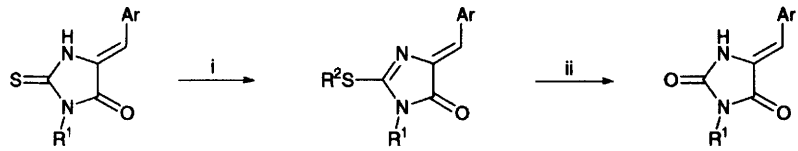
25

26 R = NHCOX, where X = Me, NH_2, NHEt, NHCSNHR[1], NHCOMe *etc.*

27 R = Thy

28 R = N_3

Glucosylation of 5-arylidene-2-thiohydantoin **30** led to the *N*,*S*-bis-glycosylated derivative **31**, but on deacetylation the *N*-glucosylated product **32** was obtained with loss of the *S*-glucosyl residue (Scheme 7); the analogous galacto-



30 R^1 = H
33 R^1 = Me, Ph

31 $R^1 = R^2$ = β-D-Glc*p*(Ac)$_4$
34 R^1 = Me, Ph; R^2 = β-D-Glc*p*(Ac)$_4$

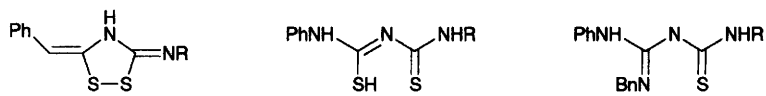
32 R^1 = β-D-Glc*p*

where Ar = heteroaryl, *e.g.* 2-thienyl *etc.*

Reagents: i, acetobromoglucose, K_2CO_2, Me_2CO; ii, NH_3, MeOH

Scheme 7

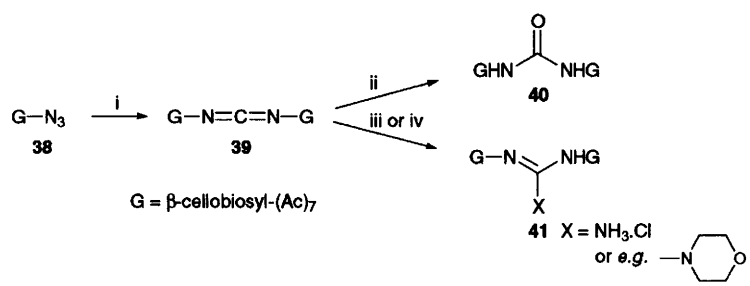
sides were also reported. The *N*-substituted thiohydantoins **33** could be *S*-glycosylated to **34** which, however, gave starting material **33** on attempted deacetylation.[36] The synthesis of the *N*-glucosylimidino-1,2,4-dithiazolidine and *N*-glycosyl-thiocarbamate derivatives **35–37** and related analogues have



35 **36** **37**

R = β-D-Glc*p*(Ac)$_4$

been described.[37] The cellobiosyl azide **38** has been converted into the carbodiimide **39**, then into either the urea **40** or the di- and tri-substituted guanidines **41** (Scheme 8).[38]



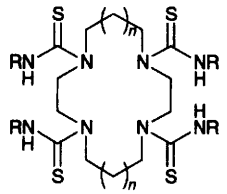
38 **39** **40** **41** X = NH_3.Cl or *e.g.*

G = β-cellobiosyl-(Ac)$_7$

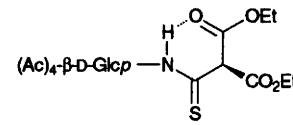
Reagents: i, Ph_3P, CO_2; ii, HOAc; iii, secondary amine; iv, NH_4Cl, DMF

Scheme 8

Reaction of tetraazamacrocycles with tetra-*O*-acetyl-α-D-mannopyranosyl isothiocyanate followed by deacetylation gave the mannosylated cluster derivatives **42**, which showed inhibition of adhesion of type 1 fimbriated *E. coli* to guinea pig erythrocytes.[39] The preparation of similar cyclodextrin-based glucocluster is covered in Chapter 4. Condensation of tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate with various carbon nucleophiles has been investigated. With the anion from diethyl malonate, only the *Z-anti*-isomer **43** was obtained of the four possible configurational and conformational isomers.

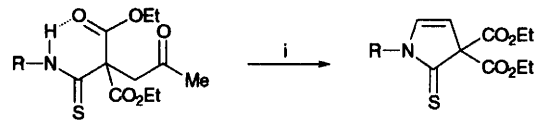


42 $n = 0$ or 1; R = α-D-Man*p*



43

The more complex thioamide **44** was obtained similarly and could be cyclodehydrated to **45** (Scheme 9).[40]



44 R = β-D-Glc*p*(Ac)$_4$

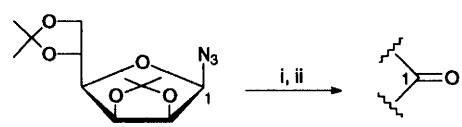
Reagents: i, Ac_2O, H_3PO_4

Scheme 9

Full details (cf. Vol. 30, p. 134, ref. 64) on the conversion of 3-deoxy-3-thioureido-D-glucose and -D-allose into cyclic thiourea derivatives (polyhydroxylated hexahydropyrimidine-2-thiones) have been reported.[41]

2 Azido-sugars

2.1 Glycosyl Azides. – Fully *O*-benzyl-, *O*-benzylidene- or *N*-phthalimido-protected mono-, di- and tri-saccharide thioglycosides were converted to the corresponding β-glycosyl azides in >90% yield by treatment with $TmsN_3$ and MeOTf.[42] Various sugar lactones, *e.g.* **47**, were obtained from the corresponding glycosyl azides, *e.g.* **46**, in two steps involving photobromination and then either photolysis or acid catalysed hydrolysis (Scheme 10).[43] Fullerene

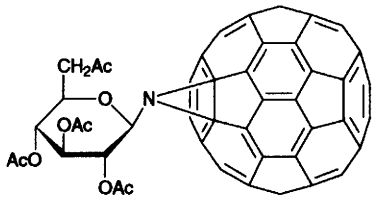


46 **47**

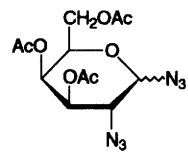
Reagents: i, NBS, *hν*; ii, *hν*, pH 6, C_6H_6 or H_3O^+ (pH 1)

Scheme 10

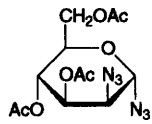
glycoconjugates, *e.g.* **48** (which could be *O*-deacetylated), were prepared by thermal cycloaddition of glycosyl azides with C_{60}. NMR spectroscopic studies indicated the products to be isomeric mixtures presumed to be a result of restricted pyramidal inversion at nitrogen.[44] Manganese(III) acetate catalysed addition of sodium azide to glycal derivatives led to 2-azido-2-deoxy-glycosyl



48

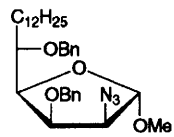


49



50

azides. Tri-*O*-acetyl-D-galactal gave a mixture of the anomeric D-*galacto*-derivatives **49**, whereas the D-glucal analogue gave mixtures containing the D-*manno*-derivative **50** (52%) and anomeric D-*gluco*-isomers.[45]



51

2.2 Other azides. – The 2-azido-L-*gulo*-derivative **51** and related compounds were obtained by displacement of a 2-triflate group with inversion.[46] Azido-transfer using triflyl azide featured in the preparation of pent-4-enyl 2-azido-2-deoxy-β-D-glucopyranoside building blocks (such as the 4,6-di-*O*-benzyl ether) needed for oligosaccharide construction. Benzylidene, benzyl and *tert*-butyldimethylsilyl protecting groups survive this reagent, although care in its use is advised. The required 2-amino-sugar precursors were obtained from the corresponding *N*-tetrachlorophthalimido- or *N*-pent-4-enamido-sugars which could be selectively deprotected in the presence of the pentenyl aglycon.[47] Direct conversion of azido-groups to *tert*-butoxycarbonylamino-groups has been effected in high yield using Me_3P and Boc-ON [2-(*tert*-butoxycarbonyl-oximino)-2-phenylacetonitrile].[48]

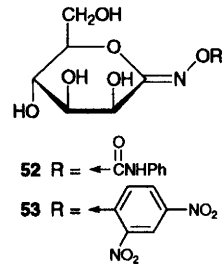
The nickel(II)-catalysed isomerization of 5-azido-5-deoxy-D-glucose and -L-idose is covered in Chapter 2.

3 Diaziridino-sugars

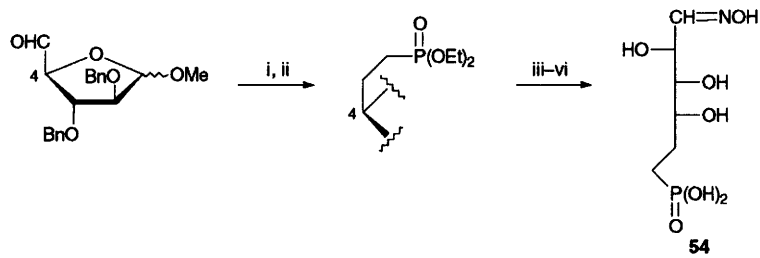
A carbene-generating biotinylated 2-acetamido-2-deoxy-β-D-glucopyranosyl-amide derivative reported previously (Vol. 30, p. 150) has been used to label the catalytic domain of bovine UDP-galactose:*N*-acetylglucosamine β-(1→4)-galactosyl transferase.[49]

4 Oximes, Hydroxylamines and Isonitriles

The potent inhibitors **52** and **53** of β-mannosidase from snails (K_i values of 25 nM and 10 μM, respectively) were synthesized by the general method of



Vasella (*cf.* Vol. 19, p. 110, Vol. 20, p. 113, Vol. 29, p. 156).[50] D-Arabinose 5-phosphate oxime, made from the sugar phosphate and hydroxylamine, is an inhibitor of glucosamine 6-phosphate synthase (K_i 14.3 μM). The methylene-phosphonate analogue **54**, prepared as shown in Scheme 11, was 25-fold less

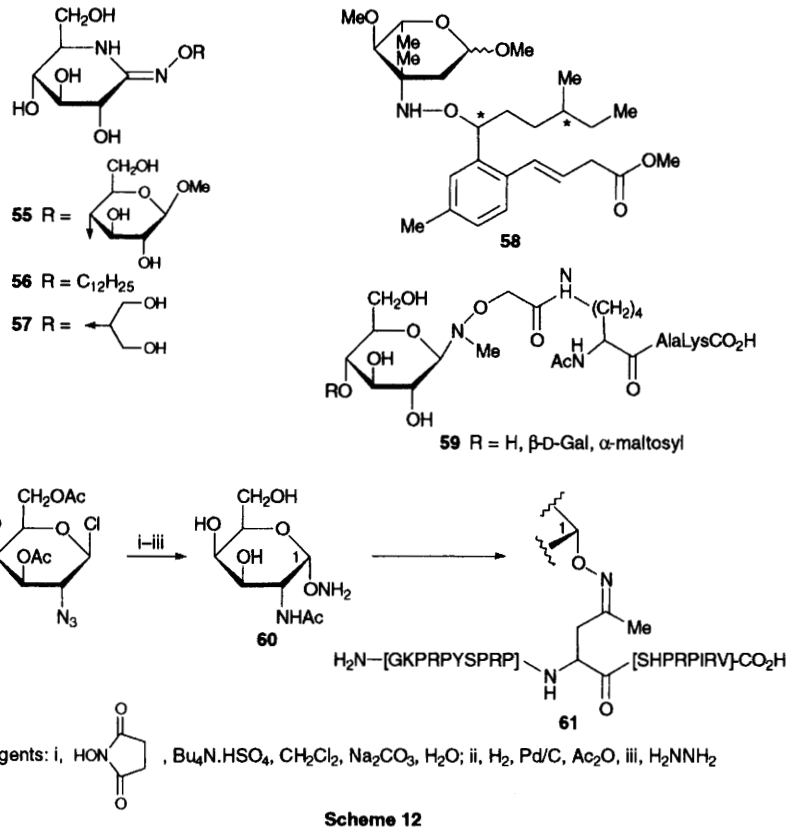


Reagents: i, $[(EtO)_2PO]_2CHNa$; ii, H_2, PtO_2; iii, H_2SO_4, HOAc; iv, Me_3SiBr; v, H_2, Pd/C; vi, NH_2OH

Scheme 11

potent.[51] The oximino-linked derivative **55** was synthesized by two alternative routes, involving either (a) displacement with inversion of a 4-triflate group from a methyl β-D-galactoside derivative by the N-OH group of an otherwise protected oximino-lactam derivative under phase transfer catalysis, or (b) condensation of a methyl 4-*O*-amino-4-deoxy-β-D-glucoside derivative with a thionolactam derivative [using $Hg(OAc)_2$], followed in both cases by removal of the *O*-benzyl protecting groups. The α-anomer of **55**, the isomer with a D-*galacto*-configured lactam and two simpler analogues, **56** and **57**, were also prepared. All were good inhibitors of one glycosidase or another.[52]

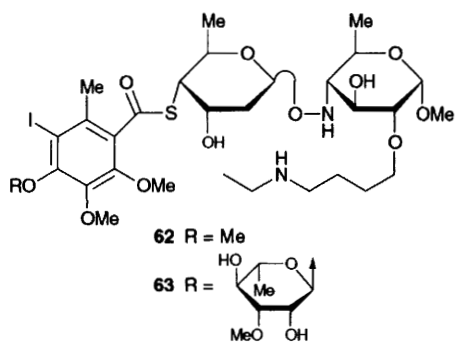
Everhydroxylaminose, a constituent sugar of the antibiotic everninomicin Sch 49088, was isolated as its anomeric methyl glycoside methyl esters **58**, in which the stereochemistry at the asterisked sites remains undetermined.[53] A general method for stereoselective coupling of unprotected oligosaccharides with *N*,*O*-disubstituted hydroxylamines has been applied to the addition of simple *N*,*O*-dialkylhydroxylamines to various mono- and di-saccharides in water or polar organic solvents. This method was then used for the synthesis of model glycopeptides such as **59**.[54] The oxime-linked neoglycopeptide **61** was prepared by synthesis of the *O*-glycosyl-hydroxylamine **60** and condensation with a peptide having a central amino acid residue with a keto-group in the acyclic side-chain (Scheme 12). It is a close analogue of the glycopeptide

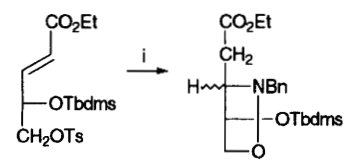


Scheme 12

drosocin, an antibiotic agent produced by insects in response to immune challenge, and had similar glycosylation-dependent activity.[55] The calicheamicin γ_1^I oligosaccharides **62** and **63**, in which the aliphatic chain on O-2 replaces an amino-sugar unit of the natural oligosaccharide, have been synthesized using methodology developed earlier for a model system (*cf.* Vol. 26, p. 130–131, Scheme 11).[56]

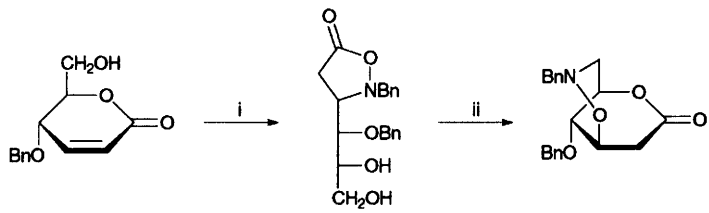
Reaction of *N*-benzylhydroxylamine (or its adduct with acetone) with the D-glyceraldehyde-derived unsaturated ester **64** gave a mixture of the adducts **65**





Scheme 13

(Scheme 13).[57] Reaction of this same hydroxylamine derivative with the unsaturated lactone **66** gave adduct **67**, and this on treatment with triflic anhydride gave the bicyclic lactone **68** by way of a series of rearrangements (Scheme 14).[58]

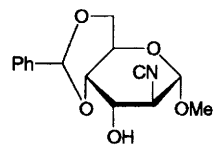


66 **67** **68**

Reagents: i, BnNHOH; ii, Tf_2O, lutidine

Scheme 14

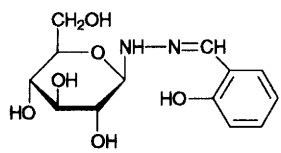
Isonitriles such as **69** were formed from *N*-formyl precursors by dehydration with Et_3N^+-SO_2-$^-NCO_2Me$, a halide-free reagent to which trimethylsilyl ether groups are stable.[59]



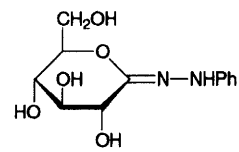
69

5 Hydrazones and Related Compounds

The formation, stability and cleavage (*e.g.* on treatment with benzaldehyde) of the hydrazone, thiosemicarbazone and bis-hydrazone (*e.g.* **70**) derivatives of D-glucose and 2-acetamido-2-deoxy-D-glucose were studied with a view to using such derivatives in the immobilization and then recovery of free sugars. These derivatives were shown by ^{1}H-NMR spectroscopic studies to be mainly in the cyclic form in aqueous solution.[60] Immobilization of the sugar hydrazones was effected by reaction with *o*-hydroxybenzaldehydo-azo-polystyrene beads. Efficient recovery was achieved by treatment with aqueous hydrazine to give the sugar hydrazone, or with ethanolic benzaldehyde or aqueous acetone to give the free sugar.[61] The preparation of adducts of aldose hydrazones with 5-arylidene-2-methylthiohydantoins[62] and of *N*-(glycopyranosyl)hydrazino-sulfonylbenzylidene-2,4-imidazolidinediones[63] have been described.

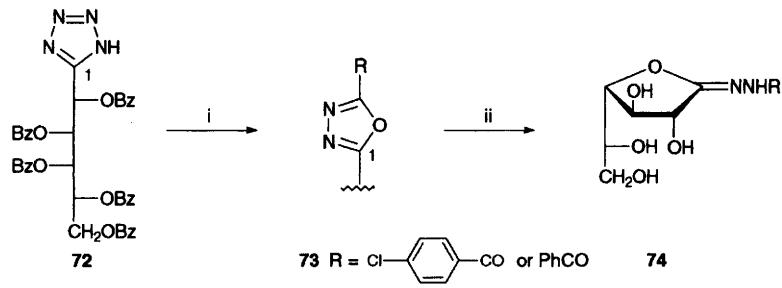


70



71

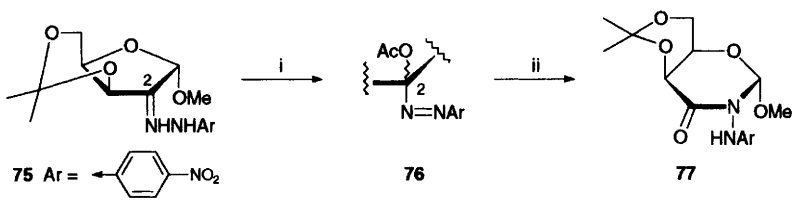
Air oxidation of the phenylhydrazone, *o*-chloro- or 2,4-dinitro-phenylhydrazone derivatives of various aldoses catalysed by cuprammonium ion in ethanolic ammonia gave the corresponding phenylhydrazonolactones rapidly and in good yields. While D-glucose and D-mannose gave hydrazono-1,5-lactones (*e.g.* **71**), D-galactose, D-arabinose and D-fucose gave the corresponding hydrazono-1,4-lactones.[64] Of several hydrazones tested, lactose 2,5-dichlorophenylhydrazone gave the best yield of 2-(2,5-dichlorophenyl)hydrazinecarbaldehyde on oxidative degradation [with H_2O_2, H^+, $(NH_4)_6Mo_7O_{24}$].[65] Aroylation of the tetrazole **72** gave the 1,3,4-oxadiazole **73**, which formed the lactone *N*-aroyl-hydrazone **74** on deacylation (Scheme 15).[66] Oxidation of the



Reagents: i, ArCl; ii, MeOH, Et_3N

Scheme 15

p-nitrophenylhydrazone derivatives of pentofuranosid-2-ulose derivatives (four examples, including **75**, Scheme 16) gave *gem*-azoacetates (*e.g.* **76**) which underwent regiospecific ring expansion on treatment with base to give the corresponding 2-aza-hex-3-ulopyranoside derivatives (*e.g.* **77**).[67]

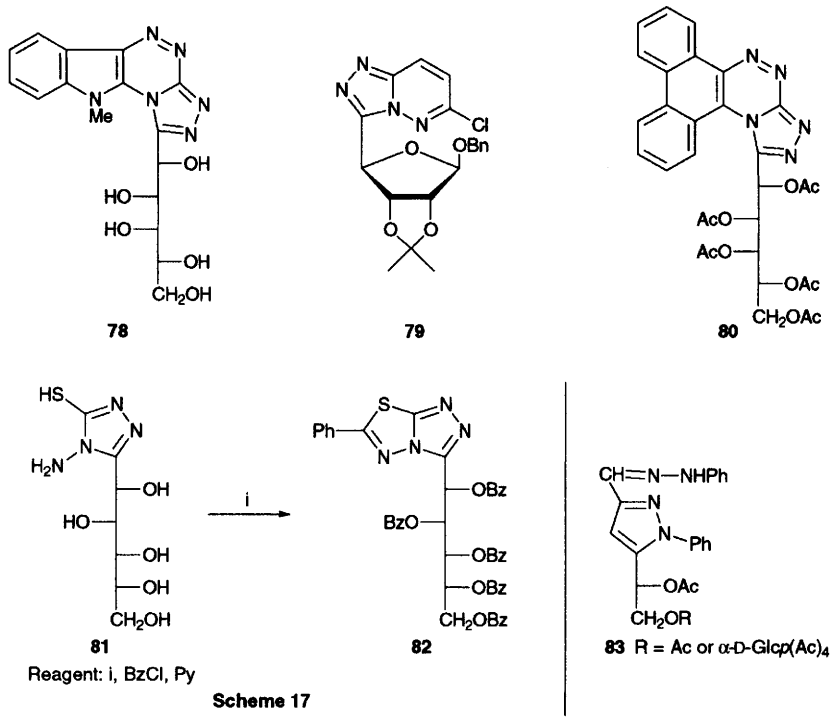


Reagents: i, $Pb(OAc)_4$; ii, NaOMe, MeOH

Scheme 16

Further examples of the formation of complex arylhydrazones of aldoses and aldehydo-sugar derivatives and their cyclization by oxidation either over Pd/C, or with $FeCl_3$ or Br_2, MeOH, *e.g.* to give **78** and **79**, or by *O*-acetylation then dehydration (with $SOCl_2$), *e.g.* to give **80**, have been described.[68–70] The 1,3-dipolar cycloaddition reactions of azomethine imines formed from aldehydo-sugar derivatives and cyclic hydrazines (cf. Vol. 26, p. 133, Scheme 15) have been reviewed.[71]

1,2,4-Triazoles such as **81** were formed from sugar lactones and thiocarbohydrazide in pyridine and were converted to fused triazolothiadiazoles such as **82** on benzoylation (Scheme 17).[72]



Reagent: i, BzCl, Py

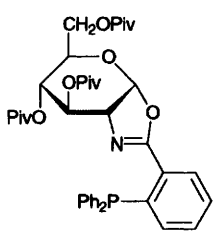
Scheme 17

The mechanism by which osotriazoles are formed on oxidation of sugar phenylosazones (1,2-bis-phenylhydrazones) with copper(II) salts has been investigated.[73] The phenylosazones derived from D-glucose and D-isomaltulose [α-D-Glc-(1→6)-D-Fru] underwent dehydrative cyclizations on reaction with acetic anhydride to form functionalized pyrazoles **83** which could be further modified.[74] The use of an osotriazole as a derivative suitable for characterizing glucose and fructose released on hydrolysis of sucrose has been reviewed.[75]

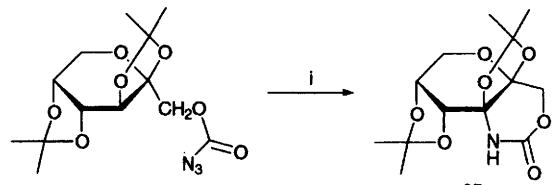
6 Other Heterocycles

The 2-(*o*-diphenylphosphino)phenyloxazoline **84** has been prepared from 2-amino-2-deoxy-D-glucose and used as a chiral ligand in palladium catalysed allylic displacement reactions employing carbon nucleophiles.[76] The useful chiral auxiliary 1,3-oxazin-2-one **85**, was synthesized from D-fructose, the key step being an acylnitrene insertion reaction (Scheme 18).[77]

On deacetonation, the thioureas **86** cyclized to the major bicyclic products **87** and the minor rearranged bicyclic products **88** (Scheme 19).[78] The bicyclic diaza-sugar **89** was obtained by reaction of the acyclic adduct prepared by condensation of D-xylose and 1,3-diaminopropane, with Ph_3P, CCl_4 and Et_3N in DMF.[79] Similar products obtained from L-arabinose and D-ribose were mixtures of interconvertible anomers in solution, but each crystallized in a



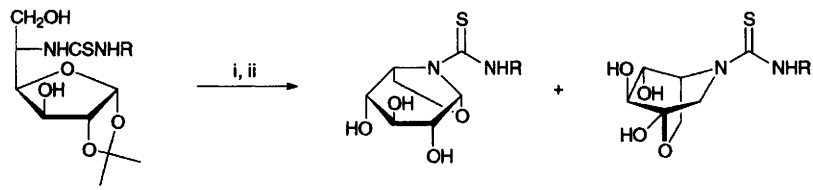
84 Piv = $COCMe_3$



Reagents: i, 147 °C, $Cl_2CHCHCl_2$

85

Scheme 18



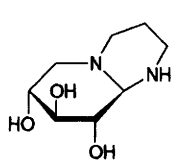
86 **87** **88**

R = Me, Ph, β-D-Glc*p*

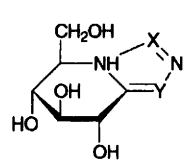
Reagents: i, CF_3CO_2H, H_2O; ii, Resin (OH^-)

Scheme 19

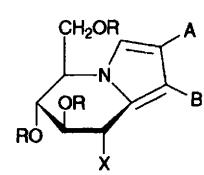
single form.[80] An explanation as to why compounds **90** with X = N or CH and Y = N are strong β-glucosidase inhibitors, but compound **90** with X = N and Y = CH is not, has been deduced from kinetic and X-ray crystallographic studies and semi-empirical calculations.[81] The acetamido-function of the pyrrole **91** was introduced by way of Lewis acid-catalysed displacement of the benzyloxy-group **X** on pyrrole **92** by azide ($TmsN_3$). In this reaction, the D-



89



90



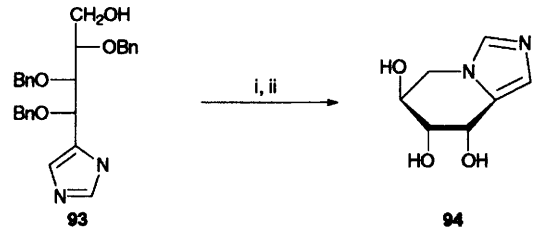
A, B = H, CO_2Me

91 R = H, X = NHAc

92 R = Bn, X = OBn

manno-isomer of **91** is the kinetic product but isomerizes to **91**.[82] Two routes have been reported for the preparation of the imidazolo-L-*lyxo*-piperidinose **94** from D-galactose. Each incorporated modest yielding steps and involved cyclization of acyclic imidazole derivatives such as **93** (Scheme 20). Compound **94** was a poor glycosidase inhibitor.[83] A synthesis of isomeric 1-deoxy-trehalamine derivatives containing 1,3-oxazoline moieties is covered in Chapter 18.

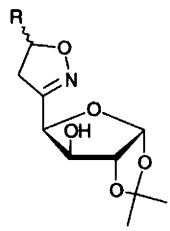
Isoxazoles **95** were obtained as 1:1 mixtures of diastereomers on dipolar cycloaddition of alkenes with the chloramine-T oxidation product of the 5-oxime derivative of 1,2-*O*-isopropylidene-*dialdehydo*-α-D-xylofuranose.[84] Antimony pentachloride-catalysed addition of the diazo-compound **96** to



93 **94**

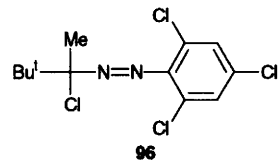
Reagents: i, $BnSO_2Cl$, Py then Ac_2O; ii, H_2, Pd/C

Scheme 20

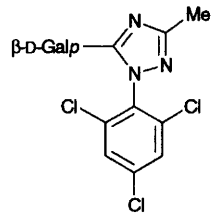


R = Ph, ^{n}BuO, *etc.*

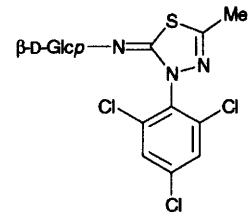
95



96



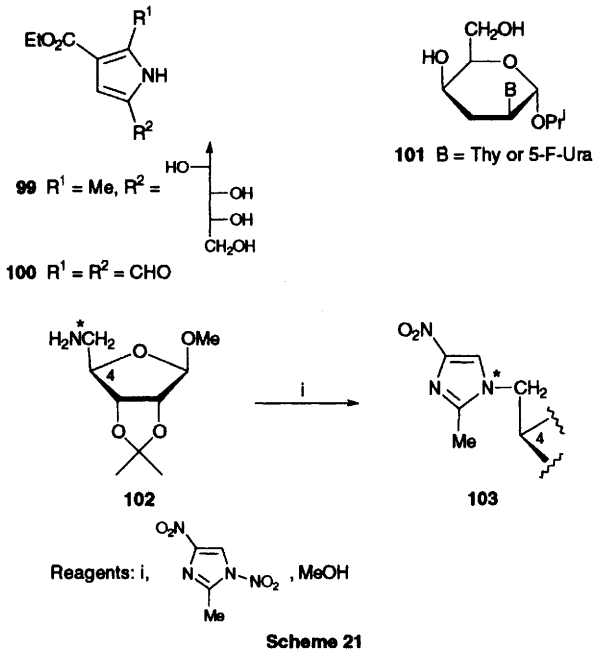
97



98

peracylated glycosyl nitriles or isothiocyanates, followed by deacylation, led to *C*-glycosylated 1,2,4-triazoles (*e.g.* **97**) or *N*-glycosylated thiadiazoles (*e.g.* **98**), respectively. The *tert*-butyl group of **96** is eliminated as butene in the conversion of quaternary ammonium intermediates into neutral products.[85] Tosylation of 4-(D-*gluco*-pentitol-1-yl)-2-phenyl-2*H*-1,2,3-triazole led to the corresponding 3,6-anhydride and its 5-tosylate.[86] Analogous results have been reported for the D-*galacto*-analogues (Vol. 29, p. 162–163, in which the structure is shown with the wrong stereochemistry at C-2).

Cerium(IV) oxidation of compound **99** gave the pyrrole-2,5-dicarbaldehyde **100**.[87] Isodideoxynucleosides **101** were prepared by conjugate addition of silylated bases to a hex-2-en-4-uloside derivative prepared from crystalline isopropyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside, followed by reduction of the 4-keto-group.[88,89] The ^{15}N-labelled imidazole derivative **103** was obtained by condensation of an *N*-nitro-imidazole with the [5-^{15}N]-5-amino-derivative **102** (Scheme 21) obtained by displacement of a 5-tosylate group with [^{15}N]-phthalimide ion. Further imidazole-substituted sugar derivatives have been prepared by sulfonate or Mitsunobu displacement reactions of primary hydroxy groups (cf. Vol. 30, p. 125–126, ref. 18).[90]



Scheme 21

References

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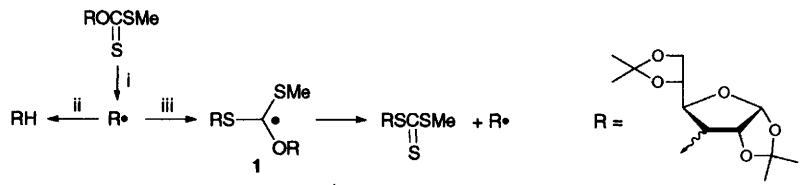
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11
Thio- and Seleno-sugars

The construction and behaviour of thiosugar-containing oligosaccharides[1] and the synthetic applications of selenium-containing sugars[2] have been reviewed, and a review on the use of aldolases in synthesis included a section on thiosugars.[3]

In a new modification of the Barton-McCombie deoxygenation, sugar xanthates were reductively cleaved by heating in boiling 2-propanol in the presence of equimolar quantities of dilauroyl peroxide. On replacement of the 2-propanol by benzene O-to-S rearrangement *via* adduct radicals, such as **1**, became the main-reaction, as indicated in Scheme 1.[4]

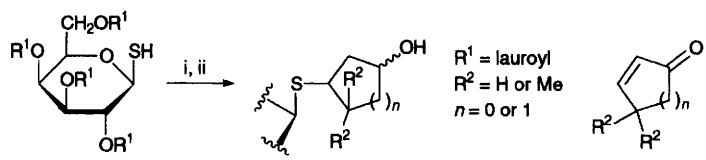


1

Reagents: i, dilauroyl peroxide; ii, Δ, PrⁱOH; iii, Δ, benzene

Scheme 1

Tetra-*O*-lauroyl-1-thio-β-D-galactopyranose (**2**) reacted with a panel of Michael acceptors, *e.g.* enones **4**, to give a library of ketones, which were reduced to alcohols **3** (Scheme 2) or reductively aminated, then deacylated. For the purification of the reaction mixtures a novel strategy was used which involved adsorbtion onto C18 silica, extraction of the excess of reagents by washing with methanol, then eluting the desired products with pentane.[5]



2 **3** **4**

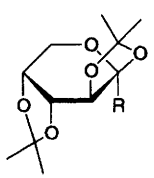
Reagents: i, **4**, CH_2Cl_2, Et_2NH; ii, $NaBH_4$

Scheme 2

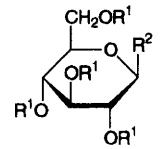
A comprehensive structure-activity relationship study on the anticonvulsant topiramate [2,3:4,5-di-*O*-isopropylidene-D-fructopyranose 1-sulfamate (**5**), see

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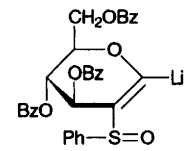
Vol. 27, pp. 102–103, ref. 100; Vol. 31, p. 98, ref. 8] described, *inter alia*, the synthesis of the isosteric analogue **6** by a Wadsworth-Emmons olefination between aldehyde **7** and $(BnO)_2P(O)CH_2SO_3Et$, followed by hydrogenation of the double bond and ammonolysis of the ethyl sulfonate.[6] The synthesis of the first anomeric sulfimides **9** by treatment of ethyl 1-thioglucopyranosides **8** with chloramine T has been reported.[7] The use of compounds **9** and of pyrimidin-2-yl 1-thiohexopyranosides as glycosyl donors is covered in Chapter 3, as is the application of the 1-*C*-lithiated 2-phenylsulfinyl-D-glucal derivative **10** to the synthesis of a *C*-linked trehalose. An efficient new method for the hydrolysis of thioglycosides is referred to in Chapter 2.



5 R = $CH_2OSO_2NH_2$
6 R = $CH_2CH_2SO_2NH_2$
7 R = CHO

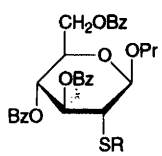


R^1 = Ac, Bn, Piv *etc.*
8 R^2 = SEt
9 R^2 = 

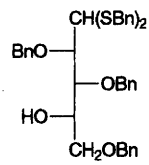


10

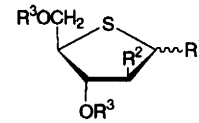
Propyl 2-thioglucopyranoside derivative **12** has been obtained from a *manno*-configured 2-triflate *via* thioacetate **11**; de-*S*-acetylation proved unexpectedly difficult but was eventually achieved by use of 2% HCl in anhydrous $MeOH/CH_2Cl_2$.[8] (See below for the synthesis of *S*-linked disaccharides from **12**).



11 R = Ac
12 R = H



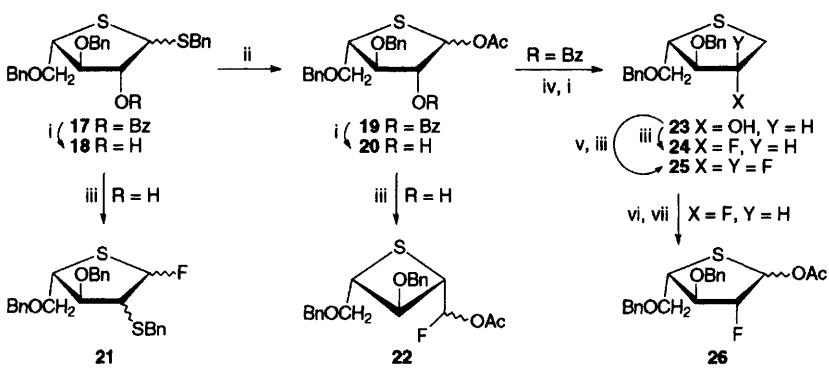
13



14 R^1 = SBn, R^2 = OBn, R^3 = Bn
15 R^1 = SBn, R^2 = H, R^3 = Bn
16 R^1 = OAc, R^2 = H, R^3 = *p*-Tol

In a new version of the well known method for making 1,4-dithioglycofuranosyl derivatives from 4-OH-unprotected dialkyl dithioacetals (see, for example, Vol. 31, Ch. 11, ref. 16; Vol. 25, p. 138, Scheme 4) the ring-closure **13**→**14** has been effected with PPh_3/I_2/imidazole.[9] A detailed procedure for the efficient and reproducible conversion of compound **15** (obtained by use of the original method involving 4-*O*-mesylation) to **16**, which is suitable for use in the synthesis of 2′-deoxythiouridine derivatives, has been published.[10] Attempts to introduce a fluorine atom at the 2-position of compound **18**, also obtained *via* a mesylate,[11] or its 1-*O*-acetyl analogue **20** were unsuccessful (Scheme 3); on exposure to DAST, the former underwent rearrangement, the latter ring-contraction, to give **21** and **22**, respectively; participation by the ring

sulfur atom to form episulfonium ions was implied. These problems were avoided by temporary removal of the anomeric substituent (**17**→**19**→**23**→**24**), which was reinstated by oxidation to the sulfone and subsequent Pummerer reaction (**24**→**26**).[11,12] Introduction of two fluorine atoms at the 2-position of **23** to give **25** was achieved by Moffat oxidation, followed by DAST treatment.[11] Fluorination at the 3-position of **27** by use of DAST proceeded uneventfully, but with retention of configuration, to give **28**.[13] The 2-*O*-benzylated derivative of compound **23** has also been prepared by reaction of dimesylate **29** with Na_2S.[14] The synthesis of novel nucleoside analogues from **24**, **25**, **26**, **28** and similar thiosugar derivatives is covered in Chapter 20.



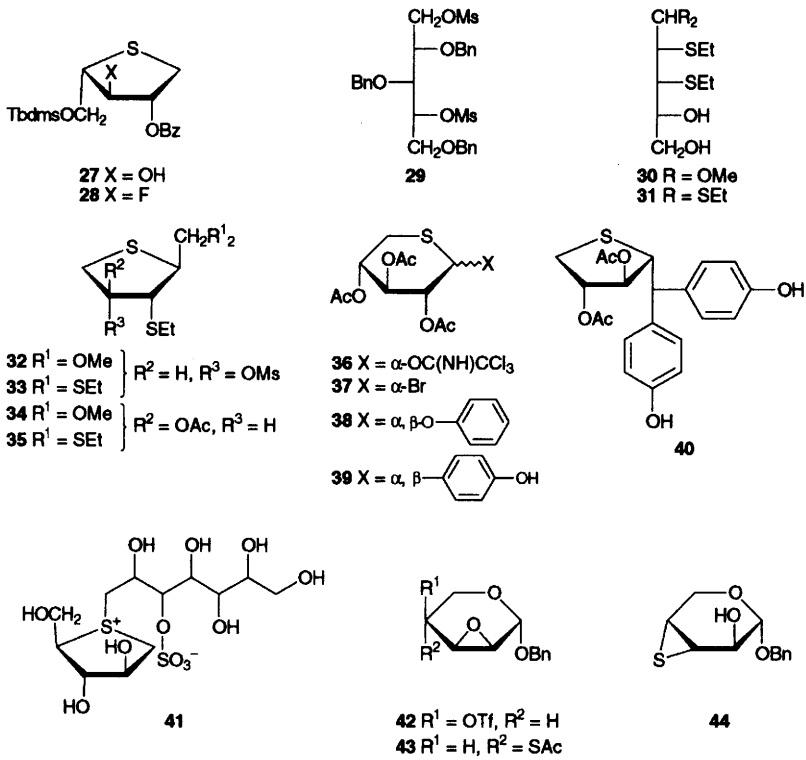
Reagents: i, MeO^-, MeOH; ii, $Hg(OAc)_2$; iii, DAST; iv, $EtSiH_3$, TmsOTf; v, DMSO, Ac_2O; vi, *m*CPBA; vii, Ac_2O

Scheme 3

Exposure of 2,3-diethylthio-D-ribose di-*O*-acetal **30** and its dithioacetal analogue **31** to standard mesylation conditions (MsCl/Py) then to sodium acetate furnished the 2,5-anhydrothiosugar products **34** and **35** *via* mesylates **32** and **33**, respectively.[15] Tri-*O*-acetyl-5-thio-α-D-xylopyranosyl trichloroacetimidate (**36**) in the presence of $BF_3.OEt_2$ and the corresponding glycosyl bromide **37** in the presence of ZnO reacted with phenol as expected to afforded mixtures of *O*-aryl 5-thioglycosides **38** and *C*-aryl 5-thioglycosides **39**. Under catalysis by $ZnCl_2$, however, bromide **37** gave mainly 1,1-*C*-diaryl 2,5-anhydrothiosugar derivative **40** *via* a sulfur transannular participation pathway.[16] Reactions of **36** and **37** with several other electron-rich aromatics[17] and with heterocycles, such as furan and thiophene,[18] proceeded similarly.

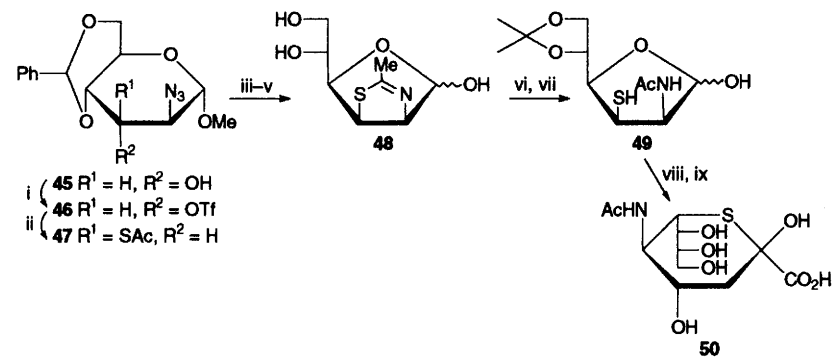
Kotanol (**41**), a potent inhibitor of intestinal disaccharidases, and related to salacinol, the active principle of a traditional Indian antidiabetic from *Salacia reticulata* (see Vol. 31, Chapter 11, ref. 29), has been isolated from the same source.[19]

Several *cis*-oriented anhydro-triflates have been converted to *trans*-oriented hydroxy-episulfides by treatment with KSAc in DMF, followed by MeONa/MeOH (*e.g.* **42**→**43**→**44**).[20] The 2-acetamido-2-deoxy-3-thio-D-mannofuranose derivative **49** was obtained from the known methyl 2-azido-D-altropyranoside derivative **45** by way of triflate **46**, thioacetate **47** and thiazolidine **48**, and then converted to 6-thio-*N*-acetylneuraminic acid (**50**), as indicated in



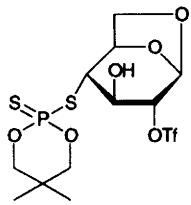
Scheme 4; the three-carbon-extension at the reducing end of **49** was achieved by Ni(II)-mediated condensation with oxaloacetic acid and subsequent decarboxylation.[21]

The sugar thiophosphoryl derivative **51** has been subjected to ^{13}P-NMR analysis; its X-ray structure is referred to in Chapter 22.[22]

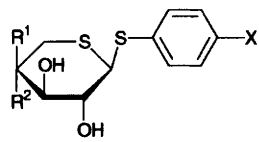


Scheme 4

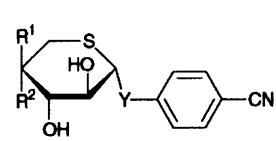
The known route to the phenolic 1,5-dithio-D-xylopyranoside beciparcil (**52**) (see Vol. 31, Chapter 11, refs. 17–20) has been optimized by improvements in the synthesis of the glycosyl donor as well as in the glycosylation reaction. Bromide **37** in conjunction with zinc oxide as promoter gave better yields of the required β-anomer than did trichloroacetimidate **36** or the corresponding 1-*O*-acetate.[23] In addition, several new analogues of this antithrombotic agent have been synthesized. A series of aglycon-modified compounds **53**,[23] the L-*arabino*-isomer **54** and the 4-acetamido-4-deoxy-L-*arabino*-analogue **55**[24] were obtained by modification of the parent compound **52**. Independent syntheses of **54** and its L-enantiomer **56** from 5-thio-D- and -L-arabinose diethyl dithioacetal derivatives, respectively, have also been reported.[25] The *O*-glycosidic analogue **57** was obtained by glycosylation of the enantiomer of bromide **37**.[26] The preparation of carbocyclic analogues of beciparcil (**52**) and of the closely related antithrombotic iliparcil by Vogel's 'naked sugar' method is referred to in Chapter 18.



51

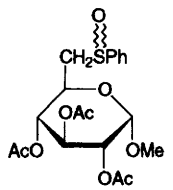


52 R^1 = H, R^2 = OH, X = CN
53 R^1 = H, R^2 = OH
X = $C(S)NH_2$, C(NH)SMe, $C(NH)NHNH_2$ *etc.*
54 R^1 = OH, R^2 = H, X = CN
55 R^1 = NHAc, R^2 = H, X = CN

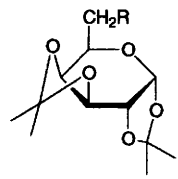


56 R^1 = H, R^2 = OH, Y = S
57 R^1 = OH, R^2 = H, Y = O

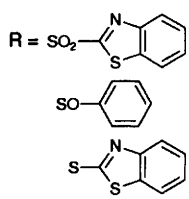
Treatment of several methyl 6-phenylthio-D-hexopyranoside derivatives with *m*CPBA at −65 °C provided diasteromeric mixtures of sulfoxides, *e.g.* **58**, which were separable into the pure 6-(*S*)- and 6-(*R*)-isomers.[27] The NMR and X-ray analyses of these compounds are referred to in Chapters 21 and 22, respectively. Chapter 22 also contains a reference to the crystal structures of diacetonegalactose derivatives **59**.

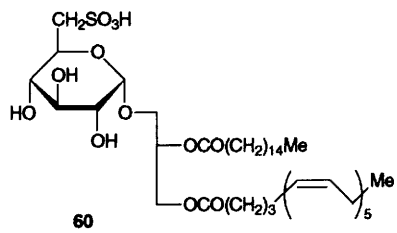


58



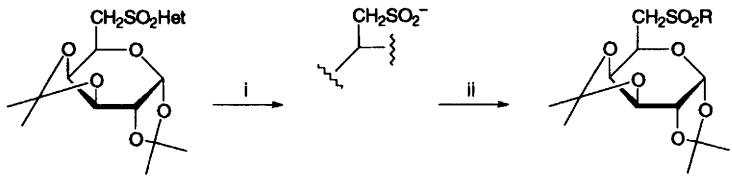
59





60

The sulfoquinovosyldiacylglycerol **60**, isolated from the seaweed *Gigartina tenella*, is a potent inhibitor of eukaryotic DNA polymerase.[28] A series of primary sugar alkylsulfones have been obtained from the corresponding heteroaryl sulfones which are prone to *ipso*-substitution (see Vol. 29, p. 170, ref. 4). Examples are given in Scheme 5.[29] Improved syntheses of allyl and α-D-glycer-1′-yl sulfoquinoside are covered in Chapter 3.



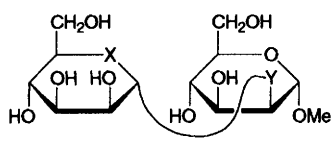
Het = benzothiazol-2-yl, 2-pyrimidyl,1-phenyltetrazol-5-yl, *etc.*
R = Me, Pr, All, farnesyl, *etc.*
X = Br or I
Reagents: i, MeO^-, MeOH; ii, RX, MeOH

Scheme 5

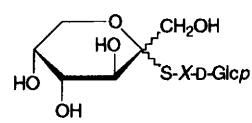
Fully protected 6-deoxy-6-sulfonato- and 6′-deoxy-6′-sulfonato-cellobioside have been prepared from disaccharide precursors with free hydroxyl groups in the required positions by consecutive treatment with TsCl/Py, KSAc and H_2O_2.[30]

Glycosylation of propyl 2-thioglucopyranoside derivative **12** with tetra-*O*-acetyl-5-thio-α-D-glucopyranosyl trichloroacetimidate gave a separable 1.6:1 mixture of peracylated propyl 2,5′-dithio-β-kojibioside (α-interglycosidic linkage) and peracylated propyl 2,5′-dithio-β-sophoroside (β-interglycosidic linkage).[8] The heteroanalogues **61–64** of α-D-Man*p*-(1→2)-α-D-Man*p*OMe have been assembled from sulfur-containing monosaccharide precursors. Compounds **61**,[31] **62**[31] and **63**[32] were made by use of tetra-*O*-acetyl-5-thio-α-D-mannopyranosyl trichloroacetimidate as glycosyl donor, compound **64**[31] by use of tetra-*O*-acetyl-1-thio-α-D-mannopyranose in the displacement of a triflate group from a glucoside derivative. The latter method has also been employed in the synthesis of 1′-thio-trehalulose **65** and its 1′-epimer **66**.[33] *N*-Acetyl-4′-thio- and -6′-thio-β-D-glucosaminyl donors, obtained by standard procedures, have been used in the preparation of 4′-thio- and 6′-thio-β-D-Glc*p*NAc-(1→6)-β-D-Glc*p*OMe.[34]

Glucosylated deoxymannojirimycins containing a sulfur atom in the glycosidic linkage and in the glucose moiety, respectively, have been prepared as potential *endo*-α-D-mannosidase inhibitors.[35]



61 X = Y = S
62 X = S, Y = O
63 X = S, Y = NH
64 X = O, Y = S



65 *X* = α
66 *X* = β

The disodium salt of 6,6β-dithio-(,β-trehalose reacted with 6^1-*O*-tosyl-cyclomaltoheptaose to give a dimer comprising two 6-thiocyclodextrin molecules linked by a trehalose bridge.[36] The synthesis of a trisaccharide containing a sulfur-linked β-L-Fuc*p*-(1(3)-D-Glc*p*NAc moiety is referred to in Chapter 4, and that of calicheamycin oligosaccharide analogues which contain a 2,6-dideoxy-4-thio-D-*ribo*-hexopyranose residue, is covered in Chapter 10.

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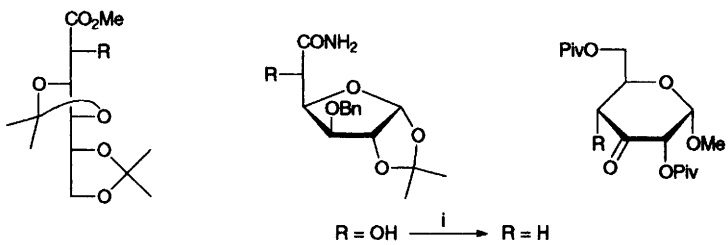
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12
Deoxy-sugars

The novel sugar 6-deoxy-4-*O*-methyl-L-glucose is a constituent of a macrolide antibiotic obtained from *Nocardiopsis* sp.,[1] and the sugar component of vicenistatin, an anti-tumour antibiotic, is 2,4,6-trideoxy-4-*N*-methylamino-D-*ribo*-hexose.[2] Two other new antibiotics which contain deoxy-sugar components are mentioned in Chapter 19.

In a practical modification of the Barton-McCombie radical reduction of *O*-xanthate esters to deoxy-sugars, lauroyl peroxide in isopropanol is used in place of Bu_3SnH – thus avoiding problems of removing tributyltin contaminants.[3] Another modified procedure for effecting the same reaction has utilized $Ph_3P.BH_3$ in place of Bu_3SnH.[4] A one-step deoxygenation of α-hydroxy-esters, amides, lactones, nitriles, and ketones has been effected using Ph_3P/I_2/imidazole (Scheme 1).[5]



Reagents: i, Ph_3P, I_2, imidazole

Scheme 1

A synthesis of 2-deoxy-L-ribose has employed the asymmetric mono-epoxidation of divinylmethanol as a key step,[6] and a synthesis of 2,3,6-trideoxy-D-*erythro*-hexose features the asymmetric hydroboration of a dihydropyran (Scheme 2).[7] Monodeoxygenated analogues of trehalose have been used as glycosyl acceptors in the synthesis of deoxygenated β-maltosyl-(1→4)-tre-



Reagents: i, Isopinocamphenylborane; ii, NaOH

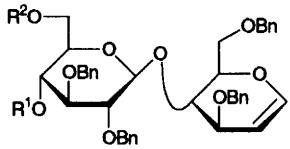
Scheme 2

Carbohydrate Chemistry, Volume 32
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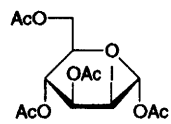
halose,[8] and 4′,6′-, 3,3′- and 6,6′-dideoxy-maltose derivatives have been used as glycosyl donors in reactions with an appropriate trehalose derivative to give the corresponding dideoxy β-maltosyl-(1→4)-trehaloses.[9]

Cellobiose-derived glycals **1** and **2** have been polymerized in the dark in the presence of iodonium dicollidine perchlorate to give products with a degree of polymerization of up to 12. Reductive removal of the iodine atoms and subsequent deprotection gave 2-deoxycellobiosyl polymers.[10] Some 3- and 4-deoxy GlcNAc derivatives and disaccharides have been prepared to study the substrate specificity of β-(1→4) galactosyltransferase,[11] and some 6^3-deoxy-malto-pentaoses and -tetraoses have been prepared enzymically.[12]

Some further examples of NIS-promoted glycosylation of glycals have been described, and glycosyl acetate **3** has been used as a glycosyl donor for the eventual synthesis of 2-deoxy glycosides.[13,14] Phosphonium salts of diacetoxy-iodine have been used as alternative reagents for the production of 2-iodoglycosyl acetates from glycals.[15]

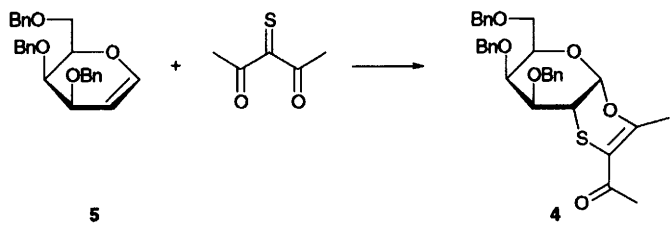


1 R^1 = H, R^2 = Bn
2 R^1 = Bn, R^2 = H



3

The 2-thio-derivative **4**, synthesized from glycal **5** (Scheme 3), has been used as a glycosyl donor, and Raney nickel desulfurization of the products afforded 2′-deoxy-disaccharides.[16]



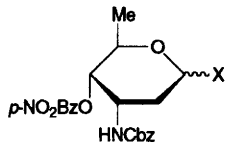
5 **4**

Scheme 3

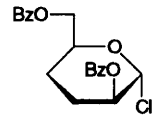
Conditions have been found to effect a one-pot mercuration–reductive demercuration that converts a wide variety of glycal derivatives into the corresponding 2-deoxy sugar derivatives. The conditions [$Hg(OAc)_2$, THF, H_2O, 0 °C; then $NaBH_4$, H_2O, 1 min; then CO_2] are compatible with ester, ether and silyl protecting groups and glycosidic linkages.[17]

The acid-catalysed addition of 1,3-di-*O*-benzylglycerol to tri-*O*-acetyl-D-glucal followed by hydrogenation of the hex-2-enopyranoside product has afforded the corresponding glycerol 2,3-dideoxy-glycoside.[18] The use of some *S*-(2-deoxyglycosyl)phosphorodithioates as glycosyl donors is discussed in Chapter 3, and the 2-deoxy-glycosyl donors **6** and **7** have been prepared in a lengthy synthesis from methyl glucoside.[19]

A synthesis of 2-deoxy-L-threose from L-ascorbic acid has utilized standard techniques,[20] while 1,2,3-tri-*O*-acetyl-5-deoxy-L-lyxofuranose has been prepared from L-lyxose and used in the synthesis of nucleosides.[21] The 3,4-dideoxy-hexosyl chloride **8** has been prepared and used in the synthesis of di- and tri-saccharides.[22]



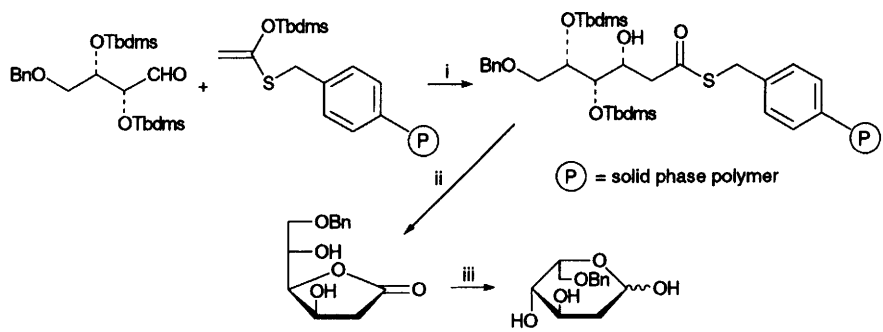
6 X = OH
7 X = SEt



8

A synthesis of 1-deoxy-D-xylulose has utilized a Sharpless asymmetric dihydroxylation of an appropriate alkene,[23] and 1-deoxy-D-xylulose, ^{13}C-labelled separately at C-2 and -3 or C-2 and -4, has been prepared using 1-deoxy-D-xylulose synthase.[24] A chemical synthesis of 1-deoxy-D-xylulose 5-phosphate has employed diethyl tartrate as starting material, whereas an alternative enzymic synthesis has utilized 1-deoxy-D-xylulose 5-phosphate synthase.[25]

A general synthesis of 2-deoxy-monosaccharide derivatives is exemplified by the synthesis of 6-*O*-benzyl-2-deoxy-L-gulose (Scheme 4).[26]

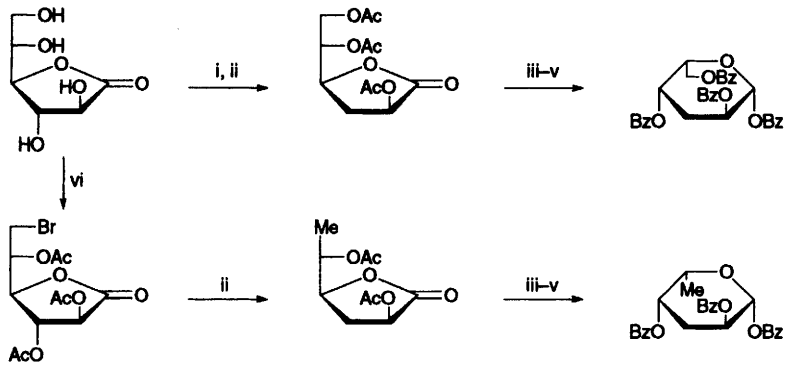


Reagents: i, $BF_3.OEt_2$; ii, Bu_4NF, HOAc; iii, DIBAH

Scheme 4

Cycloheptatriene has been converted separately by long multi-step linear sequences into 2-deoxy-D-*xylo*-hexose and 2-deoxy-D-*arabino*-hexose.[27]

A practical synthesis of 2,6-dideoxy-D-*lyxo*-hexose from D-galactose in eight steps and 25% overall yield has been reported,[28] as have facile new syntheses of L-fucose, 3-deoxy-L-galactose and 3,6-dideoxy-L-galactose from L-galactono-1,4-lactone (Scheme 5).[29]



Reagents: i, Ac_2O; ii, H_2, Pd/C, Et_3N; iii, Disiamylborane; iv, NaOMe; v, BzCl, py; vi, HBr/HOAc

Scheme 5

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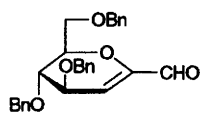
13
Unsaturated Derivatives

1 General

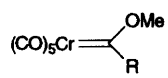
A review has appeared covering the period of June 1996 to June 1997 on the synthesis of thiols, selenols, sulfides, selenides, sulfoxides, selenoxides, sulfones and selenones. Some of the reactions described include additions to glycals and the formation of several *C*-glycosides with unsaturated side chains.[1]

2 Pyranoid Derivatives

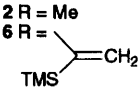
2.1 1,2-Unsaturated Compounds and Related Derivatives. – The α,β-unsaturated aldehyde **1** treated with the chromium carbene complex **2** gave the new conjugated complex **3**;[2] treatment of **3** with trimethylsilylacetylene followed by acetylation resulted in benzannulation to give the aryl *C*-glycoside **4**. Several examples are given; the acetylenic *C*-glycoside **5** reacted with the related chromium carbene **6** to give the aryl *C*-glycoside **7** (see Chapter 3).

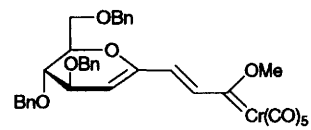


1

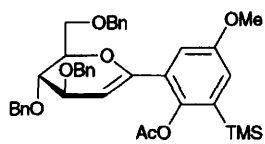


2 R = Me
6 R =

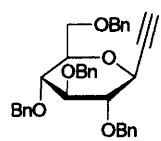




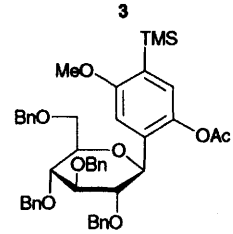
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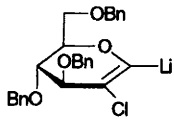
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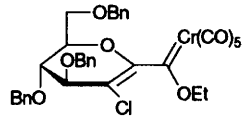
7

2-Chloro-tri-*O*-benzyl-D-glucal has been metallated with *sec*-butyllithium to give the alkenyl lithium species **8**, which has been treated with chromium-hexacarbonyl and Meerwein's salt to produce the carbene complex **9**.[3] Reaction with acetylenes and oxidation with CAN/nitric acid produced the annullated compounds **10** (see Chapters 14 and 17).

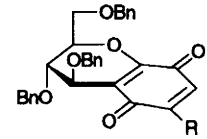
Carbohydrate Chemistry, Volume 32
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8

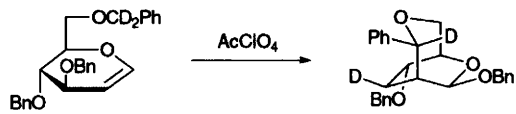


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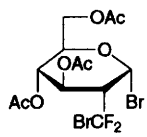
10

A report confirming the presence of a hydride shift in a previously described rearrangement[4] has appeared.[5] Specifically deuterated tri-*O*-benzyl-D-glucal, when treated with a Lewis acid, loses the benzyloxy group at C-3, hydride then migrates from the O-6 benzyl group to C-3 and the new oxonium ion closes onto C-2 to form the bicycle. Addition of benzyloxy then completes the rearrangement to give the bicyclic benzyl glycoside (Scheme 1).

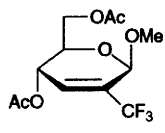


Scheme 1

The elements of CBr_2F_2 can be added across the double bond of tri-*O*-acetyl-D-glucal to give the branched chain glucosyl bromide **11**,[6] which can be converted to the methyl glucoside and the $CBrF_2$ group reduced to CHF_2 with Bu_3SnH or treated with fluoride to give the 2-deoxy-2-*C*-trifluoromethyl-2,3-alkene **12** (see Chapter 14). The same sequence could be performed with tri-*O*-pivaloyl-D-galactal but requires sonication during the first step to improve the solubility of the starting material and increase the rate of reaction.

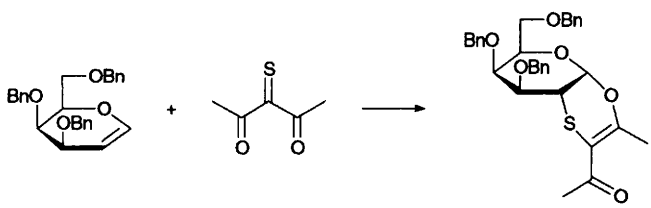


11



12

A preliminary report on the preparation of 2-deoxy-β-glycosides[7] from glycals has been expanded to a full paper.[8] The key step is the cycloaddition reaction between the glycal and the diacylthione which gives the adduct, which is methylenated at the carbonyl position (Scheme 2). This compound is a

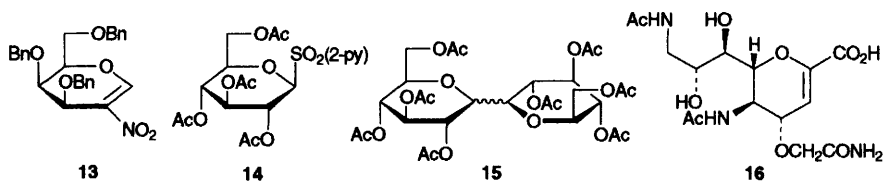


Scheme 2

useful glycosyl donor, which can later be desulfurized (see Chapter 12) to give the 2-deoxy-β-glycosides. The stereochemical outcome of this cycloaddition reaction has been investigated further[9] and the adducts are *anti* to the allylic substituent. Furanoid glycals react similarly. The cycloaddition was studied quantitatively and the reactivity correlated with the HOMO–LUMO gap between the glycal and the heterodienic species.

An oxidative glycosylation of glycals using diphenyl sulfoxide, triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine has been studied (see Chapter 3).[10] High diastereofacial selectivity in the Pd-on-carbon catalysed hydrogenation of a D-glucose derived *endo*-alkene bearing a CF_3 group has been observed.[11]

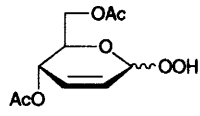
The 2-nitro-D-galactal derivative **13** has been prepared from tri-*O*-benzyl-D-galactal by treatment with nitric acid and acetic anhydride followed by base elimination.[12] It undergoes conjugate additions of alcohol to give glycosides, and the nitro group may be reduced (see Chapter 9). Tri-*O*-acetyl-D-glucal was produced in 92% yield when the pyridyl sulfone **14** was reduced with SmI_2 in THF.[13] If HMPA was added the glucosyl radical dimerized to give **15** (74%) as a mixture of three isomers at the anomeric positions (see Chapter 3) with some glucal (20%) also produced.



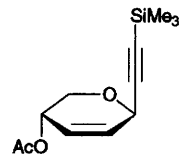
In the search for new inhibitors of sialidase from influenza virus, the *N*-acetylneuraminic acid analogue **16** was prepared by a chemoenzymatic synthesis from 2-acetylamino-6-azido-2,6-dideoxy-D-glucose.[14] 6-*O*-Pivaloyl-D-glucal has been made from D-glucal by the dibutyltin oxide method.[15] Direct pivaloylation gives a mixture of 3,6-diester and the 3- and 6-monoesters. [U-^{13}C]-D-Glucose has been transformed into [U-^{13}C]-D-glucal and [U-^{13}C]-D-galactal, and these compounds were then used in Danishefsky solid-phase synthesis of oligosaccharides.[16]

C-Linked disaccharides derived from tri-*O*-acetyl-D-glucal, -galactal, and 3,4-di-*O*-acetyl-L-fucal have been dihydroxylated with good stereoselectivity.[17] 4,6-*O*-Benzylidene-3-deoxy-3-*C*-nitro-D-gulal has been found to be thermodynamically more stable than its 3-epimer. This was predicted theoretically and determined by finding conditions for epimerization and C-3 deuteration[18]

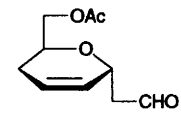
2.2 2,3-Unsaturated Compounds. – *2.2.1 Syntheses Involving Allylic Rearrangements of Glycals.* – Tri-*O*-acetyl-D-glucal was oxidized with H_2O_2 and MoO_3 to give the 1-hydroperoxy-D-*erythro*-hex-2-enose **17** in 52% yield as a mixture of anomers.[19] Benzyl ethers, and glycals other than glucal, gave only low yields. Ethyl 4,6-di-*O*-benzyl-α-D-*erythro*-hex-2-enoside gave the corre-



17 R = Ac
18 R = Bn



19

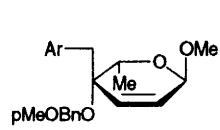


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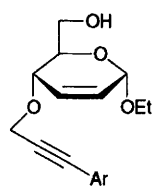
sponding hydroperoxy derivative **18** in 60% yield under the same conditions. These hydroperoxides were used to oxidize allylic alcohols and sulfides (see Chapter 24).

1,2-Bis(trimethylsilyl)acetylene was added to di-*O*-acetyl-D-xylal with $TiCl_4$ catalysis to give the *C*-glycoside **19** with good stereoselectivity.[20] Di-*O*-acetyl-L-arabinal gave a similar product with the opposite anomeric stereochemistry. The methodology could be used to prepare several *C*-glycosides (see Chapter 3). During the synthesis of the blue-green algal product scytophycin C,[21] 3,6-di-*O*-acetyl-D-glucal was subjected to a Barton deoxygenation at C-4 and treated with a silyl enol ether and $LiClO_4$ to give the γ,δ-unsaturated aldehyde **20**. This aldehyde was elaborated into a major portion of the macrocyclic lactone section of scytophycin C (see Chapter 3).

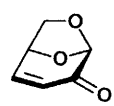
2.2.2 Other Syntheses and Reactions. – During the synthesis of an advanced precursor for daunomycinone (see Chapter 14), a 2,3-orthoacetate, ultimately derived from L-rhamnose, was heated with acetic anhydride to give the 2,3-unsaturated compound **21**.[22] When ethyl 2,3-dideoxy-4-*O*-propargyl-α-D-*erythro*-hex-2-enoside was treated with aromatic iodides and $Pd(OAc)_2/Ph_3P$, two different products were obtained depending on the temperature.[23] At room temperature a Heck reaction gave the substituted propargylic ether **22**, while at 80 °C tandem Sonogashisa/Heck reaction gave a bicyclic glycal. The addition of Grignard reagents with transition metal catalysis to 4-(*tert*-butyl)phenyl 4-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enoside gave *C*-glycosides. $PdCl_2$ gave α-products while $NiCl_2$ gave β-products.[24]



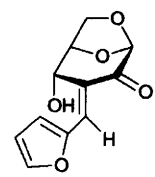
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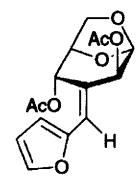
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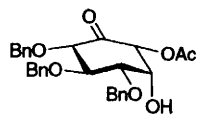


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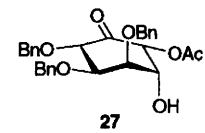
2.3 3,4-Unsaturated Compounds. – The levoglucosenone **23** was treated with furfural and aqueous $NaHCO_3$ to give the α,β-unsaturated **24**, which was further elaborated to give the diacetate **25**.[25]

2.4 5,6-Unsaturated Compounds and Exocyclic Glycals. – A study has been published of the regio- and stereo-chemistry of the 1,3-cycloaddition reaction

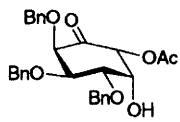
between ethyl (*E*)-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranuronate and various aromatic nitrones and nitrile oxides.[26] A variety of cyclohexanones were obtained by $PdCl_2$-mediated Ferrier II cyclizations of methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-hex-5-enopyranosides.[27] These pyranosides were derived from D-gluco-, D-manno- and D-galacto-pyranosides by oxidation of the primary alcohol to an aldehyde and formation of the enol acetate. The cyclization of the D-glucose derived enol acetate gave all four possible stereoisomers, with cyclohexanone **26** predominating in 49% yield. The D-mannose derived enol acetate gave only the cyclohexanone **27** in 76% yield, while the D-galactose derived enol acetate gave a 98% yield of the three cyclohexanones **28**, **29** and **30** in a 1:4:4 ratios. When this last reaction was repeated with $Hg(OCOCF_3)_2$ as the rearranging agent, a one to one ratio of **28** and **29** was formed in 75% yield.



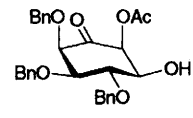
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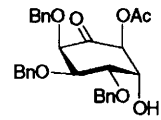
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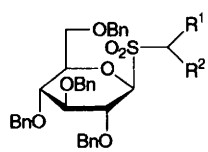


29

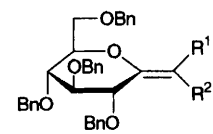


30

A report on the Ramburg-Bäcklund approach to *exo*-glycals (2,6-anhydrohept-1-enose derivatives) has appeared.[28] Methyl glycosides are converted, *via* the anomeric acetate, thioglycoside and oxidation with oxone, to the sulfones **31**. Methyl, ethyl, benzyl and diphenylmethyl thioglycosides may be used and compounds of *gluco-*, *galacto-*, *manno-*, *xylo-*, *fuco-* and *ribo-* configurations have been tested. Treatment of the sulfone **31** with CBr_2F_2 and KOH/Al_2O_3 gives the Ramburg-Bäcklund product **32**. With limited reagents and low temperature α-bromo compounds with bromination on the aglycon have been isolated. *Z*-Alkenes predominate and α-sulfones gave greater *Z*-selectivity, but generally α/β mixtures have been employed. A further paper details the uses of the *exo*-glycals in oxidation, cycloaddition and radical reactions (see Chapters 2, 3 and 6).[29]



31



32

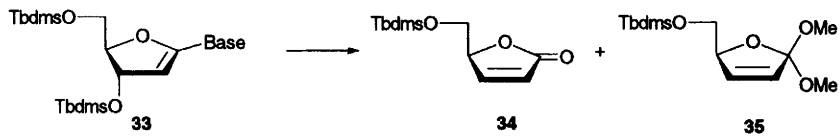
The same reaction is reported in a paper that deals with the mono magnesium peroxyphthalate oxidation of a benzyl thioglycoside to a benzyl sulfone and its use in a Ramberg-Bäcklund reaction to yield the *exo*-glycal.[30]

Some other cases including 2-deoxy sugar examples were given and again predominantly *Z*-alkenes were formed. These alkenes could be hydrogenated to give (mainly) β-*C*-glycosides (see Chapter 3).

3 Furanoid Derivatives

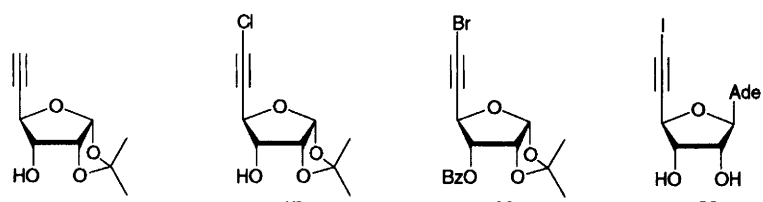
3.1 1,2-Unsaturated Compounds. – Furanoid glycals are found to undergo cycloaddition reactions with the diacylthione (see Scheme 2) to give adducts which can be activated for use as glycosyl donors (see Section 2.1 and Chapter 12).

3.2 2,3-, 3,4- and 5,6-Unsaturated Compounds. – In an attempt to induce radical addition of dimethyl malonate to the alkene **33** (*cf.* Vol. 30, p. 189 for glycals), a mixture of the two was treated with CAN in methanol.[31] However, the result was a mixture of the rearranged 2,3-unsaturated lactone **34** and orthoester **35** readily hydrolysed to the lactone (Scheme 3). The absence of dimethyl malonate did not affect the reaction. When the base was uracil in **33** the reaction was catalytic in CAN, but required stoichiometric CAN if the base was adenine.

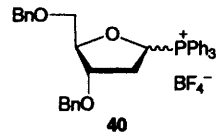


Scheme 3

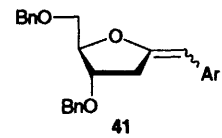
The alkyne **36**[32] was prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-allose by treatment with H_5IO_6 and reaction of the thus formed pentose 5-aldehyde with Ph_3P/CBr_4 to give the 6,6-dibromo-5,6-dideoxy-5-enose compound. *n*-Butyl-lithium then generated the alkyne **36** and hypochlorite gave the 6-chloroalkyne **37**. Alternatively the alkyne **36** could be benzoylated and treated with $NBS/AgNO_3$ to give the bromoalkyne **38**. These haloalkynes were used to generate nucleosides (see Chapter 20). Another paper by the same authors detailed the synthesis of the related iodoalkyne **39** by similar methods.[33]



3.3 Exocyclic Glycals. – Phosphonium salts **40** can be used to prepare *exo*-glycals **41** by a Wittig reaction of the ylid generated with $KOBu^t$ and various benzaldehydes.[34] Reduction gave *C*-glycosides (see Chapter 3).



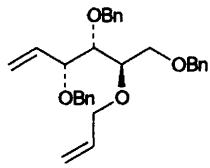
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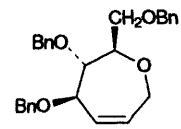
41

4 Septanoid Derivatives

When the diene **42**, obtained by Wittig methylenation and allyl ether formation from 2,3,5-tri-*O*-benzyl-D-arabinose, was treated with Grubbs' catalyst, a ring closing metathesis reaction yielded the septanoid derivative **43** in 68% yield.[35]



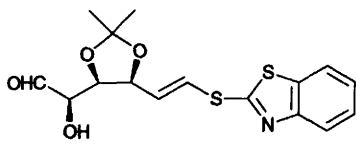
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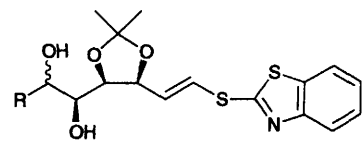
43

5 Acyclic Derivatives

When Grignard reagents were added to 6-*S*-(benzothiazo-2-yl)-1,2:3,4-di-*O*-isopropylidene-6-thio-α-D-galactose, a Grob-like ring opening occurred to give the aldehyde **44**, which underwent addition of the Grignard reagents to form the diols **45**.[36]



44



45

References

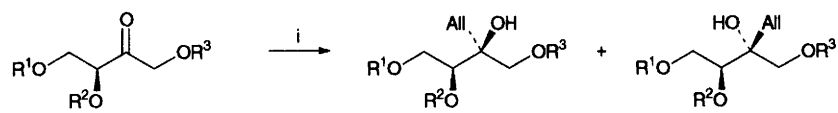
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14
Branched-chain Sugars

1 Compounds with a C–C(R)–C(=O) Branch-point

1.1 Branch at C-2 or C-3. – Facile indium-mediated allylation of L-erythrulose derivatives in anhydrous, as well as more recently, in aqueous, media has been illustrated with several examples (Scheme 1).[1,2] With the diastereoselective nucleophilic addition of metallated allyl ether as a key step, synthesis of 2-*C*-trifluoromethyl-substituted pentoses has been described (Scheme 2).[3] Ni(II) halide-mediated transformations of fructose (see Vol. 29, Chapter 14, ref. 1) have been extended to the C-5, C-6 and C-5 and C-6 modified fructose derivatives (Scheme 3). While the 6-azido-6-deoxy derivative gave results comparable with those of fructose, the C-5 modification as well as C-5/C-6 disubstitution led to degradation products (see also Chapter 16).[4]

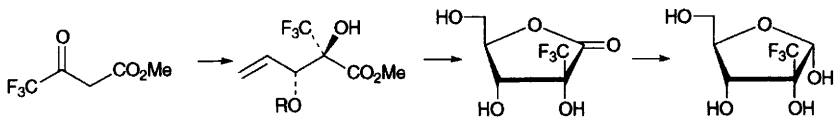


$R^1 = R^2 = R^3$ = H, Bn, Tr,Tbdps

95:5, 95%, for $R^1 = R^2 = R^3$ = Tbdps

Reagents: i, In, AllBr in THF/H_2O

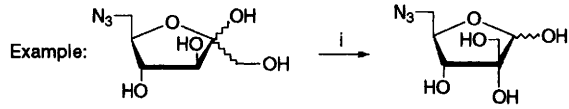
Scheme 1



Scheme 2

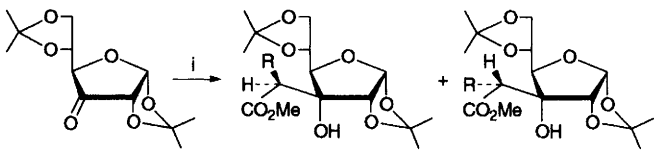
Synthesis, separation and NMR spectral analysis of methyl apiofuranoside and some of its isomers have been reported.[5] The novel C-3 branched-sugar residue of the GPL-type pentasaccharide antigen of *Mycobacterium avium* and its C-4 epimer have been synthesized.[6]

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Reagents: i, *N,N*-diethylenediamine, $NiCl_2.6\ H_2O$, dry MeOH, RT, 45 min.

Scheme 3

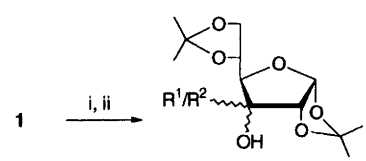


R	% Yield (2:3)
Me	44:38 in THF
	32:19 in Et_2O
i-Pr	64:10 in THF
	40:7 in Et_2O

Reagents: i, RCH_2COOMe, LDA, THF/Et_2O

Scheme 4

A solvent-dependent stereochemical anomaly has been observed in the nucleophilic addition of ester enolates to 3-ulose **1** (Scheme 4).[7] No convincing explanation for the observed stereochemical outcome is forthcoming; the products obtained from nucleophilic addition of α,β-unsaturated ester-derived enolates have also been characterized.[7] Addition of fluorinated alkyl organometallics to **1** has also been described (Scheme 5).[8] It has been noted that while the yield of trifluoromethylation with CF_3Tms is quantitative the analogous or similar conversion did not go to completion with longer chain fluoroalkyl reagents irrespective of the associated metal (see also Chapter 8).[8] Reaction of the 3-ulose **1**-derived epoxide with lithium followed by treatment with electrophiles has led to the formation of branched-chain D-glucose derivatives such as **4** (Scheme 6). The X-ray-derived structure of one of the diastereomers obtained using benzaldehyde as the electrophile has been reported (see also Chapter 22).[9]

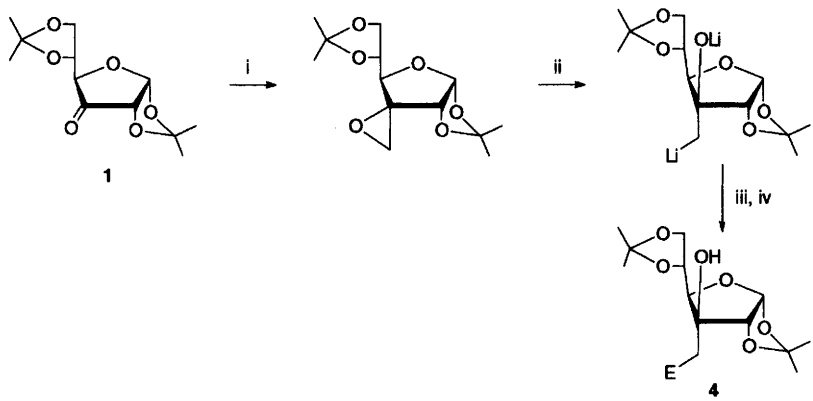


	D-allo-/D-gluco- (% yield)
i	100:0 (88)
ii	Approx. 3:1 (60)

Reagents: i, R^1SiMe_3, $^nBu_4N(Ph_3)SnF_2$, CH_2Cl_2, then H_3O^+or TBAF; ii, R^2MgBr, Et_2O, then H_3O^+

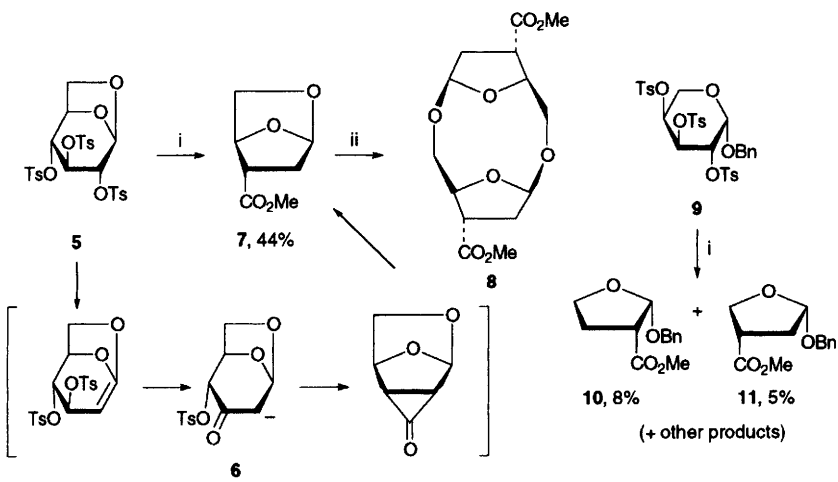
Scheme 5

Formation of 2,3-dideoxy-3-methoxycarbonyl-D-*erythro*-pentofuranose derivative **7** from the tri-*O*-tosylate **5** has been attributed to the Favorski rearrangement of the intermediate **6** as depicted in Scheme 7.[10] Compound **7** underwent dimerization on standing in $CDCl_3$ or on silica gel chromatography



Reagents: i, *t*-BuOK, $Me_3SO^+I^-$, *t*-BuOH, 50 °C, 2.5 h , then H_2O; ii, Li, DTBB, THF; iii, E^+; iv, H_2O
E = H_2O/ D_2O, Me_3SiCl, PhCHO, Me_2CO, $(CH_2)_5CO$
DTBB = 4,4'-di-*t*-butylbiphenyl

Scheme 6



Reagents: i, NaOMe, $CHCl_3$; ii, $CDCl_3$ or SiO_2

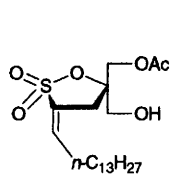
Scheme 7

to yield **8**. The poor stability of **7** may be due to the strain in the bicyclic ring system, which is considerably eased upon dimerization. The structure of **8** was confirmed by X-ray crystallography. This unprecedented tandem elimination-Favorski rearrangement of a tri-*O*-tosylate was further investigated using the arabinoside **9**, and the Favorski products **10** and **11** were indeed among the compounds formed.[10]

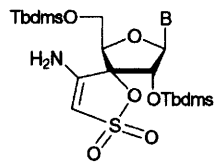
The synthesis and utility of the glycosyl trichloroacetimidate derivative of 3-deoxy-3-formylamino-D-glucose as a building block in the synthesis of a spacer-linked pentasaccharide have been reported (see Chapters 4 and 9).[11]

In an attempt to throw light on the roles of *sn*-1 and *sn*-2 carbonyl groups in

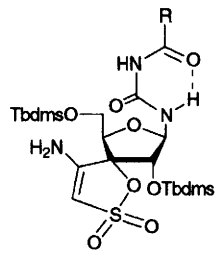
diacyl glycerol (DAG), the conformationally restrained DAG mimetic **12** has been prepared as a possible isostere for protein kinase C binding studies.[12] Another set of SO_2 group-containing branched-chain sugar derivatives such as **14**, prepared as abasic analogues of TSAO-T (**13**), have been among the first of such compounds to inhibit HIV-1 reverse transcriptase.[13] Compounds that resemble, in their H-bonded form, the base unit of **13**, as shown in **15**, gave the best results. A few examples of 2-*C*- and 3-*C*-branched-chain methyl α-D-glucoside derivatives are discussed under Section 3.1.



12



13 B = Thy
14 B = NHC(=X)Y

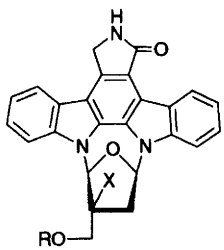


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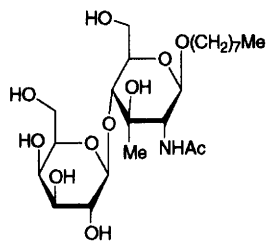
X = O, S; Y = Me, NH_2, NHR; R = alkyl

Synthesis and buffer stability of several mono- and dipeptide esters of indolocarbazole CEP-751 (KT-6587) (See structure **16**) have been described in which the dipeptide prodrug Lys-β-Ala (CEP-2563/KT-8391) proved most promising.[14]

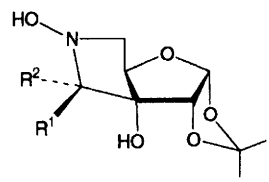
Synthesis of the 3-*C*-branched lactosaminide **17** has been reported. Oxidation (DMSO/Ac_2O) of the 3-OH of a lactose derivative and addition of MeLi to the resulting ulose derivative were the key step in the synthesis.[15] Conversion of **17** into LeX analogues is covered in Chapter 4. A new synthesis of the branched-chain sugar **18** (see Vol. 30, Chapter 14, p. 187) and its epimer (**19**), involving an intramolecular reverse Cope elimination as the key step for the



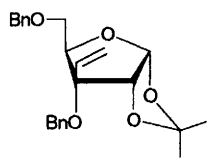
16 X = OMe
R = H, CEP-751
R = Lys-β-Ala, CEP-2563
R = other mono-/dipeptides



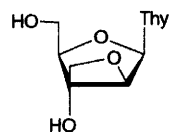
17



18 R^1 = H, R^2 = Me
19 R^1 = Me, R^2 = H



20



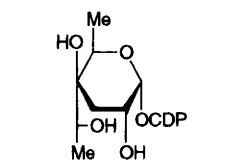
21

bicyclic ring formation, has been described.[16] These compounds were then converted into novel nucleoside analogues and subjected to EPR and NMR studies (see Chapter 20). Similarly synthesis of the 3-*C*-branched D-riboside **20** and its conversion (see Chapter 20) to 2′-*O*-,3′-*C*-linked bicycloarabinonucleosides (oligomers of **21**)[17] and some 3′-*C*-branched 2′-deoxy nucleosides[18] (see also Chapter 20) have also been reported. The usefulness of a number of branched-chain sugars in the synthesis of branched-chain azasugars, which are potential glycosidase inhibitors, has been reviewed.[19]

New isolations of 2-*C*-hydroxymethyl-D-ribose (hamamelose) from plant leaves and its characterization have been reported.[20]

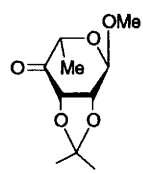
1.2 Branch at C-4. – Studies on the biosynthesis of the antibiotic moenomycin A have enabled the identification of methionine as the source of the branch-methyl group of the 4-*C*-branched-sugar component of this antibiotic.[21] Studies on the biosynthesis of yersiniose A (**22**), on the other hand, have revealed that the attachment of the two-carbon branching group (obtained from pyruvate) at C-4 is catalysed by a thiamine pyrophosphate-dependent flavoprotein.[22]

Conversion of L-rhamnose to the C-4 branched derivative **24** (Ar = 2,5-dimethoxybenzyl) through the ketone **23** and further reactions of **24** (see also Chapter 13) have been reported.[23] Likewise, synthesis of the C-4 branched sugar synthon **25** and its chemospecific activation for coupling with bases to yield α-LNAs (locked nucleic acids) (see also Chapter 20) have been described.[24] Based on a synthesis of 4′-deuterionucleosides (see Vol. 28, p. 5, ref. 18 and pp. 263–264, ref. 9) the synthesis of 4′-trifluoromethyl nucleoside analogues has been achieved.[25] In a convergent approach that allows access to natural squalestatins/zaragozic acids and their analogues, elegant syntheses of standardized intermediates such as the bicyclic lactone **27** (which in turn was obtained from D-mannose-derived alcohol **26** in 13 steps) have been reported (also see Chapter 24).[26]

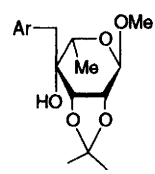


CDP = cytidine diphosphate

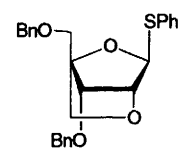
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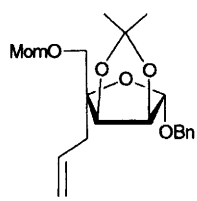
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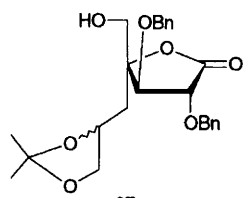
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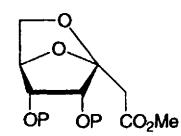
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26



27



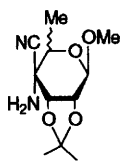
P = protecting group

28

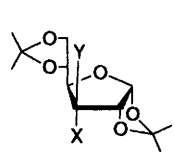
1.3 Other Branched-chain Sugars. – Studies on the biosynthesis of novobiosin, a gyrase inhibitor from *streptomyces*, have revealed that both additional methyl groups (4-*O*- and 5-*C*-) of the aglycon moiety originate from methyl-*S*-adenosylmethionine.[27] In separate studies a new short enantioselective total synthesis of D-noviose that lends accessibility to the natural L-sugar has been developed.[28] Wittig olefination of the 2,3-di-*O*-protected D-ribonolactone has been described as a possible step in the synthesis of the bicyclic adduct **28**.[29]

2 Compounds with a C–C(R)–C Branch-point (R = C or H)

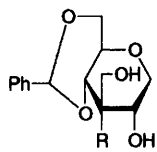
Stereoselective addition of organolithium reagents to various protected erythrulose oximes has led to interesting branched-chain acyclic derivatives.[30] Application of the Stecter reaction to the 4-ulo-rhamnose derivative **23** has yielded the branched-chain sugar derivatives **29** and **30**.[31] The reaction, carried out in two steps involved treatment of **23** with KCN and $(NH_4)_2CO_3$ followed by treatment with ammoniacal methanol in the presence of NH_4Cl. However, they have also been obtained from **23** by direct treatment with KCN in the presence of NH_3 and NH_4Cl in MeOH.



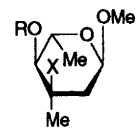
29 L- series
30 D- series



31 X = thiazol-2-yl, Y = OH
32 X = OH, Y = thiazol-2-yl



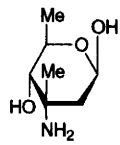
33 R = NO_2
34 R = H



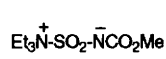
35 X = $NHCOCF_3$, R = H
36 X = NO_2, R = sugar unit

Treatment of **1**, on the one hand, with Dondoni's reagent [2-(trimethyl)-silylthiazole] yielded D-*gluco*-configured derivative **31**. Isomer **32** was proved to be the product obtained on carrying out the addition reaction using lithium thiazolide, obtained *in situ* from thiazole and BuLi.[32] Successive introduction of a nitro group and a hydroxymethyl group was used as a convenient method to generate the branched-chain anhydrohexitol derivative **33** starting from D-ribose. Subsequent tinhydride reduction gave **34** which, after coupling at C-2 with appropriate bases, was converted to desired 3′-*C*-branched anhydrohexitol nucleosides (see Chapter 20 for details).[33] Conversion of the branched-chain sugar **35** to disaccharide components of some anthracyclinone antibiotics such as cororubicin after coupling with glycosyl donors, and subsequent transformation of 3-*C*- trifluoroacetamido functionality to the nitro group has been reported (see also Chapters 3, 12 and 19).[34] The branched-chain sugar residue of **36** is decilonitrose.[34] The novel branched-chain sugar **37**, which has been named saccharosamine, has been shown to be a constituent of the new heptadecaglycoside antibiotics isolated from *Saccarothix*[35] (see also Chapters

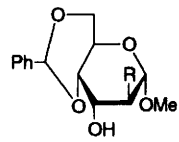
4, 9 and 19). Using the Burgess reagent (**38**) *N*-formamides **39** and **40** have been transformed into their respective isocyanides **41** and **42**.[36] As a halide-free reagent, **38** offers advantages (for example, TMS ethers are stable) over the conventional dehydrating agents. Compounds **41** and **42** may be converted into other useful products. By the application of Mitsunobu conditions for cyclization, pipecolic acid (2,6-dideoxy-2,6-diimino-2-*C*-methyl-L-*lyxo*-hexonic acid) derivatives were prepared in excellent yields from polyhydroxylated α-alkyl-α-aminoacids obtained from aldol reactions of amino-acid ester enolates and chiral aldehydes.[37]



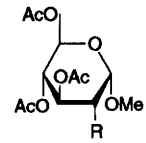
37



38



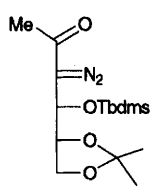
39 R = NHCHO
41 R = NC



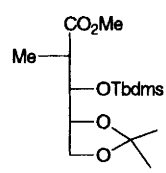
40 R = NHCHO
42 R = NC

3 Compounds with a C–C(R)(H)–C Branch-point

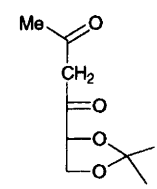
3.1 Branch at C-2. – Full details on the conversion of 2-diazo-2-deoxy-aldonates to 2-*C*-methyl-aldonolactones by alkylation and to natural 3-deoxy-2-keto-aldonic acids by Rh(II)-mediated rearrangements have now become available[38] (*cf.* Vol. 28, Chapter 16, p. 205, ref. 35 and p. 206, ref. 40; Vol. 29, Chapter 14, p. 197, ref. 29). Wolff rearrangement of the diazo compound **43**, prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde, to **44** (obtained in 41% yield along with the H-rearrangement product **45**, obtained in 55% yield) has also been discussed (see also Chapter 16).[38] The influence of structural parameters on diastereoselectivities in the endocyclic cleavage reactions of several 2-*C*-methyl pentosides (*e.g.* **46** to **47**, Scheme 8) and some 3-*C*-methyl pentosides using trimethylaluminium has been studied.[39] A cyclic hydrogen bonded model suggested for the intermediate could predict the stereochemical outcome of the reaction in many cases. Synthesis of several C-2 branched-chain 2-deoxy-oct-3-ulosonic acids **49**/or enol **50** have also been completed starting from the corresponding acid chlorides (**48**) [Scheme 9 (also see Chapters 2 and 16)].[40]



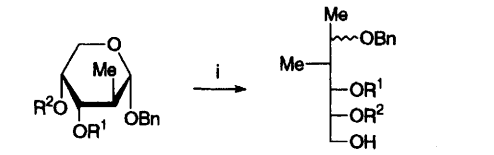
43



44

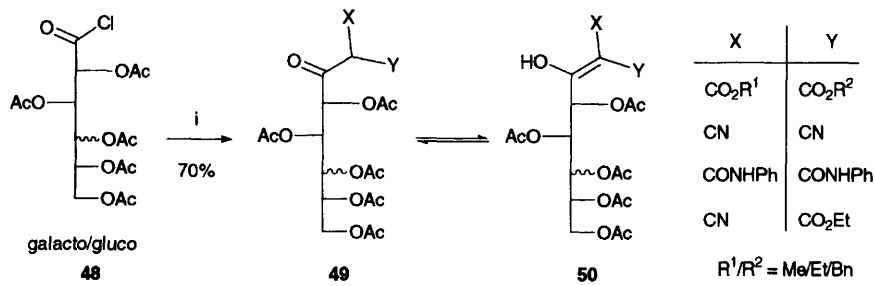


45



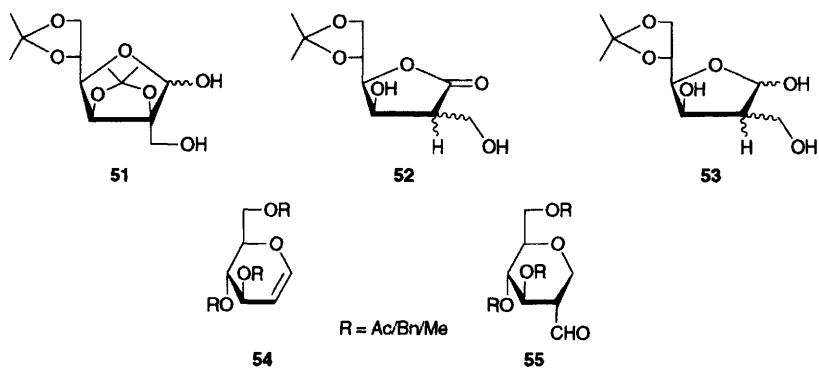
Scheme 8

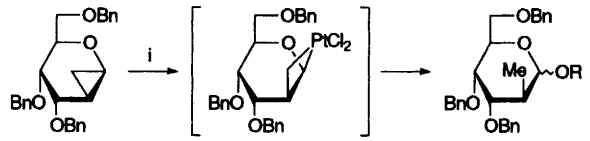
Syntheses of 2-deoxy-2-*C*-hydroxymethyl-D-*gluco*- and D-*manno*-derivatives **53** have been carried out from the hemiacetal **51** by reduction of the derived lactone **52** obtained by treatment of **51** with PCC followed by samarium iodide.[41]



Scheme 9

Rh-Catalysed hydroxyformylation of glucals **54** has been shown to give the 2-*C*-branched-chain sugars **55** predominantly (55–60% yield).[42] Novel Pt-catalysed ring opening (using Zeie's dimer) of 1,2-cyclopropanoid sugar derivatives **56** with alcohols has led to branched-chain sugar derivatives **57** (Scheme 10, see also Chapter 3).[43] NBS-Activated ring opening of similar systems with sugar alcohols has also been carried out to afford functionalized



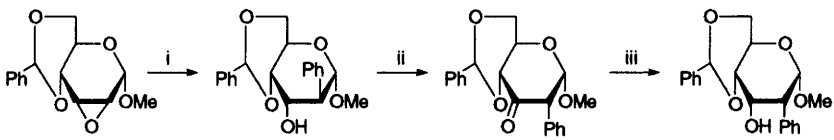


56 **57** R = Me/All/Bn/Ph

Reagents: i, $[Pt(C_2H_4)Cl_2]_2$, ROH

Scheme 10

2-deoxy-2-*C*-branched-chain disaccharides.[44] Pyranosides (such as **60**) having C-2 or C-3 aryl substituents have likewise been prepared in good yield (Scheme 11) by lithium diphenylcuprate opening of 2,3-anhydroaldohexopyranosides (such as **58**) followed by PCC oxidation to give the ketone **59** and its subsequent borohydride reduction (see also Chapter 5).[45] Interestingly the β-anomer of **58** did not undergo the reaction, presumably due to steric hindrance caused by the methoxy group being on the face of the sugar ring from which the nucleophilic attack had to occur. Other examples to illustrate the influence of steric factors on this reaction were also provided.

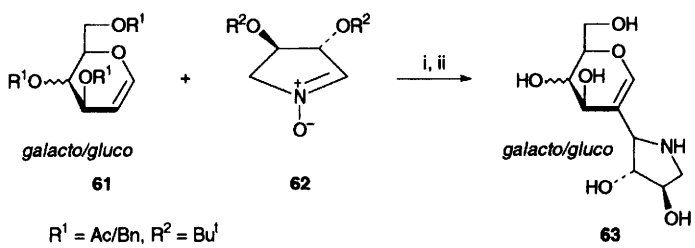


58 **59** **60**

Reagents: i, Li diphenyl cuprate; ii, PCC, TEA; iii, $NaBH_4$

Scheme 11

(1,2)-Linked *pseudo*-aza-*C*-disaccharide glycals **63** have been prepared by a novel intermolecular cycloaddition reaction (Scheme 12) of enantiopure cyclic nitrones **62** to **61**.[46] Several examples have been discussed. Confirmatory evidence on the hydride shift that occurs from the *O*-6 benzylmethylene group to C-3 in the rearrangement of tri-*O*-benzyl-D-glucal to bicyclic product **64** (*J. Org. Chem.*, 1997, **62**, 2195) has been obtained.[47] Pd-Catalysed cyclization of 2,3-unsaturated sugar derivative **65** to give the bicyclic adduct **66** has

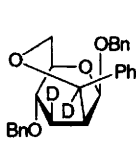


galacto/gluco **61** **62** R^1 = Ac/Bn, R^2 = Bu^t *galacto/gluco* **63**

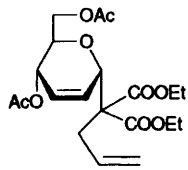
Reagents: i, 100 °C; ii, NaOMe; CF_3CO_2H; H_2, Pd/C

Scheme 12

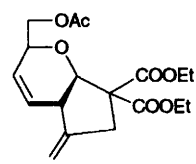
likewise been briefly discussed along with some related cyclization reactions.[48] Efficient use of glycals in the synthesis of certain iridoid glycosides through successive Ferrier and Pauson-Khand reactions has been demonstrated as in the case of conversion of the glycal derivative **67** to the *nor*-iridoid aglycon **68**.[49]



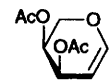
64



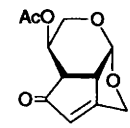
65



66



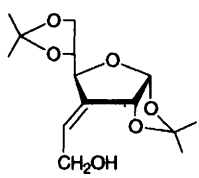
67



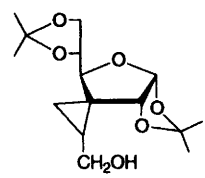
68

A review of work (between May 1996 and April 1997) on the application of organotransition metal complexes in organic synthesis has been published that features examples of the Pauson-Khand reaction for preparation of branched-chain carbohydrates.[50] Some bicyclic and tricyclic ring systems prepared by Pd(0)-catalysed cyclizations onto carbohydrate templates have been covered in a review[51] on saturated and partially unsaturated carbocycles (see *J. Org. Chem.*, 1997, **62**, 1341 and *Tetrahedron*, 1997, **53**, 3957). Some examples of branched-chain carbohydrates can be seen in another review (that covers the period, June 1996–June 1997)[52] on the application of organosulfur and selenium reagents in organic synthesis (also see Chapters 3, 13, 18, 20 and 24). Also, reactions of some methyl furanosides having C_7 carbon-bonded bridges between C-2 and C-4 (for their synthesis, see Vol. 27, Chapter 14, ref. 44) have also been published.[53] Further, using diacetone mannitol as the starting material, a new multi-step synthesis of (−)-malyngolide, an antibiotic active against *Mycobacterium smegmatis*, has been reported.[54]

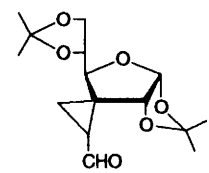
3.2 Branch at C-3. – 3,3-Spiro-cyclopropyl derivatives (**70** and **71**) of diacetone glucose and their reactions to give various 3-*C*-branched-chain compounds (**72** and **73**) have been described.[55] While addition of Simmons-



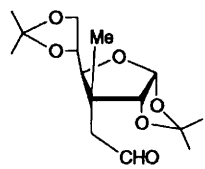
69



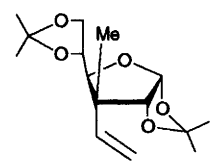
70



71



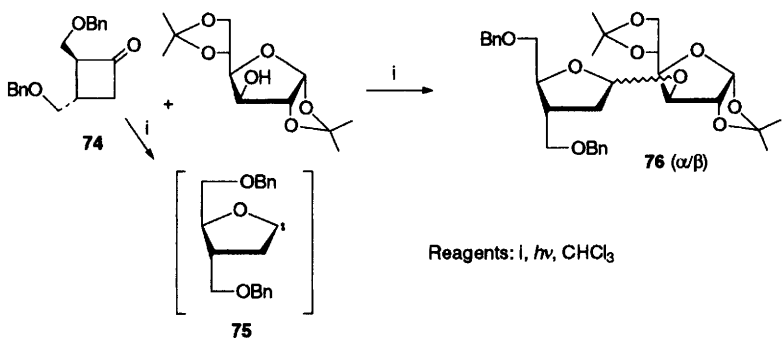
72



73

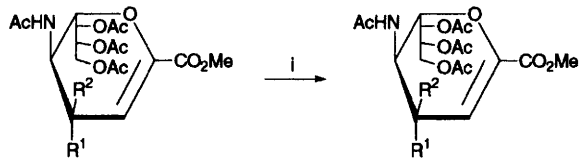
Smith reagent (Et_2Zn/CH_2I_2) to the exocyclic double bond in **69** was the key step in the spiro-cyclization reaction, conversion of **70** to **71** was effected by PDC-oxidation. By an organotin-mediated free radical process 3-*C*-alkynylated diacetone glucose derivatives have been prepared in moderate yields from the corresponding 3-deoxy-3-iodo-allose derivative (see also Chapter 3).[56] Synthesis of 1,5-anhydro-3-deoxy-3-*C*-hydroxymethyl D-mannitol and its conversion into different nucleoside analogues for testing anti HSV-I activity have been achieved in a multistep synthetic sequence starting from D-ribose.[57]

Photoinduced addition of (5*S*)-(5-*O*-*tert*-butyldimethylsilyloxymethyl)furan-2(5*H*)-one to methanol has been reported as a method for the synthesis of (4*R*,5*S*)-4-hydroxymethyl-(5-*O*-*tert*-butyldimethylsilyloxymethyl)furan-2(5*H*)-one.[58] By adding chiral photochemically active synthons, such as the cyclobutanone derivative **74**, presumably *via* an initially formed transient carbene intermediate **75**, to diacetone glucose, 3′-*C*-branched-chain difuranosyl disaccharides (**76**) could be obtained (Scheme 13), albeit in low yields.[59] Other examples of photochemical glycosylation, including *N*-glycosylation, have also been described (see also Chapter 3). Preparations of C-3′–C-6 direct-linked disaccharides based on aldol chemistry have also been published.[60]



Scheme 13

3.3 Branch at C-4. – A number of novel 4-*C*-branched-chain 2,3-unsaturated *N*-acetyl neuraminic acid analogues were reported.[61] They were made from the 4-chloro-4-deoxy-derivatives by using Pd(0)-mediated coupling with organostannanes (Scheme 14). The reaction occurred with complete inversion of stereochemistry at the C-4 position as evidenced from the epimeric products **79** and **80** obtained respectively from the epimeric halides **77** and **78** respectively (see also Chapter 16). Synthesis of partially protected polyhydroxylic lactones **83** and **84** from the esters **81** and **82** and their further elaboration to the silyl protected lactone aldehyde **85** have been described.[62] Reaction of **81** with super AD-mix β formulation was key in its two-step transformation to **83**. On the other hand **82** underwent spontaneous cyclization to **84** on treatment with TBAF in THF (Scheme 15). Interestingly, while **83** proved active against certain tumour cell lines compound **84** exhibited no antitumour activity. Compound **85** serves as an intermediate building block for the synthesis of the

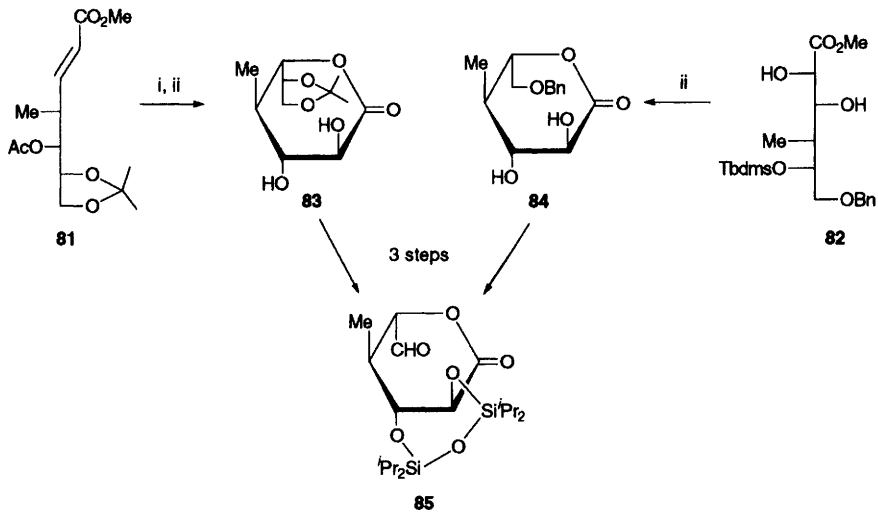


77 R^1 = H, R^2 = Cl
78 R^1 = Cl, R^2 = H

79 R^1 = R, R^2 = H
80 R^1 = H, R^2 = R
R = CH_2=CH_2, TmsCH=CH, Ph, $CH_2C(CO_2Me)$

Reagents: i, Pd(0), Ph_3P, $RSnBu_3$

Scheme 14



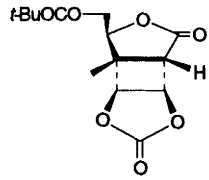
Reagents: i, Super AD-mix β formulation, $MeSO_2NH_2$, *t*-BuOH/H_2O; ii, TBAF

Scheme 15

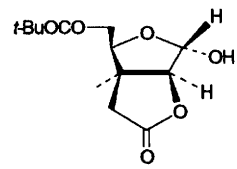
marine macrolide altohyrtin A (see Chapter 16). A synthesis of the lactose analogue and its α-methyl glycoside bearing a CH_2- or CD_2- inter-unit bridge have been made for conformational studies by NMR and X-ray crystallography (see also Chapter 3 and 22).[63]

4 Compounds with a C–C(R)(R)–C Branch-point

Fused γ-butyrolactones of carbohydrates (*e.g.* **87**) have been reported as unexpected products in the reaction of photocycloadducts (*e.g.* **86**), prepared from the corresponding α,β-butenolides and vinylene carbonate (*Tetrahedron Lett.*, 1998, **39**, 6961), with nucleophiles, albeit only in moderate yields. Excellent stereoselectivity was observed in the reaction.[64]



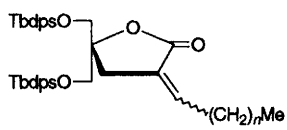
86



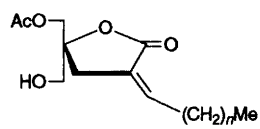
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5 Compounds with a C–C(R)=C or C=C(R)–C Branch-point

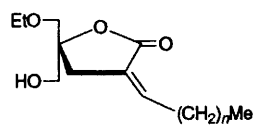
Reactions of branched-chain lactone **88** under reductive as well as other conditions to yield further derivatives (**89** and **90**) required as conformationally constrained analogues of diacylglycerol (see also ref. 12 in Section 1.1) have been reported[65] as part of a continuing programme of work on the investigation of binding of diacylglycerol-lactones to protein kinase C (see also Chapters 16 and 24). Synthesis of another 4-*C*-branched-chain semi-rigid sugar lactone (**92**) that bears similarities to the newly emerging bryostatin family of cancer chemeotherapeutic agents was also reported. It was prepared from the 3-*C*-branched-chain sugar acetonide derivative **91** obtained from D-xylose. The (*R*)-1-hydroxyethyl group at the C-4 position seems to be of importance as seen from the results of bilogical tests (see also Chapter 24).[66]



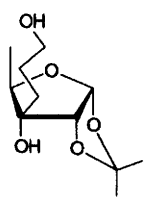
88 $n = 1$ or 2



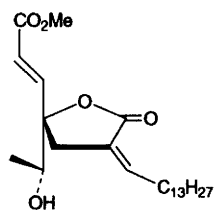
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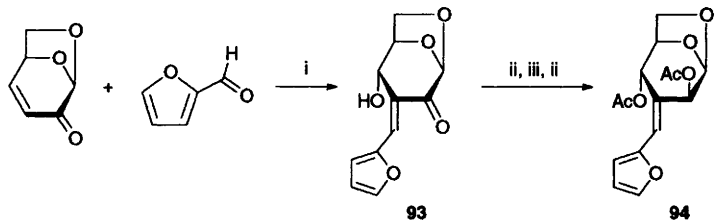


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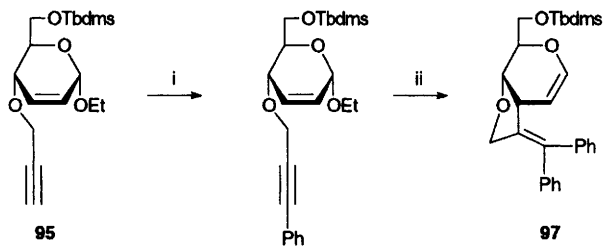
Alkaline condensation of levoglucosenone and fufural followed by an acetylation-reduction-acetylation reaction sequence (Scheme 16) has afforded the 3-*C*-branched-chain sugar derivative **94**. Other reactions of the condensation product **93** have also been reported (also see Chapter 13).[67] In another set of condensation/cyclization reactions promoted by $Pd(OAc)_2/PPh_3$ (Sonogashira-Heck type), repeated reaction of 4-*O*-propargylated 2-enopyranoside **95** with iodobenzene at 80 °C has led to the bicyclic glycal **97** (from the initial coupling product **96**) *via* coupling of the phenyl group and a subsequent rearrangement process (Scheme 17). Use of allyl glycoside analogue of **95** led to tricyclic products (also see Chapter 13).[68]



93 94

Reagents: i, aq. $NaHCO_3$; ii, Ac_2O/Py; iii, $NaBH_4$

Scheme 16

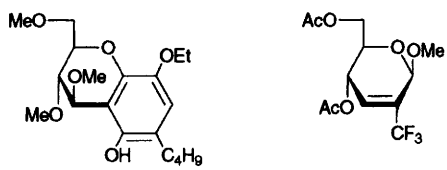


95 96 97

Reagents: i, PhI, $Pd(OAc)_2$, PPh_3, NEt_3, Bu_4NHSO_4, 25 °C; ii, condition (i) at 80 °C

Scheme 17

Benzannulation reactions of Fischer carbene complexes, obtained from 2-chloro-tri-*O*-benzyl/methyl-D-glucal by metallation [carried out by treatment with *s*-BuLi in THF followed by a two-step reaction with $Cr(CO)_6$) and triethyloxonium tetrafluoroborate], with acetylenes to give various unsaturated branched-chain sugar derivatives such as **98** have been reported.[69] Synthesis of the branched-chain unsaturated sugar derivative **99** from tri-*O*-acetyl-D-glucal has been reported.[70] The reaction involved addition of CF_2Br_2 (CF_2Br and Br) across the double bond followed by conversion of the resulting glycosyl bromide to the methyl glycoside under Koenigs-Knorr conditions and then a fluoride displacement (also see Chapter 13).



98 99

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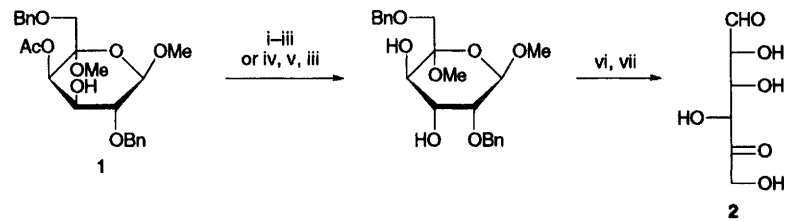
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15
Aldosuloses and Other Dicarbonyl Compounds

1 Aldosuloses

Oxidation of D-glucose with pyranose dehydrogenase from *Agaricus bisporus* has afforded a mixture of the 2- and 3-keto-products, whereas D-galactose gave only the corresponding 2-keto-compound (D-galactosone).[1] Similar use of pyranose oxidase from *Peniophora gigantea* has given rise to 2-keto-sugars from a number of D-hexoses.[2]

The L-*arabino*-hexos-5-ulose derivative **1** has been epimerized at C-3 and the product deprotected to give L-*lyxo*-hexos-5-ulose **2** (Scheme 1), which exists in

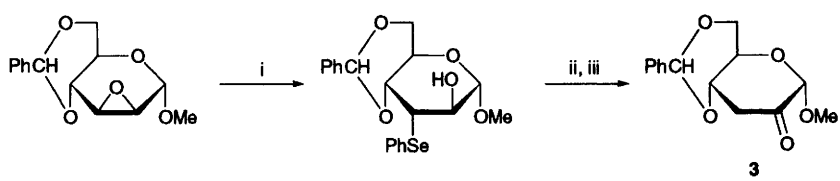


Reagents: i, Tf_2O, py; ii, Bu_4NOBz; iii, NaOMe, MeOH; iv, Pr_4NRuO_4, NMO; v, $NaBH_4$; vi, H_2, Pd/C; vii, aq. TFA

Scheme 1

solution as a complex mixture of at least eight tautomers.[3] A synthesis of L-*xylo*-hexos-2-ulose by oxidation and then acid hydrolysis of 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose has been reported,[4] and the 3-deoxy-2-ulose derivative **3** has been prepared by use of a selenoxide elimination (Scheme 2).[5]

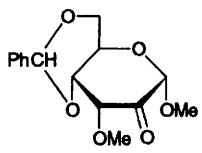
Protons adjacent to carbonyl groups have been readily exchanged with deuterons (dioxane, THF, Et_3N, D_2O) so that **4** gave **5**, and **6** afforded **7**.[6]



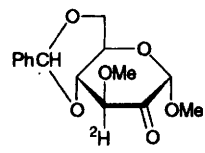
Reagents: i, $PhSe^-$, EtOH; ii, H_2O_2, EtOH; iii, py, Δ

Scheme 2

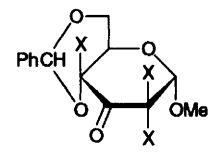
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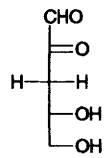
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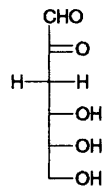
6 X = H
7 X = ^{2}H

Photolysis of D-ribose-5-phosphate at 193 nm has given the dicarbonyl derivatives pentos-4-ulose, 5-deoxy-pentos-4-ulose and pento-1,5-dialdose as major products. They are thought to arise by H-abstraction from C-4 or C-5 by an oxygen-centred phosphate radical.[7]

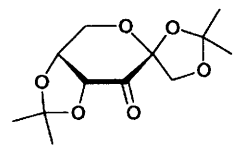
The 3-deoxyaldos-2-uloses **8** and **9** have been prepared for study of their reactivity under Maillard reaction conditions.[8]



8



9



10

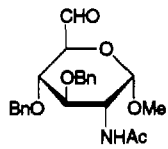
Methyl 2,3,6-tri-*O*-methyl-α-D-*xylo*-hexopyranosid-4-ulose on reduction with Li $^{sec}Bu_3BH$ has afforded the *galacto* isomer as the only detectable product.[9] The stereochemical preference of the hydride transfer to and from the coenzyme in CDP-D-glucose-4,6-dehydratase (in the biosynthetic pathway of 3,6-dideoxy sugars) has been determined to be pro-*S* by use of labelled substrates.[10]

2 Other Dicarbonyl Compounds

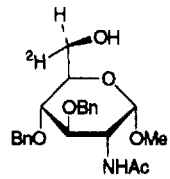
The asymmetric epoxidation of olefins using the D-fructose-derived ketone **10** as catalyst has been further studied and the enantiomer of **10** (prepared from L-sorbose) has given products with opposite enantioselectivity.[11]

The dialdose glycoside **11** has been stereoselectively reduced ((*R*)-Alpine-Borane-*d*) to give **12**, and the same selectivity was obtained with the corresponding β-anomer.[12]

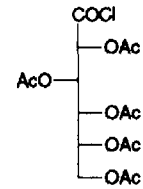
Treatment of the D-gluconyl chloride **13** with acetoacetate esters has afforded adducts **14** (R = alkyl) which after hydrolysis and decarboxylation gave the dicarbonyl products **15**.[13]



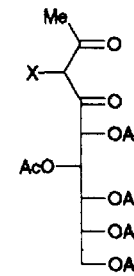
11



12



13



14 X = CO_2R
15 X = H

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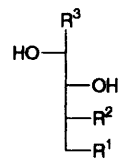
12 M.L. Falcone-Hindley and J.T. Davis, *J. Org. Chem.*, 1998, **63**, 5555.

13 R. Meisel, K. Peseke and H. Reinke, *J. Prakt. Chem./Chem.-Ztg.*, 1998, **340**, 264 (*Chem. Abstr.*, 1998, **128**, 294 945).

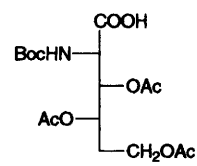
16
Sugar Acids and Lactones

1 Aldonic Acids and Lactones

The kinetics of oxidation of the threose series of pentoses and hexoses by chloramine-T in aqueous alkali to yield aldonic acids have been reported with an account of the dependence of the product profile on the nature of the aldose used.[1] An electrochemical oxidation of glucose to gluconic acid has also been reported.[2] An efficient two-step synthesis of *N*-hydroxy-D-arabinonamide 5-phosphate from fructose-6-phosphate and its inhibitory activity on phosphoglucose isomerase revealed it as the strongest competitive inhibitor known to date with respect to substrate D-fructose-6-phosphate.[3] Ni(II)-catalysed oxidative degradation of C-5-modified fructose derivatives in the presence of *N*,*N*-diethylenediamine in anhydrous methanol has been reported (*e.g.*, **2** from **1**). In contrast, reaction of the 5,6-modified fructose derivatives (*e.g.*, **3**) led to untraceable products (also see Chapter 14 and Vol. 29, Chapter 14, ref. 1).[4]



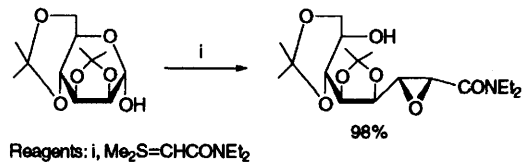
1 R^1 = OH, R^2 = N_3, R^3 = $C(O)CH_2OH$
2 R^1 = OH, R^2 = N_3, R^3 = COOMe
3 R^1 = F, R^2 = N_3, R^3 = $C(O)CH_2OH$
5 R^1 = OH, R^2 = OH, R^3 = $C(O)NHCH_2COOH$
6 R^1 = OH, R^2 = OH, R^3 = $C(O)NHCH_2P(O)(OR)_2$
R = Na/$NHEt_3$



4

By use of simple aldehydes as unnatural electrophilic substrates the practical usefulness of 2-keto-3-deoxy-6-phosphogalactonate aldolase, isolated from *Pseudomonas cepacia*, in stereospecific aldol addition reactions has been well demonstrated.[5] 6-Amino-2,5-di-anhydro-3.4-di-*O*-benzyl-6-deoxy-D-gluconic- and mannonic acids have been synthesized and, after their conversion to Leu-enkephalin peptidomimetic analogues, have been subjected to conformational analysis by CD and NMR methods.[6] The implications of conformation on their biological activity have been discussed. Michael-type addition of homochiral nitrogen nucleophiles to α,β-unsaturated ester enolates[7,8] as well as

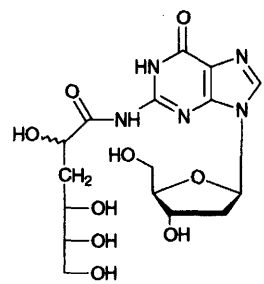
Carbohydrate Chemistry, Volume 32
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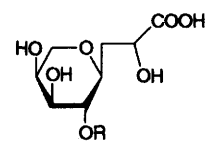
Scheme 1

Grignard reaction of vinyl magnesium bromide on unsaturated amino alcohols[9] has been employed in the synthesis of various amino aldonic acids (*e.g.*, **4**). Synthesis of *N*-arabinononylglycine (**5**) and the isosteric methyl phosphonate **6** from D-arabinose have been described as acyclic analogues of NeuNAc. However, they showed no significant sialidase inhibitory activity.[10] Wittig reaction of methylbromoacetate in the presence of tri-*n*-butylphosphine and zinc in dioxane on unprotected aldoses were used as a convenient method for preparing the respective α,β-unsaturated methyl aldonates[11] and a further chain-extension reaction is illustrated in Scheme 1.[12] The preparations of alkylaminoalkyl esters of gulonic acid derivatives,[13] as well as those of *N*-alkyl maltonamides[14] and the surfactant properties of the latter have been reported. The use of certain maltobionamides in enantioselective hydrolysis of α-amino acid esters has been described.[15] Conversions of L-malic acid to polyfunctionalized aldonic acid derivatives and their coupling with oligosaccharides have been discussed.[16] Characterization of Maillard-type products (*e.g.*, **7**) in the reaction of 3-deoxyglucosone with 2′-deoxyguanosine nucleosides has been reported (*cf.* Vol. 28, p. 155–156, refs. 89 and 90).[17] Reactions of methyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside with certain acetyl-iron complexes leading to the formation of *ribo*- and *arabino*-configured heptonic acids have been discussed.[18]

Isolation of an anhydrodeoxyoctonic acid derivative **8** esterified with a dicarboxy-lignan from the liverwort *Bazzania trilobata* has been documented.[19]

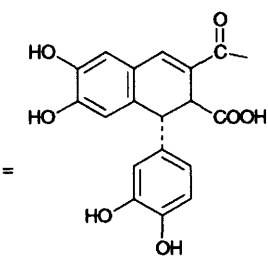


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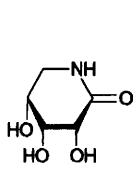


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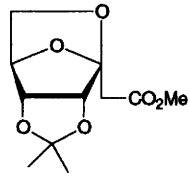
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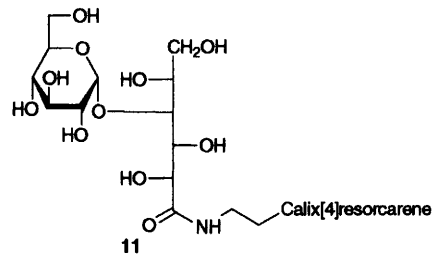
Several accounts of syntheses of ribono-,[20–22] arabinono-,[20,22] mannono-,[21–23] and gulonolactones[23] and their derivatives including some branched-chain compounds[24–27] have been published (see also Chapter 14). Diels-Alder adducts reported previously (Vol. 30, Chapter 24, ref. 104) have been further transformed into sugar lactam derivatives (*e.g.*, **9**).[28]



9

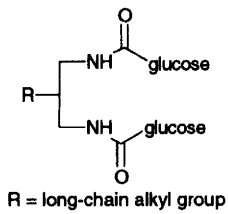


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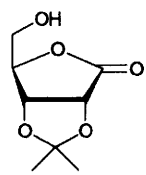


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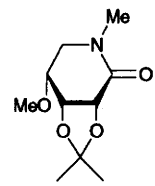
Wittig olefination was used as a direct entry into dioxabicyclic systems from sugar lactones (*e.g.*, **10** from the corresponding D-ribofuranono-1,4-lactone derivative).[29] Reactions of aldonolactones with various amino compounds have been utilized to synthesize a range of compounds that function as protease inhibitors[30] and immobilized macrocyclic sugar clusters (*e.g.*, the amide **11** obtained from maltonolactone and a calix[4]resorcarene-substituted amine bearing long-chain alkyl groups on the macrocyclic residue was immobilized on a hydrophobic sensor and used for lectin-binding studies)[31] to those with surfactant properties (*e.g.*, the amide **12** obtained from gluconolactone and an amine).[32] Facile conversion of L-galactono-1,4-lactone to L-galactose, 3-deoxy-, 6-deoxy- and 3,6-dideoxy-L-galactoses has been described.[33] Lactones have also been converted to lactams (*e.g.*, condensation of 4,5,6-triaminopyrimidine and D-ribono-1,4-lactone to give the corresponding 5-amidopyrimidine derivative)[34] and iminosugars (*e.g.*, conversion of **13** into **14**).[35] The reaction of α,β-unsaturated δ-lactones with *N*-hydroxybenzylamine to yield isoxazolidin-5-ones by a conjugate addition-rearrangement has likewise been reported.[36]



12

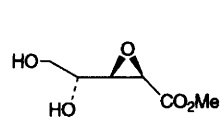


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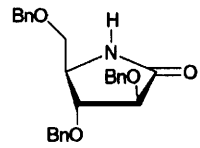


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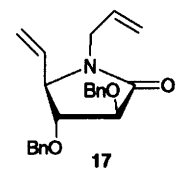
Other transformations of lactones reported include conversion of D-glucofuranono-6,3-lactone into 1,2-anhydro-5-*O*-tosyl-β-D-mannofuranurono-6,3-lactone[37] and the preparation of methyl 2,3-epoxy-D-xylonate **15**.[38] Kinetics and mechanism of oxidation of D-galactono-1,4-lactone by Cr(V) and Cr(VI) to give D-lyxonic acid have been reported. The reaction was found to proceed faster in the presence of Cr(V) than did in the presence of Cr(VI).[39] 'Ring closure metathesis' has been used for the conversion of lactams into pyrrolizidine and quinolizidine aza sugars. Thus lactam **16**, for example, was transformed into the diene **17** which on a ruthenium-catalysed carbocyclation reaction gave the pyrrolizidine derivative **18**.[40] Branched-chain sugar lactone



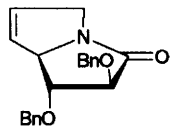
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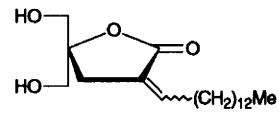
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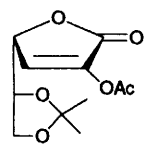
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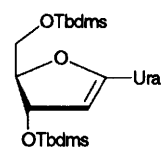
19

19 has been described as an analogue of diacylglycerol and was used in binding studies with protein kinase C to demonstrate the role of the carbonyl groups in diacylglycerol, which is the natural binding-motif for the protein (see also Chapter 14).[41]

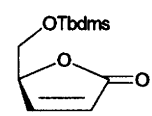
A facile five-step chemical synthesis of 2-keto-3-deoxy-6-phosphogalactonate described involves β-elimination of the 5,6-*O*-isopropylidene derivative of D-galactono-1,4-lactone to give the 2,3-unsaturated lactone derivative **20** as the key step.[42] Ferrier rearrangement of unsaturated nucleosides in the presence of CAN has led to the formation of unsaturated lactone derivatives (*e.g.*, formation of **22** from **21**). A catalytic amount of CAN was sufficient for the conversion of **21** into **22**. However, the substitution of Ade for Ura in **21** required stoichiometric quantities of CAN for the reaction to take place.[43] Synthesis of certain β-lactam analogues from unsaturated lactones have also been described.[44]



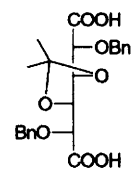
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21



22



23

2 Aldaric Acids

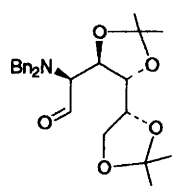
Potassium D-idarate isolated from *Lespedeza cuneata* G. Don has been reported as the leaf-closing factor in this nyctinastic plant.[45] Synthesis of L-mannaric acid derivative **23** from L-mannono-1,4-lactone and its use as a peptidomimetic scaffold has been described.[30]

3 Ulosonic Acids

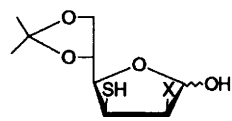
A very successful completely enzymatic synthesis of NeuNAc on a multi-kilogram scale has been reported using GlcNAc and pyruvate as building

blocks in the presence of a mixture of *N*-acetylneuraminate lyase and GlcNAc-2-epimerase.[46] A review on the use of aldolases in carbohydrate synthesis describes methods for the synthesis of sialic acids (for other examples see Chapter 2, 4, 11 and 18).[47] In a chemical approach to NeuNAc synthesis, an elegant total synthesis of the enantiomerically pure acid was achieved from 3-chloro-*cis*-1,2-dihydrocatechol, which is accessible by microbial oxidation of chlorobenzene. The work has been modelled on the synthesis of Kdn by the same authors[49] and involved a fifteen-step sequence in which **24** served as the key intermediate.[48]

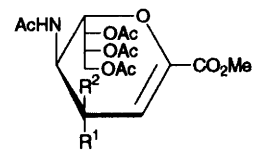
Chemical syntheses of several NeuNAc analogues and derivatives have been described. 6-Thio-NeuNAc was, for example, made in a multi-step sequence beginning with methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside and *via* the thiofuranose derivative **25**.[50] On the other hand, C-4-modified sialic acid derivatives **27** were obtained from **26** by Pd(0)-mediated coupling with organostannanes (see also Chapter 14).[51] Some C-7–C-9 chain truncated analogues of NeuNAc have been obtained in completely stereo-controlled manner from ascorbic acid.[53] A full account of the synthesis and biological activity of some carboxamides (Vol. 30, pp. 207–208, ref. 55) related to NeuNAc and Zanamavir has been published [54]



24

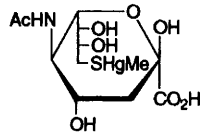


25 X = NHAc

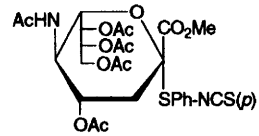


26 R^1/R^2 = H/Cl
27 R^1/R^2 = H/All/TmsAll/Ph

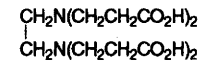
Synthesis of the mercury-labelled NeuNAc derivative **28** and its enzymatic incorporation into oligosaccharides and glycoconjugates have been described (see also Chapters 4 and 17).[55] The incorporation of the metal atom finds use as an aid in the structure determination of oligosaccharides and glycoconjugates by X-ray crystallography. A kinetic study of the solvolysis of CMP-*N*-acetyl neuraminate with azide, which results in both anomers of 2-deoxy-2-azido-NeuNAc as well as NeuNAc, has provided evidence that the *N*-acetylneuraminyl oxocarbenium ion is an intermediate in reactions in the presence of anionic nucleophiles.[56] A NeuNAc-taxol conjugate has been prepared in which the taxol residue is linked to the sialic acid unit through a glycosidically bonded spacer arm (see also Chapter 24).[57] The preparations of starburst α-thiosialodendrimers for probing multivalent carbohydrate–protein binding properties have been reported. The dendrimers were built up through amide bonds using **29** and a variety of terminal amines amide-bonded *via* branching units to **30** as basic building units.[58] Solid phase syntheses of sialo-oligomers (ranging from dimer to octamer) linked through intermolecular (1,5)-amide bonds have likewise been described[59] as have preparations of a ^{15}N,^{13}C-labelled lactam analogue of ganglioside GM_4, a cell surface glycolipid,



28



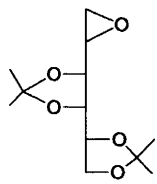
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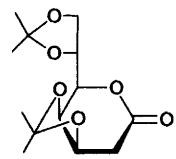
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in which four contiguous labelled atoms are present. A chemoenzymatic approach was employed (see also Chapter 3).[60] Lactam analogues of Sialyl Le^x have also been described (see also Chapter 4).[61] A review on the preparation of selectin inhibitors covers synthesis of several sialic acid derivatives and analogues.[62]

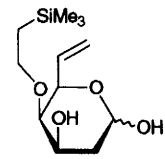
Several new chemical/chemo-enzymatic syntheses and reactions of Kdo and their derivatives,[63–68] as well as a few other ulosonic acids,[69–72] have been reported in the literature. Whereas in the chemical syntheses of Kdo compounds **31** (obtained from D-mannitol),[63] **32**[64] and **33** (obtained from non-carbohydrate source)[65] served as the corresponding starting materials, the enzymatic method utilized D-arabinose-6-phosphate and phospho(enol) pyruate as the substrates.[66]



31



32

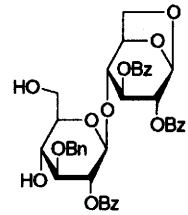


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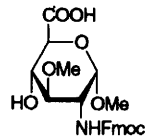
4 Uronic Acids

Oxidation of the primary hydroxyl group of thioglycosides using chromium reagents (Jones reagent or PDC) has been described as a convenient route to uronic acid thioglycosides.[73,74] Application of the NaOCl-TEMPO reagent system for the selective oxidation of the primary hydroxyl group in **34** to give the corresponding aldobiuronic acid derivative (see also Chapter 3)[75] has been noted. This reagent system has also been applied to the oxidation of α-, β- and γ-cyclodextrins (see also Chapter 4). Exclusive oxidation of the primary hydroxyl groups in these compounds was observed and the controlled oxidation to give 1, 2, 3, 4, 5 or 6 carboxyl groups per cyclodextrin moiety proved possible.[76] Synthesis of glucuronic acid glycosyl donors with a latent C-4 acceptor group,[77] and bile acid acyl glucuronides (linked to the C-24 carboxyl group)[78] (see also Chapter 7) have been reported. 17α-Ethynylestradiol glucuronides (3-*O*- and 17-*O*-) have been prepared enzymatically using dog microsome preparations.[79]

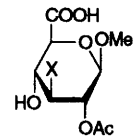
Taking advantage of the unique molecular characteristics of carbohydrates



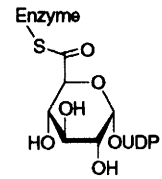
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36 X = NHFmoc

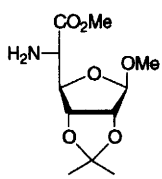


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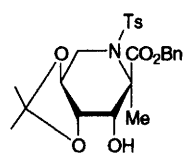
and the ease of solid phase chemistry, a new strategy for preparing universal pharmacophore mapping libraries based on carbohydrates has been developed. The report contains details of the synthesis of sixteen 48-member libraries based on the scaffolds **35** and **36**.[80] Site directed mutagenesis experiments have been employed as a tool in the investigation of enzymatic oxidation of UDP-glucose to UDP-glucuronic acid by UDP-glucose dehydrogenase. Evidence was obtained for the involvement of an enzyme-thioester intermediate **37**.[81] Prodrugs of anthracyclins containing a glucuronide residue linked through certain pre-designed spacer arms have been reported as candidates for antibody-directed enzyme prodrug therapy (see also Chapter 19).[82]

With a view to investigating the presence of protein–pectic polysaccharide amide linkages in plant cell walls, galacturonic acid and polygalacturonic acid peptidically linked to amino acids were prepared using the water-soluble carbodiimide coupling protocol and their susceptibility to acid, alkaline and enzymatic hydrolysis was studied.[83] Likewise, hard wood xylan-related aldobiuronic acid derivatives have also been prepared in a form suitable for linking to proteins (see also Chapter 3).[84] Some galacturonide residue-containing disaccharides have been reported as galactobiose analogues in protein binding studies by $PapG_{J96}$ from *E. coli* (see also Chapters 3 and 9).[85] Synthesis of some glycoglycines (*e.g.*, the 5-amino-5-deoxy-β-D-allofuranuronate **38**) and other model studies toward the synthesis of directly linked peptidyl nucleoside antibiotics of current topical interest have also been reported (see also Chapter 9).[86]

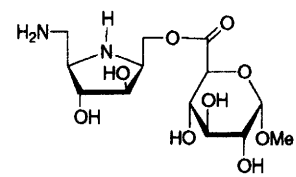
Short syntheses of thymine polyoxin C and uracil polyoxin C[87] (see also Chapter 19) as well as of some selectively modified ribonucleosides (see also Chapter 20)[88] and certain alduronic acid lactones[89] have been recorded. Several examples of modified iminosugars related to uronic acids (*e.g.*, **39**)[90] as well as ester and amide-linked pseudo-azadisaccharides (*e.g.*, **40**, see also Chapter 14)[91] have also been described.



38



39



40

5 Ascorbic Acids

The first synthesis of ascorbic acid from a non-carbohydrate source has been documented.[92] D-Erythro-ascorbic acid and its 5-*O*-(α-D-galactopyranoside) have been isolated from extracts of the fungal pathogen, *Sclerotina sclerotiorum*.[93]

In the area of reactions of ascorbic acid and its derivatives, exchange of the O-2 and O-3 atoms with those of water has been demonstrated by mass spectrometric studies using suitably labelled ascorbic acid derivatives and $H_2{}^{18}O$.[94] In the case of dehydroascorbic acid on the other hand, the interaction with water resulted in the exchange of three oxygen atoms. The results suggest spontaneous reversible hydrolysis and dehydration of dehydroascorbic acid in aqueous solution in contrast with slow hydrolysis for ascorbic acid under similar conditions.[95] From another study on the formation of the dehydro acid from 2,3-diketo-L-gulonic acid in aqueous solutions, it has been suggested that in the biological oxidation of ascorbic acid, the diketogulonic acid–dehydroascorbic acid equilibrium reaction is practically reversible, in contrast to what was previously believed.[96]

Interaction of ascorbic acid with certain transition metal complexes has been studied in relation to the possible intervention of these metal ions in reactions of the vitamin in biological systems.[97,98] Studies conducted on the autoxidation of D-isoascorbic acid in methanol in the absence of metal ions seem to suggest a mechanism similar to that of ascorbic acid that proceeds *via* the C-2-oxygen adduct.[99] Conversion of commercially available D-isoascorbic and L-ascorbic acids into 2-*O*-methyl-D-erythrose, 2-*O*-methyl-L-threose, 2-deoxy-D-and L-erythrose and the corresponding acetonides have been reported (see also Chapters 2, 5 and 12).[100] Preparation of 3-*O*-retinoyl-ascorbic acid for use as an antioxidant by nucleophilic substitution using sodium L-ascorbate and retinoyl fluoride has been documented.[101] Reaction of L-ascorbate with substituted nitrosobenzenes was used as a model system to suggest a mechanism for ascorbate–α-tocopherol interaction in its important redox cycle.[102]

Micellar effects on the oxidative electrochemistry of 6-*O*-caproyl/lauroyl/palmitoyl-ascorbic acid have been investigated by cyclic voltametry.[103] The hydrophobic/lipophilic interaction of the hydrocarbon chain and the electrostatic interaction of the ascorbate anion moiety were found to be the significant factors controlling the electrochemical behaviour in micellar solutions. The voltammograms were used to calculate the electron-transfer rate constants and the diffusion coefficients. 3-*O*-Diphenylphosphinyl and 3-*O*-acetyl derivatives of 5,6-*O*-isopropylidene-ascorbic acid and their rearrangements in the presence of a proton donor to give the respective 2-*O*- esters have been described (see also Chapter 7).[104]

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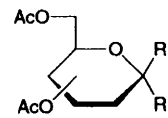
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17
Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

Some 1-thiazolidinyl hexosyl acetates (**1**) (of galactose, 2-azido-2-deoxy-galactose, glucose and mannose) have been converted [$P(OEt)_3$, TmsOTf] to the glycosyl phosphonates **2** and then the heptulose derivatives **3**.[1] Similar

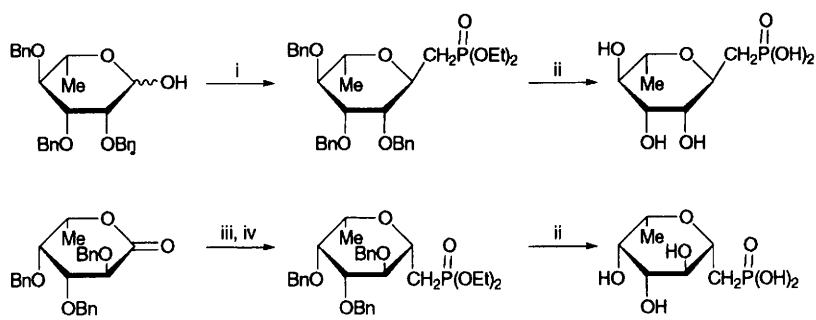


1 R =  ; R^1 = OAc

2 R =  ; R^1 = $P(O)(OEt)_2$

3 R = CH_2OH, CO_2Me; R^1 = $P(O)(OEt)_2$

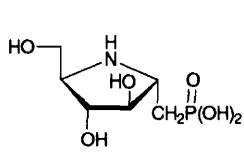
treatment [$P(O^iPr)_3$, BF_3OEt_2] of pentofuranosyl acetates has afforded the corresponding glycosyl phosphonates.[2,3] The isosteric phosphonate analogues of α-L-rhamnose 1-phosphate and β-L-fucose 1-phosphate have been prepared (Scheme 1),[4] and the 1,4-dideoxy-1,4-imino-D-arabinose-derived phosphonate **4** has been synthesized as a potential inhibitor of D-arabinosyltransferases.[5] An alternative *C*-glycosylphosphonate synthesis has utilized the reaction of a pyranose anomeric radical derivative with a vinyl phosphonate.[6]



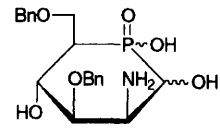
Reagents: i, NaH, $CH_2[P(O)(OEt)_2]_2$; ii, Me_3SiI; iii, $LiCH_2P(O)(OEt)_2$; iv, Et_3SiH, $BF_3.OEt_2$

Scheme 1

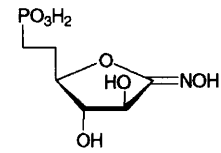
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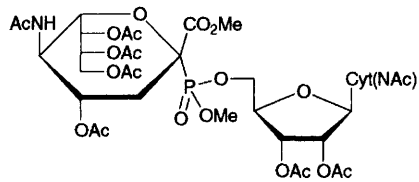


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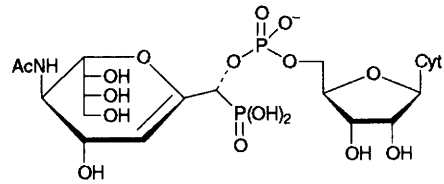


6

The 2-amino-2,5-dideoxy-5-hydroxyphosphinyl-D-mannose derivative **5** has been prepared.[7] The methylenephosphonate analogue **6** of D-arabinonolactone 5-phosphate oxime has been made as a potential inhibitor of glucosamine 6-phosphate synthase,[8] and phosphonate analogues **7** and **8** of CMP-Neu5Ac have been prepared.[9,10]



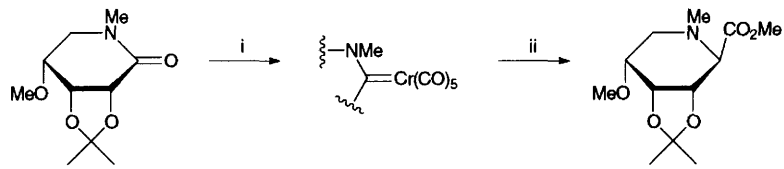
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8

2 Other Carbon-bonded Derivatives

Photolysis of the sugar-chromium species **9** in methanol has led to the 2,6-imino-D-allonate **10** (Scheme 2),[11] and previous work by the same group using



9 10

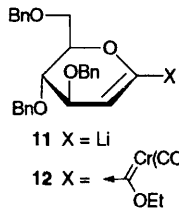
Reagents: i, $K_2Cr(CO)_5$; ii, *hν*, MeOH

Scheme 2

carbohydrate-chromium compounds has been reviewed.[12] The lithiated glycal **11** has been converted [$Cr(CO)_6$ then Et_3OBF_4] to the chromium species **12**[13] and ammonolysis of metallated derivatives **13** has afforded **14**.[14] An alkyl cobaloxime **15** has been prepared from tetra-*O*-benzoyl-α-D-glucopyranosyl bromide [with $ClCo(dmg)_2py$, $NaBH_4$].[15]

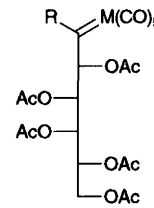
Some ferrocenyl esters of carbohydrates are covered in Chapter 7, and a number of carboranyl glycosides such as **16** have been prepared for evaluation in boron neutron-capture cancer therapy.[16]

An improvement to the radical stannylation of 1-phenylsulfonyl glycals

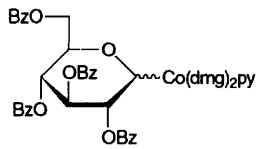


11 X = Li

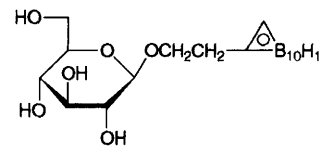
12 X =



13 R = OMe
14 R = NH_2
} M = Cr, W, Mo

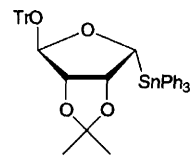


15 dmg = dimethylglyoxime



16

(Bu_3SnH, AIBN), to give the corresponding 1-tributylstannyl derivatives, has involved increasing the amounts of radical 'initiator' to stoichiometric quantities.[17] The synthesis of stannane **17** has been described.[18]



17

3 Oxygen-bonded Derivatives

The interactions between D-ribose or 2-amino-2-deoxy-D-glucose and copper(II) ions in aqueous solutions at high pH have been studied spectroscopically. It was concluded that the oxygen coordination geometry around the Cu(II) ion (distorted octahedral) and the Cu–O bond lengths were similar to those in the hexaaqua copper(II) ion.[19]

The transport of monosaccharides through a chloroform layer mediated by lipophilic alkaline earth metal complexes (*e.g.* $M\{OP(O)[OCH_2CH(Et)\text{-}C_4H_9]_2\}_2$ has been studied. It was found that the barium complex was best for the transport of ribose.[20]

Further work has been described on the design of arylboronic acid derivatives as fluorophores for the specific detection of particular monosaccharides in aqueous solutions.[21] Other arylboronic acid–carbohydrate adducts have been used to bind metals into chiral complexes.[22] The thermodynamics of borate ester formation on D-*glycero*-D-*gulo*-heptonamide, *N*-methyl-D-glucamine and diglucitylamine in aqueous solutions has been studied by ^{11}B NMR spectroscopy.[23]

Applications of mostly *O*-linked organotin-containing intermediates in cabohydrate chemistry have been reviewed.[24] Treatment of 1,2-*O*-dibutylstannylene-β-D-mannopyranose with various carbohydrate triflate ester electrophiles has allowed the synthesis of β-D-mannopyranosyl disaccharides,[25] and the use of polymer-supported trialkyltin ethers of carbohydrates has been investigated in regioselective acylation studies. The same selectivity was obtained as with normal tributyltin ethers.[26]

References

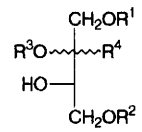
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11 M. Klumpe and K.-H. Dötz, *Tetrahedron Lett.*, 1998, **39**, 3683.
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13 M.R. Hallett, J.E. Painter, P. Quayle and D. Ricketts, *Tetrahedron Lett.*, 1998, **39**, 2851.
14 R. Ehlenz, W. Straub, J.C. Weber, K. Airola and M. Nieger, *J. Organomet. Chem.*, 1997, **548**, 91 (*Chem. Abstr.*, 1998, **128**, 128 223).
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18
Alditols and Cyclitols

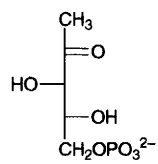
Sections on the preparation of imino-sugars and cyclitols were included in a review on the use of aldolases in synthesis.[1]

1 Alditols and Derivatives

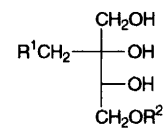
1.1 Alditols. – A wide range of branched tetritols **1** have been prepared by organometal addition to the carbonyl group of L-*glycero*-tetrulose carrying various *O*-protecting groups.[2]



1 R^1 = Tr or Tbdms



2

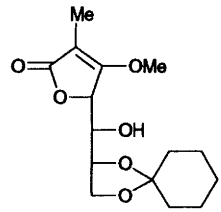


3 R^1 = H, $R^2 = PO_3^{2-}$
4 R^1 = OH, R^2 = H
5 $R^1 = R^2$ = H

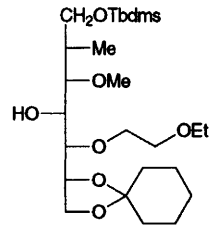
The single-step transformation of 1-deoxy-D-xylulose 5-phosphate (1-deoxy-D-*threo*-pentulose 5-phosphate, **2**) to 2-*C*-methyl-D-erythritol-4-phosphate (**3**) under catalysis by a recombinant oxidoreductase in the presence of NADPH provided evidence for an alternative, non-mevalonate route to isopentenyl diphosphate,[3] and it has been demonstrated that the rearrangement **2**→**3** takes place in the leaves of certain plants.[4] Alditol **4** bearing an unusual hydroxymethyl branch has been isolated from fruit of *Torillis japonica* along with the more widespread 2-*C*-methyl-D-erythritol (**5**). The possible involvement of the branched alditols **4** and **5** in the biosynthesis of the branched pentose apiose has been suggested.[5]

2,3-*O*-Cyclohexylidene-D-glyceraldehyde and methyl α-methyltetronate underwent chelation-controlled aldol condensation to furnish mainly adduct **6**, which was transformed in seven conventional steps to the 2-deoxy-2-*C*-methylheptitol derivative **7**. The use of compound **7** in the synthesis of antifungals is covered in Chapter 24.[6] *O*-Protected 1,2-dideoxypent-1-enitols reacted with organolead(IV) reagents under Pd-catalysis to give chain-extended products (*e.g.* **8**→**9**).[7] Dideoxyhex-1-enitol derivative **10** and its substituted-amino

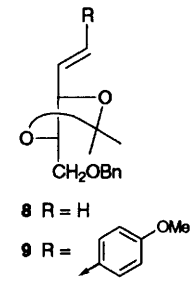
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6

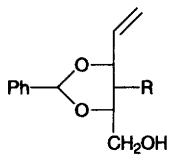


7

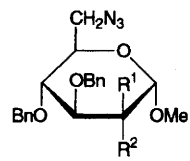


analogue **11** have been synthesized by standard methods from diacetone-D-glucose and the corresponding 3-deoxy-3-(*N*-methoxycarbonyl-*N*-methylamino)-derivative, respectively. The use of these compounds in the synthesis of the *C*-glycosidic moiety of nogalamycin is covered in Chapter 19.[8–10]

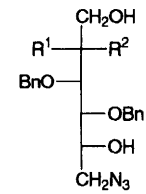
A paper on the reactions of epoxides with lithium halides on silica gel without added solvents mentioned the opening of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol to give 1,6-dihalides selectively in yields of 60–75% as the only carbohydrate examples.[11]



10 R = OBn
11 R = N(Me)OCOMe

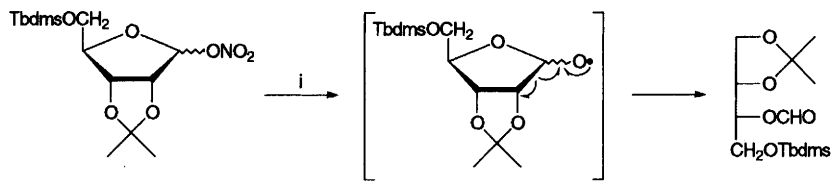


12 R^1 = H, R^2 = OBn, or R^1 = OBn, R^2 = H



13

Hydrolysis of 6-azides **12** and reduction of the resulting free sugars gave 6-azido-6-deoxy-D-hexitol derivatives **13** which formed aziridines on treatment with triphenyl phosphine in hot toluene. The use of these compounds in the synthesis of furanoid sugar amino acids is covered in Chapter 16.[12]

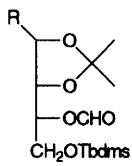


Reagents: i, Bu_3SnH, AIBN, Py, PhH

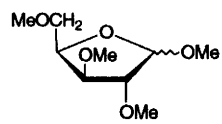
Scheme 1

Treatment of glycosyl nitrates with Bu_3SnH/AIBN caused C-1–C-2 fragmentation furnishing alditols *via* anomeric alkoxy radicals. An example is given in Scheme 1.[13] Radical cleavage of the C-1–C-2 bond in pentofuranose derivatives on exposure to (diacetoxyiodo)benzene and iodine (see Vol. 31, Chapter 2, ref. 7 and this Vol., Chapter 2, ref. 10) gave tetrose equivalents, such as **14**, suitable for radical chain-extension with, for example, allyltributyltin to afford products such as **15**.[14] Chelation-controlled, regioselective *endo*-C–O-cleavage of methyl

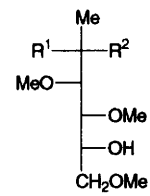
furanosides **16** with $ZnMe_2/TiCl_4$, followed by *in situ* stereoselective *C*-1 methylation, gave 1-deoxyhexitols **17** and **18** in the ratio 99:1. While the stereoselectivity was excellent for this and other 2-*O*-methylated furanoid starting compounds, it was poor in the 2-deoxy series.[15] Satisfactory stereoselectivity was also observed in a similar cleavage reaction of benzyl 2-deoxy-2-*C*-methyl-α-D-pentopyranoside **19**. Its isomer **20**, on the other hand, did not react at all when exposed to $ZnMe_2/TiCl_4$, in contrast to observations made in earlier experiments in which Me_3Al was used (see Vol. 25, p. 330, ref. 76).[16]



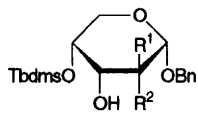
14 R = I
15 R = All



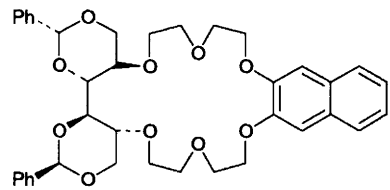
16



17 R^1 = OMe, R^2 = H
18 R^1 = H, R^2 = OMe



19 R^1 = Me, R^2 = H
20 R^1 = H, R^2 = Me



21

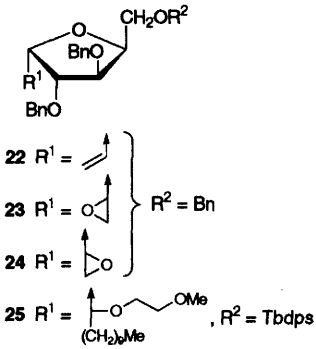
The alditol-based crown ether **21** has been prepared by treatment of 1,3:4,6-di-*O*-benzylidene-D-mannitol successively with $(ClCH_2CH_2)_2O$/aq. NaOH and 2,3-dihydroxynaphthalene/$CsCO_3$ /*n*-BuOH.[17]

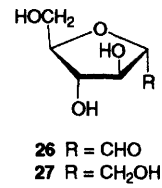
Two crystalline forms of D-mannitol, precipitated in the presence of Keggin heteropolyanions $\{[PW_{12}O_{40}]^{3-}$ or $[SiW_{12}O_{40}]^{3-}\}$, have been characterized by X-ray diffraction and solid state ^{13}C NMR spectroscopy.[18] The thermal and rheological properties of gels formed from 2,4-*O*-benzylidene-, 1,3:2,4-di-*O*-benzylidene- and 1,3:2,4:5,6-tri-*O*-benzylidene-D-glucitol in ethyleneglycol solution have been studied.[19]

Additional acyclic alditols are referred to in Section 1.4.2. below.

1.2 Anhydro-alditols. – Epoxidation of alkene **22**, readily available from 2,3,4,6-tetra-*O*-benzyl-D-glucose, by use of MCPBA gave epimers **23** and **24** in the ratio 3:1, whereas the wanted isomer **24** was the main product when Payne conditions ($PhCN/H_2O_2$) were applied. Transformation to **25**, an intermediate in the synthesis of oxygenated analogues of acetogenins (see Chapter 24), involved four conventional reaction steps.[20]

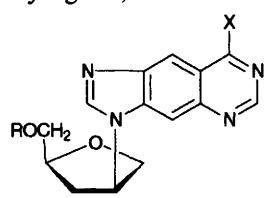
2,5-Anhydro-D-mannitol (**27**) has been obtained from D-glucosamine hydrochloride by nitrous acid deamination with concurrent ring-contraction to give aldehyde **26**, and subsequent $NaBH_4$ reduction. It served as the chiral, tetrafunctional core of dendrimers.[21]

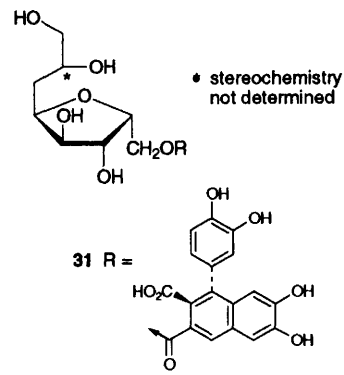




5′-Monophosphates of several novel dideoxynucleosides containing tricyclic bases, *e.g.* compound **30**, have been synthesized from 1,4-anhydro-5-*O*-benzoyl-3-deoxy-2-*O*-tosyl-D-*erythro*-pentitol by displacement of the tosylate with the appropriate base carrying a methylthio group to afford, in this case, **28**; exposure to methanolic NH_3, then phosphorylation gave the target **30** by way of **29**.[22]

The 2,5-anhydro-6-deoxy-octitol derivative **31**, esterified at O-1 with a dicarboxy-lignan, has been isolated from the liverwort *Bazzania trilobata*.[23]

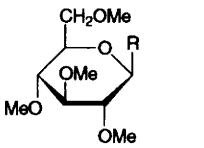




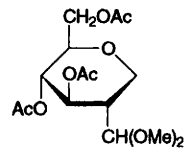
A new, electrochemically promoted reductive cleavage of permethylated methyl pyranosides and furanosides (*e.g.* **32**→**33**), which might be suitable for sequencing polysaccharides, has been reported. It uses BH_3(SMe as reducing agent and $ZnClO_4.6\ H_2O$ as electrolyte and is based on the fact that a strongly acidic environment is established in the vicinity of the anode surface. This method has the advantage over the standard chemical one employing Et_3SiH that it is very fast and insensitive to moisture; it is, on the other hand, potentially explosive.[24]

One-pot hydroformylation/acetalation of tri-*O*-acetyl-D-glucal in 2,2-dimethoxypropane using a rhodium complex and PPTS, respectively, as catalysts for the two reactions gave dimethylacetal **34**, whereas tri-*O*-benzyl-D-glucal furnished methyl tri-*O*-benzyl-2-deoxy-α-D-*arabino*-hexopyranoside under similar conditions. Evidently, when the double bond is not deactivated by ester groups in the neighbourhood, attack by a proton is faster than coordination

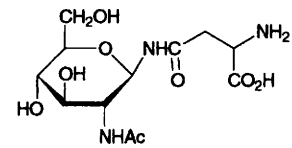
with the rhodium complex.[25] The anhydro-alditol-based mimetic **37** of N^4-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-L-asparagine (**35**) has been prepared by coupling of the known hydrochloride **36** with an appropriately protected and activated asparagine derivative, followed by deprotection.[26]



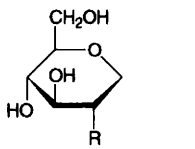
32 R = OMe
33 R = H



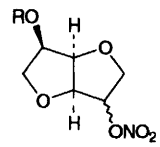
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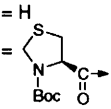
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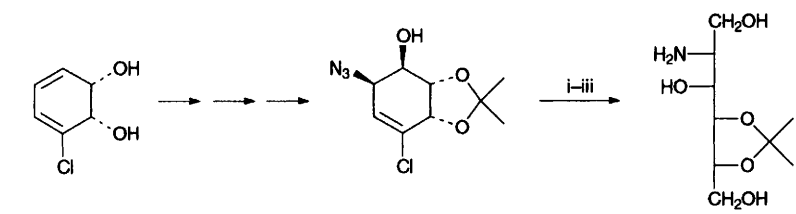


36 R = $NH_3^+Cl^-$
37 R = NHC(=O)CH(NH$_2$)CO$_2$H



38 R = H
39 R =





40 **41** **42**

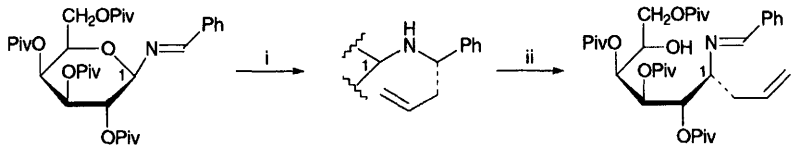
Reagents: i, BnBr, NaH, DMF; ii, O_3, then $NaBH_4$; iii, H_2, Pd/C

Scheme 2

A series of 2-*O*-acylated 1,4:3,6-dianhydrohexitol-5-nitrates, *e.g.* compounds **39**, have been prepared as potential vasorelaxing agents by DCC-promoted coupling of alcohols **38** with *N*-protected, sulfur-containing amino acid derivatives.[27]

1.3 Acyclic Amino- and Imino-alditols. – In the first seven steps of a fifteen-step synthesis of (−)-*N*-acetylneuraminic acid from enantiopure cyclohexadiene *cis*-1,2-diol **40** (the product of a biocatalytic oxidation of chlorobenzene) the known azide **41** was prepared and converted by ozonolysis, $NaBH_4$ reduction and hydrogenolysis to 2-amino-2-deoxy-D-mannitol derivative **42**, as shown in Scheme 2.[28]

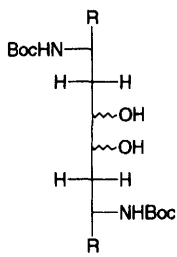
A stereocontrolled, Lewis acid-catalysed aza-Cope rearrangement of *N*-glycosyl homoallylamines gave chain-extended aminoalditols in high yields. An example is shown in Scheme 3.[29]



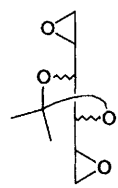
Reagents: i, AllTms, $SnCl_2$, THF, ii, $BF_3.OEt_2$, xylene

Scheme 3

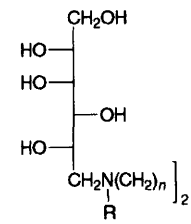
A large number of acyclic peptidomimetic HIV-1 protease inhibitors of general structure **43** have been prepared by various routes, mostly *via* the 1,2:5,6-diepoxides **44**.[30] Compounds **45** have been made as bolaamphiphiles and their aggregation behavior has been investigated.[31] Glucitol 2-aminoacridines **46** have been prepared and evaluated as fluorescent tags.[32] 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-dioctylamino-D-altritol, an efficient catalyst for the enantioselective addition of diethyl zinc to aldehydes is referred to in Chapter 24.



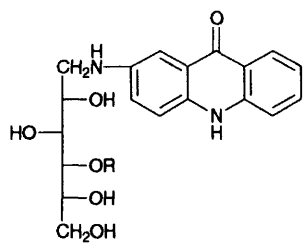
43 R = Ph or PhO



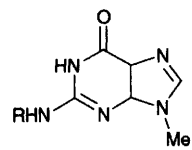
44



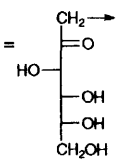
45 $n = 3, 4, 5$
R = $CO(CH_2)_{12}Me$



46 R = H or oligosaccharide



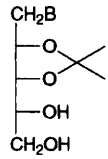
47 R =



48 R =

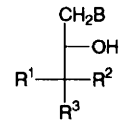


D-Glucose reacted with 9-methylguanine in the presence of air to form *N*-fructosyl-9-methylguanine (**47**). On extended exposure to air, degradation to N^2-(1-carboxymethyl)-9-methylguanine (**48**), an Amadori oxidation product, was observed.[33] 9-(2,3-*O*-Isopropylidene-D-ribityl)purines **49** (for their preparation see Vol. 27, p. 270, ref. 266) have been transformed into a series of acyclonucleosides **50** by modification of the sugar moiety employing standard reactions.[34]



B = Ade or Gua

49



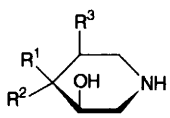
50 R^1, R^2 = H, OH
R^3 = CH_2OH, CO_2H, CN *etc.*

The oximes of cellobiose and lactose, obtained by an improved procedure using hydroxylammonium sulfate and ammonium acetate in aq. solution, have been subjected to electroreduction to furnish 1-amino-1-deoxy-4-*O*-β-D-gluco- and -galacto-pyranosyl-D-glucitol, respectively.[35]

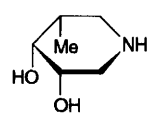
A number of aminoalditols which were prepared as intermediates in the synthesis of cyclic imino compounds are referred to in Section 1.4.2. below.

1.4 Monomeric, Five- or Six-membered Cyclic Imino-alditols. – A review on 1-*N*-iminosugars as transition state analogues of equatorial glycoside formation and cleavage covered mostly the work of M. Bols' group in this area.[36] Full details on the synthesis of 1-*N*-iminosugars **51**–**53** by Ichikawa's group have been published together with an account of their activities as glycosidase inhibitors (see Vol. 29, p. 234, refs. 68, 69).[37]

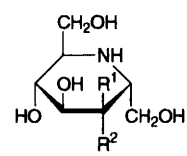
α-Homonojirimycin (**54**) and α-homomannojirimycin (**55**) and their β-isomers, all isolated from natural sources, together with the known synthetic *N*-methyl and *N*-butyl derivatives of **54**, were used in a study probing the relationships between bioactivity and structural alterations at the anomeric position as well as conformational changes.[38]



51 R^1 = H, R^2 = OH
R^3 = CH_2OH or CO_2H
52 R^1 = OH, R^2 = H
R^3 = CH_2OH



53

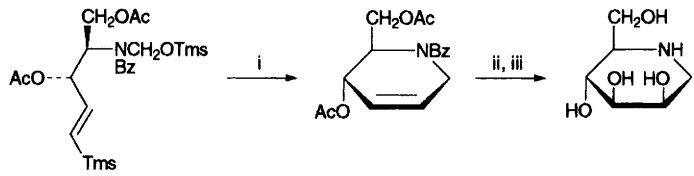


54 R^1 = H, R^2 = OH

55 R^1 = OH, R^2 = H

As usual, numerous dideoxy-iminitol derivatives have been synthesized as potential glycosidase inhibitors. Several new approaches to the formation of the nitrogen-containing cyclic structures have been reported. Alternatively, acyclic precursor prepared by novel routes were cyclized by one of the well established methods, in particular intramolecular displacement of a good leaving group by an amine, electrophilic addition to a double bond or reductive amination.

1.4.1 New Approaches to the Formation of Nitrogen-containing Rings. An oxidative method for promoting Mannich cyclizations has been applied to the



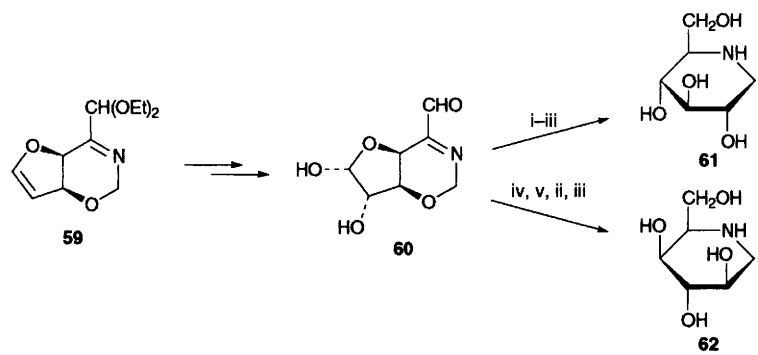
56 **57** **58**

Reagents: i, CAN; ii, OsO_4, NMO; iii, aq. HCl, then ion exchange

Scheme 4

synthesis of azasugars, as shown in Scheme 4. The tetrahydropyridine ring of compound **57** was formed by CAN-induced generation of the iminium cation of the D-serine-derived α-silylamido-vinyl silane **56**, resulting in ring-closure. Dihydroxylation of the double bond, followed by acid hydrolysis, furnished 1-deoxymannojirimycin (**58**) and its *allo*-isomer.[39]

The racemic furoisoxazoline-3-aldehyde **60** was obtained from the 1,3-dipolar cycloaddition product **59** of furan and 2,2-diethoxyacetonitrile *N*-oxide. The resolved enantiomers were converted to 1-deoxynojirimycin (**61**) and 1-deoxyidonojirimycin (**62**) (or their enantiomers) in three and four steps, respectively, as outlined in Scheme 5. These experiments were carried out to demonstrate the versatility of carbaldehyde **60** as a latent iminohexitol moiety.[40]



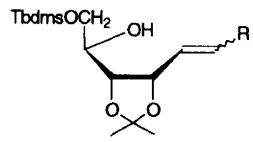
59 **60** **61** **62**

Reagents: i, $NaBH_4$; ii, aq. TFA; iii, H_2, Pd/C; iv, LAH; v, CbzCl, $NaHCO_3$

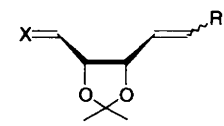
Scheme 5

A reverse-Cope elimination process was used in a novel approach to *N*-oxides of aza-sugars. Enals **64** resulting from glycol cleavage of the ribose-derived alkenes **63** were converted to nitrones **65** under standard conditions. Addition of $PhSO_2Li$ afforded the unstable hydroxylamines **66** as single isomers. Ring-closure to give all-*cis*-products **67** with high selectivity took place spontaneously at ambient temperature.[41]

A very short route to the racemic diazasugar (±)-1-azafagomine (**69**) involved cycloaddition between 2,4-pentadien-1-ol and the azadienophile 4-phenyl-1,2,4-triazoline to form adduct **68**. The two *trans*-disposed hydroxyl

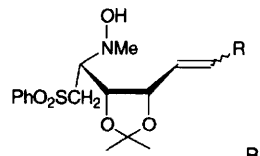


63



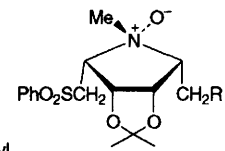
64 X = O

65 X = $\overset{+}{N}Me$ O^-

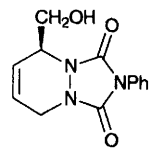


66

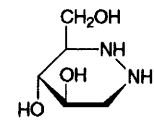
R = H, Me, Ph or 2-furyl



67



68



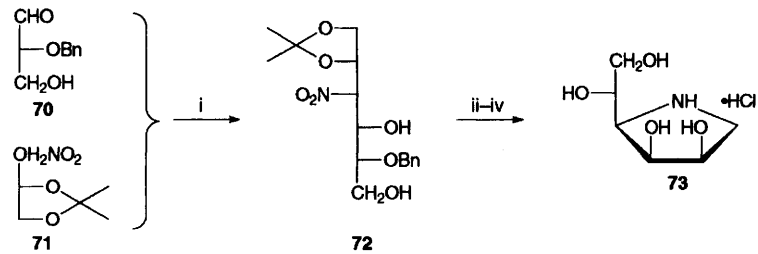
69

groups were introduced with moderate selectivity by way of an epoxide, and *N*-deprotection was brought about by hydrazinolysis.[42]

1.4.2 Ring-Closure by Displacement of a Leaving Group by an Amine. The stereoselective nitroaldol addition between the two 3-carbon building blocks **70** and **71** to form predominantly the D-mannitol derivative **72** was the key-step in the synthesis of 1,4-dideoxy-1,4-imino-D-mannitol (**73**), as indicated in Scheme 6. Cyclization was achieved by activation of the free hydroxyl group at C-6 of **72** with PPh_3. Use of the D-serine-derived nitro-compound **74** instead of **71** afforded by slightly modified routes the 5-amino-5-deoxy analogue of **73** and the 4-amino-4-deoxy analogue **75** of 1-deoxymannojirimycin (**58**).[43] Similar methodology has been employed in the synthesis of the 1-deoxyaltronojirimycin precursor (**78**) from acyclic benzyl hexonate **77**, which in turn was obtained by condensation between the chelated enolate of glycine ester **76** and 4-*O*-Tbdms-2,3-*O*-isopropylidene-D-erythrose. Following desilylation, Mitsunobu conditions were applied to effect ring-closure. Reduction of the benzyl ester was carried out as the last step prior to deprotection to give 1-deoxyaltronojirimycin (**79**).[44]

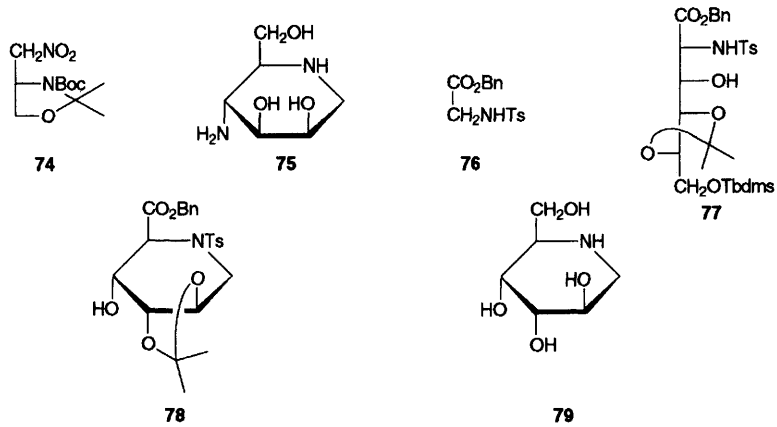
Alkenes **81**, available by reaction of aldehyde **80** with allyl bromide in the presence of Cr(II) chloride, isomerized to the epimeric *O,O*-acetals **82** under the influence of acid (Scheme 7). Ozonolysis of the *erythro*-isomer, followed by $NaBH_4$-reduction, gave the 4-aminopentitol derivative **83** with high selectivity. Cyclization *via* tosylate **84** afforded in three further steps 1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol (**85**).[45]

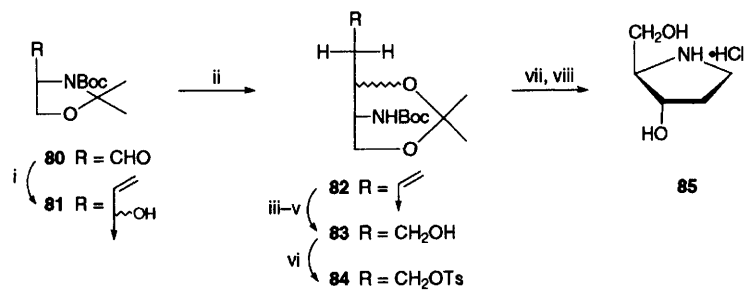
Dibenzyloxydisulfoxide **86** was obtained as a single isomer in four steps



Reagents: i, Bu_4NF, H_2O, THF; ii, H_2, Pd/C; iii, PPh_3, Et_3N, CCl_4; iv, aq. HCl

Scheme 6



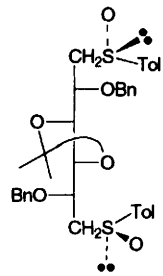


Reagents: i, AllBr, $CrCl_2$; ii, TsOH, $Me_2C(OMe)_2$; iii, separation of isomers; iv, O_3; v, $NaBH_4$; vi, TsCl, Et_3N; vii, NaH; viii, aq. HCl

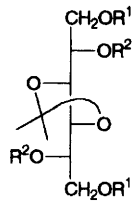
Scheme 7

from dimethyl 2,3-*O*-isopropylidene-L-tartrate. One-pot Pummerer rearrangement/reduction led to the optically pure D-iditol derivative **87** which was converted to dimesylate **88**. Cyclization by intermolecular displacement of the mesylate groups by benzylamine gave after deprotection 2,5-dideoxy-2,5-imino-L-mannitol **89**.[46] By a very similar route amphiphilic *N*-alkyl-2,5-dideoxy-2,5-imino-D-iditol derivatives were prepared by use of a *manno*-configurated 2,5-dimesylate and long-chain alkylamines.[46a]

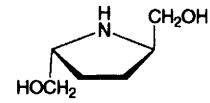
A new, asymmetric synthesis of 1-deoxynojirimycin (**61**) from an achiral



86

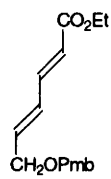


87 R^1 = H, R^2 = Bn
88 R^1 = Mom, R^2 = Ms

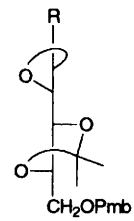


89

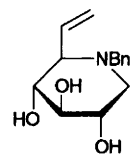
starting material involved regio-, stereo- and enantio-selective hydroxylation and Sharpless epoxidation of ethyl 6-*p*-methoxybenzyloxy-hexa-2,4-dienoate (**90**), followed by routine ester reduction and acetonation to give L-iditol derivative **91**. Chain-extension by use of Wittig methodology, then replacement of the protecting group at O-7 by mesylate furnished the required vinyl epoxide **92**. Aminolysis with $BnNH_2$ proceeded with attack at the allylic position, as expected, and with concomitant displacement of the mesyl group to give **93**. Refunctionalization of the side-chain and deprotection afforded the target **61** in fourteen steps and 12.5% overall yield.[47]



90

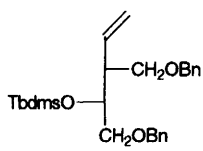


91 R = CH_2OH
92 R = $CH{=}CH_2$

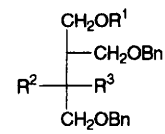


93

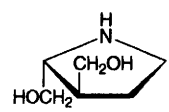
The known alkene **94** was hydroborated and further elaborated into the branched deoxypentitol **95** and hence into the primary mesylate **96** with an azido group at the 4-position. On reduction of the azide, ring-closure took place to give bis-(hydroxymethyl)pyrolidine **97** as a building block for novel nucleoside analogues.[48]



94

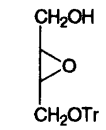


95 R^1 = Ac, R^2 = OTbdms
R^3 = H
96 R^1 = Ms, R^2 = H
R^3 = N_3

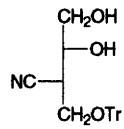


97

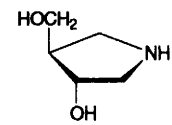
The key-operation in a multigram synthesis of the 2-deoxyribose-type 1-*N*-iminosugar **100** from fumaric acid monomethyl ester was the regioselective opening of epoxide **98**, obtained by Sharpless epoxidation of the corresponding alkene, with Et_2AlCN (**98**→**99**). Primary tosylation, followed by hydrogenation over Raney nickel resulted in ring-closure with concomitant loss of trityl to furnish the desired product **100**.[49] In a similar manner, the D-xylose-derived epoxide **101** was converted to the bicyclic product **102**. Hydrolysis to the free sugar **103**, then glycol cleavage and $NaBH_4$-reduction furnished the 1-*N*-iminosugar **104**.[50]



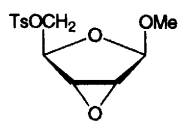
98



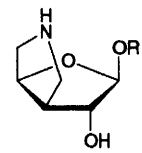
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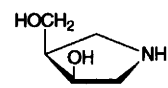
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101

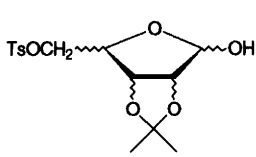


102 R = Me
103 R = H

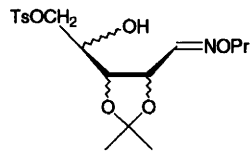


104

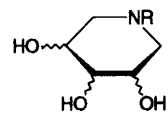
N-Alkoxy-trihydroxypiperidines **107** with D-*ribo*-, D-*lyxo*- and L-*lyxo*-configuration have been prepared in four easy and efficient steps from the corresponding 2,3-*O*-isopropylidene-6-*O*-tosyl-pentofuranoses **105**. The prospective ring-nitrogen atoms were introduced by formation of the *O*-propyloximes **106**, and ring-closures were effected by intramolecular displacement of the tosyl groups on reduction with $NaCNBH_3$. Acetal hydrolysis then furnished the targets **107**. The disaccharide **108** was made in an analogous manner.[51]



105



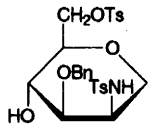
106



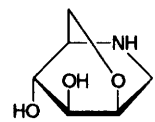
107 R = OPr
108 R = D-glucos-6-yl
(D-*ribo* configuration)

Formation of the nitrogen-containing ring of the bicyclic 2,6-anhydro-1-deoxymannojirimycin (**110**) was brought about by intramolecular displacement of the tosyloxy group of the *N,O*-ditosylate **109**, obtained in ten standard steps from D-glucose.[52]

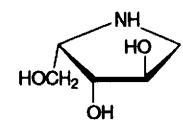
Iodine in methanol has been used for the convenient, one-pot deprotection/cyclization of some aminomesylates. 1-Benzyloxycarbonylamino-1-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-5-*O*-Tbdms-D-arabinitol, for example, gave 1,4-



109



110

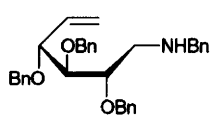


111

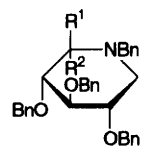
dideoxy-1,4-imino-L-lyxitol (**111**) in 75% yield after purification on Dowex 50W-X8 (NH_4OH as eluant).[53]

1.4.3 Ring-Closure by Electrophilic Addition of an Amine to a Double Bond. The cyclization of D-glucose-derived aminoalkenes on exposure to NIS or $Hg(OAc)_2$/KBr has previously been shown to give predominantly *gluco*-configured products (*e.g.* **112**→**113**). In a detailed investigation of these processes it has now been discovered that use of excess of $Hg(OAc)_2$ under anhydrous conditions, followed by KBr, favours formation of the alternative stereoisomer **114**.[54]

The 1,2,5-trideoxy-2,5-imino-1-phosphonate **117** was prepared from 2,3,5-tri-*O*-benzyl-D-arabinose stereoselectively by way of alkene **115** and iodide **116**. The *arabino*-stereochemistry was retained by employing two consecutive Mitsunobu reactions for the introduction of the amino group, and the cyclization which occurred on exposure of **116** to NIS was highly α-selective.[55]

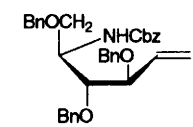


112

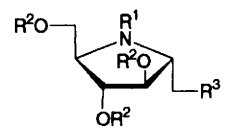


113 $R^1 = CH_2X$, $R^2 = H$ (X = Br or I)

114 $R^1 = H$, $R^2 = CH_2Br$

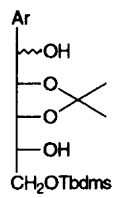


115

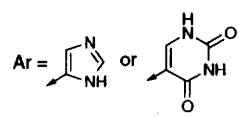


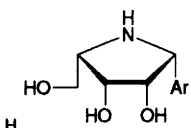
116 R^1 = Cbz, R^2 = Bn, R^3 = I

117 $R^1 = R^2 = H$, $R^3 = PO(OEt)_2$



118





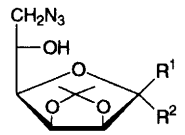
119

1.4.4 Ring-Closure by Reductive Amination. Ring-closure of 1-*C*-aryl-D-pentitol derivatives **118** by Swern oxidation to the corresponding diketones, then reductive amination with $NaBH_3CN$ in the presence of ammonium formate, furnished after acetal hydrolysis *C*-aza-L-*lyxo*-nucleosides **119** (in a previous report, Vol. 30, p. 230, ref. 53, similarly obtained products were incorrectly assigned D-*ribo*-configuration).[56]

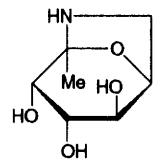
Preparation of the rigid, bicyclic 1,6-dideoxy-1,6-iminoheptitol **122**, a potent

fucosidase inhibitor, from L-gulonolactone required a 1-carbon chain extension at the 'reducing end' which was achieved by reaction of the 6-azido-intermediate **120** with methyl lithium to form **121**. Acid hydrolysis gave the free 7-azido-1,7-dideoxyheptulose which ring-closed under reductive amination conditions.[57] The synthesis of some closely related 6-amino-1,6-anhydro-6-deoxy-sugars is referred to in Chapter 10.

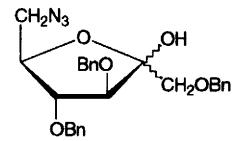
1-Deoxymannojirimycin and 2,5-dideoxy-2,5-imino-D-mannitol with deuterium labels at C-5 and C-2, respectively, were readily obtained when the Raney Nickel catalysed cyclizing reductive amination reactions of azides **123** and **124** were carried out in MeOD under D_2.[58]



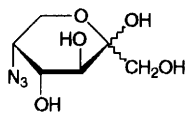
120 $R^1, R^2 = =O$
121 $R^1 = Me, R^2 = OH$



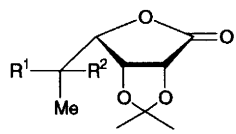
122



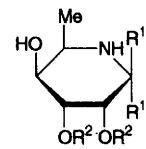
123



124



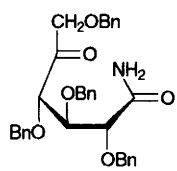
125 $R^1 = OH, R^2 = H$
126 $R^1 = H, R^2 = N_3$



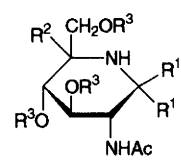
127 $R^1, R^1 = =O, R^2, R^2 =$ 
128 $R^1 = R^2 = H$

1.4.5 Ring-Closure by Other Methods. Lactone **125** was the starting material for a brief synthesis of 6-deoxy-D-gulonojirimycin (**128**) by way of azide **126** which on hydrogenation to the corresponding amine formed lactam **127**. Reduction of the carbonyl group to a methylene group was achieved by treatment with BH_3. L-Gulonojirimycin was made analogously from an appropriate lactone precursor.[59]

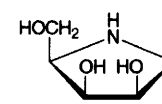
Lactam **131** was obtained from 2-acetamido-2-deoxy-D-gluconolactone by way of ketoamide **129** which ring-closed to **130** on exposure to acetic acid. Removal of the tertiary hydroxyl group by use of Et_3SiH, followed by debenzylation and reduction of the carbonyl group by use of $NaBH_4$/$BF_3.OEt_2$, gave 2-acetamido-1,2-dideoxynojirimycin (**132**).[60]



129



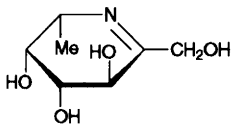
130 $R^1, R^1 = =O, R^2 = OH, R^3 = Bn$
131 $R^1, R^1 = =O, R^2 = H, R^3 = Bn$
132 $R^1 = R^2 = R^3 = H$



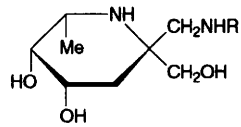
133

New syntheses of 1-deoxynojirimycin (**61**) and isomers thereof[61] and of the potent α-galactosidase inhibitor **133**[62] from pyroglutamic acid and from 4-hydroxy-L-proline, respectively, have also been reported.

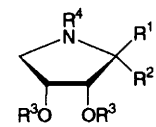
1.4.6 Modification of Known Azasugars. In an effort to increase the potency and linkage-selectivity of the known fucosidase-inhibitor **134**, obtained by an aldolase-catalysed condensation (see Vol. 31, Chapter 18, ref. 66), an amino-methyl-branch was introduced by reaction with KCN and subsequent hydrogenation. The free amino group of the amino-iminocyclitol **135** thus produced was acylated with various amino acids to afford, for example, glycine derivative **136**.[63]



134

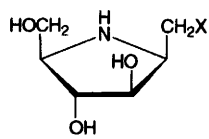


135 R = H
136 R = $COCH_2NH_2$

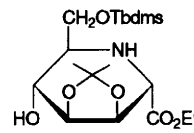


137 R^1 = OMe, R^2 = H, R^3 = Ac
R^4 = Cbz
138 R^1 = CO_2H or CH_2NH_2
$R^2 = R^3 = R^4$ = H
139 R^1 = H, R^2 = CO_2H
$R^3 = R^4$ = H

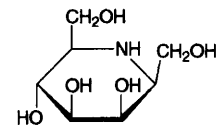
Lewis acid-catalysed cyanation of the fully protected azasugar glycoside **137** gave, after some further elaborations, the new aminoazasugar derivatives **138** and **139**.[64] Replacement of one primary hydroxyl group of the known 2,5-anhydro-2,5-iminoalditol **140** by a thioether function was readily achieved by way of selectively protected intermediates. Sulfides **141** are of interest as potential inhibitors of arabinosyltransferases.[65]



140 X = OH
141 X = SR
R = $(CH_2)_nMe$
n = 9, 11, 15 *etc.*



142



143

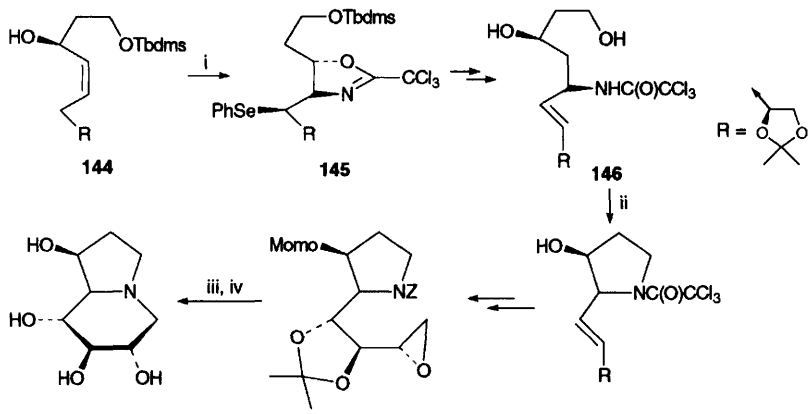
1-Deoxynojirimycin (**61**) has been transformed into 1-deoxymannojirimycin (**58**) and 1-deoxygalactojirimycin by simple inversion reactions at carbon atoms 2 and 4, respectively, of suitably protected intermediates.[66]

The propensity of ester **142**, a known precursor of α-homomannojirimycin (**57**) (see Vol. 26, p. 193, ref. 4; Vol. 23, p. 181, ref. 32) to isomerize under basic conditions has now been exploited to gain access to β-homomannojirimycin (**143**).[67]

1.4.7 Natural Products. Two potent new natural β-glycosidase inhibitors, Broussonetines G and H, closely related to Broussonetines A–G (see Vol. 31,

Chapter 18, refs. 41 and 42) have been isolated from the branches of *Broussonetia kazinoki*.[68]

1.5 Fused-ring Azasugars. – A new multi-step total synthesis of (+)-castanospermine (**149**) from (*S*)-butane-1,2,4-triol is outlined in Scheme 8. Key-steps were the unprecedented phenylselenoamidation (**144**→**145**), a first cyclization under Mitsunobu condition (**146**→**147**), and a second one by intramolecular opening of an epoxide on deprotection of an amino function, followed by complete deprotection (**148**→**149**).[69]

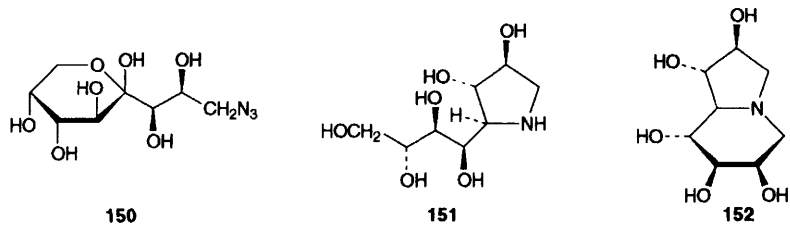


Reagents: i, Cl_3CCN, DBU, then PhSeCl, $MeOC(NH)CCl_3$, Et_3N; ii, DIAD, PPh_3, THF; iii, Pd/C, cyclohexene, EtOH; iv, HCl, MeOH, then ion exchange

Scheme 8

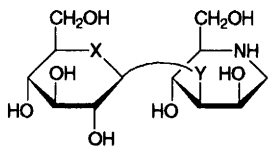
Azide **150**, formed in three steps from the known 2,3:4,5:6,7-tri-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose, cyclized on reduction to give the 1,4-dideoxy-1,4-iminooctitol derivative **151**, which was protected at nitrogen, then *O*-mesitylsulfonylated at the primary position. On hydrogenolysis, ring-closure to give the catanospermine analogue **152** took place.[70]

The NMR spectra of naturally occuring alexins are referred to in Chapter 21.

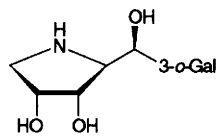


1.6 Azasugar-containing Disaccharides. – 1-Deoxynojirimycin (**61**) has been α-galactosylated at the 6-position by use of *p*-nitrophenyl α-D-galactopyrano-

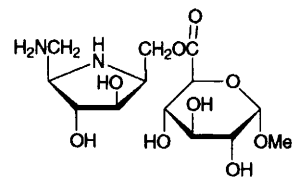
side and an α-galactosidase from green coffee beans.[71] 3-*O*-Glucosylated 1-deoxymannojirimycins containing a sulfur atom in the glucose moiety and in the glycosidic linkage, compounds **153** and **154**, respectively, have been prepared as potential *endo*-α-D-mannosidase inhibitors.[72] A full report on the synthesis of compound **155** and nine closely related, racemic, *C*-linked iminodisaccharides from non-carbohydrate sources by Vogel's group has been published (see Vol. 31, Chapter 18, ref. 76; Vol. 29, p. 200, ref. 42).[73]



153 X = S, Y = O
154 X = O, Y = S

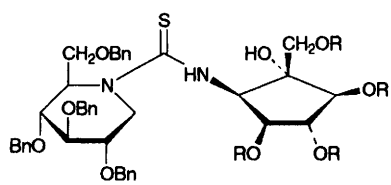


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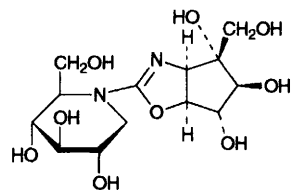


156

Ester-linked pseudo-azadisaccharides, such as **156**, as well as amide-linked analogues, were formed by condensing the appropriate, selectively *O*-benzyl- and *N*-Boc-protected monomers, with the help of DCC, followed by hydrogenolysis.[74] An *N*-alkoxy-linked heterodisaccharide is referred to in ref. 51 above (Structure **108**).



157 R = Tbdms



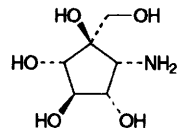
158

Coupling of the two glycosidase inhibitors 1-deoxynojirimycin and trehalamine was realized in compound **158**. Its precursor, the thiourea derivative **157** was readily obtained by reaction of per-*O*-benzylated 1-deoxynojirimycin with the *O*-silyl-protected isothiocyanate derivative of trehalamine.[75]

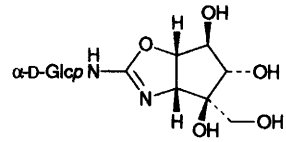
2 Cyclitols and Derivatives

A *Chemical Society Review* has covered the synthesis of carbocyclic compounds from sugar derivatives by free-radical methods.[76]

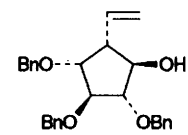
2.1 Cyclopentane Derivatives. – SmI_2 has proved to be of appreciable value for cyclizing various monosaccharide derivatives to cyclopentanes. D-Xylose-derived 2-*O*-benzyl-3,4-di-*O*-*p*-methoxybenzyl-D-*xylo*-pentodialdose was cyclized with this reagent to the two substituted cyclopentanes with *cis*-1,2-diols which were used to make cyclopentane pentaol tris- and tetrakisphosphates as



159

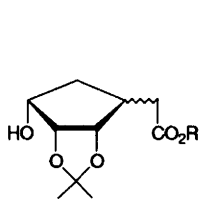


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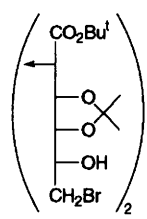


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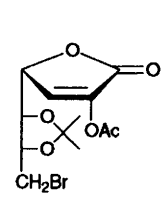
inositol phosphate analogues.[77] In related work trehazolamine (**159**) has been made by SmI_2-promoted cyclization of tetra-*O*-benzyl-D-*xylo*-hexos-5-ulose which gave the two cyclopentane 1,2-*cis*-diols in equal proportions one of which afforded the target compound *via* a cyclopentene derivative.[78] Related work used similar cyclization of a related *N*-methylaldoxime and converted the product to trehazolin (**160**).[79] The same reagent, together with $Pd(PPh_3)_4$, converted methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-α-D-*gluco*-hept-6-enoside into the vinylcyclopentane **161** (main product) and its three possible stereomers in 78% yield,[80] and a study of the closure of alkyl 2,3,7-trideoxy-7-halo (I or Br)-4,5-isopropylidene-D-*ribo*-hept-2-enonates, made from D-ribonolactone with SmI_2 found that cyclopentane (**162**) formation was favoured in HMPA. Amongst other products encountered were dimeric compounds *e.g.* **163**.[81] Further versatility of the reagent was exhibited by the pinacol condensation effected on 2,3,4,6-tetra-*O*-benzyl-hexitols derived from the corresponding methyl hexopyranosides, the D-glucitol ether giving the hexaol equivalent to **159** (with OH replacing NH_2 with configurational inversion), and the other vicinal *cis*-diol-containing isomer (61%, 40:60). In the galactose and mannose series higher yields and better selectivities were obtained.[82]



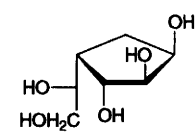
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163



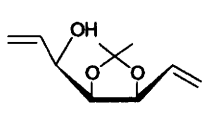
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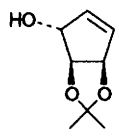
165

Normal Bu_3SnH-induced radical cyclization of bromide **164** allows relatively straightforward access to various carbafuranoses [*e.g.* β-D-mannose, α-L-glucose (**165**), 5-amino-5-deoxy-α-L-glucose, α-L-xylose, β-D-lyxose),[83] and Grubbs' catalysed cyclization of diene **166**, derived from 5,6-dideoxy-2,3-*O*-isopropylidene-D-*lyxo*-hex-5-enose by Wittig methylenation afforded cyclopentene **167** (95% yield). Amination with allylic rearrangement was effected intramolecularly *via* the trichloroacetimidate to give the cyclopentene unit **168** of nucleoside Q of *E. coli* t-RNA. A galactosyl derivative was made for comparison with a natural glycoside.[84]

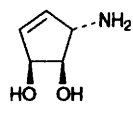
Periodate oxidation of a five-membered cyclohexylidene inositol acetal gave *meso*-2,3-cyclohexylidene tartardialdehyde which, following base-catalysed cyclization with nitroethane, gave a set of 2,3,4,5-tetrahydroxy-1-*C*-methyl-



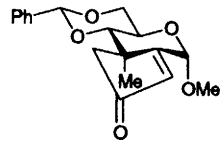
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167



168

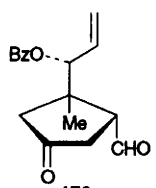


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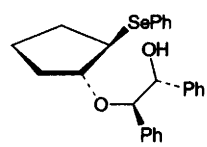
cyclopentylamines in modest yields.[85] An aldol-like cyclopentannulation carried out on a hexopyranosid-2-ulose bearing methyl and acetylmethyl substituents at C-3 gave compounds **169** and hence **170**, the latter being required for steroidal and vitamin D syntheses.[86]

Several further routes to functionalized cyclopentanes from simple cyclopentenes have been recorded. Compound **171** was made from cyclopentene itself and converted into more complex enantiopure derivatives, *e.g.* **172**,[87] and the cyclopentenes **173** (R^1 = OH, R^2 = NHBoc) and **173** (R^1 = NHCbz, R^2 = OAc) were produced as single enantiomers. The former is relevant to the preparation of L-carbanucleosides from cylopentadiene and was made following the dipolar cycloaddition of cyclopentadiene to 1-nitroso-mannofuranosyl chloride,[88] and the latter was needed for D-carbanucleoside synthesis and was obtained following enzymic acylation of the racemic hydroxy analogue.[89] A similar approach using a *meso*-2,5-anhydroallitol derivative gave an enantiomerically pure 1-acetate and hence the (+)-cyclaradine precursor **174**.[90]

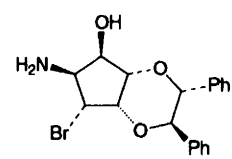
The reverse carbanucleosides **175** were made from a known monosilylated *cis*-3,5-dihydroxycyclopentene,[91] and the homo-carbauridine **176** was built up in nine steps from norbornadiene.[92]



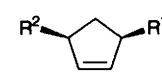
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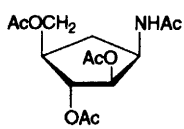
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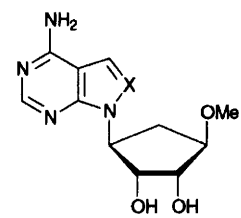
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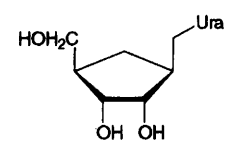
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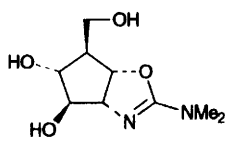
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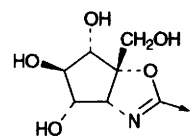
175 X = CH, N



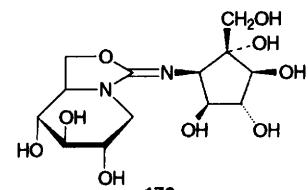
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177



178



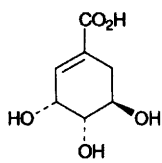
179

Carbofuranose compounds of potential biological interest to have been reported are 5-*O*-acetyl-3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-carbaribofuranose (from 1-oxa-2-oxo-bicyclo[3.3.0]oct-6-ene)[93] and β-D-carbofructofuranose 2,6-bisphosphate (by nzymicphosphorylation of the 6-ester).[94]

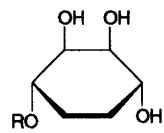
Amino-compounds to have been made for work connected with enzymic inhibition are (−)-allosamizoline **177** (from a 3,5-dihydroxy-4-hydroxymethylcyclopentene by asymmetric desymmetrization *via* a chiral bis-sulfoxide);[95] the disaccharide-like compound based on methyl glucosaminide with the unit **178** bonded to nitrogen, and the trisaccharide analogue with glucos-3-yl in place of methyl;[96] the analogous 1-deoxynojirimycin-linked **179** which was made together with compounds having various alkylamino linkages between the two nitrogen atoms.[97]

2.2 Inositols and Other Cyclohexane Derivatives. – A review has appeared on the use of L-quebrachitol in the synthesis of chiral natural products,[98] and on the synthesis of natural products (including cyclophellitols and nagstatins and several central nervous system-affecting compounds) from carbohydrates.[99] In a related survey the syntheses of mannostatins and cyclophellitol and analogues and other cyclitol inhibitors of glycoside metabolism were treated.[100] The preparations of conduritols, carbasugars and carbadisaccharides from 3-silylated-1,4-cyclohexadiene,[101] of inositol derivatives by chemoenzymic methods,[102] of carbasialic acid analogues[103] and of shikimic acid (**180**) from carbohydrate derivatives and other sources[104] have all also been surveyed.

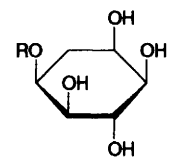
2.2.1 Inositols. The dideoxyinositol **181** and the deoxy-compound **183** are two new cyclitols to have been found in plants; they appear as their α-D-galactoside (**182**) and β-D-glucoside (**184**) respectively.[105] Other new related natural compounds to have been reported are **185** and two compounds of similar structure.[106]



180



181 R = H
182 R = α-D-Gal

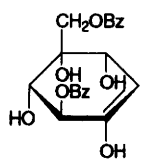


183 R = H
184 R = β-D-Glc

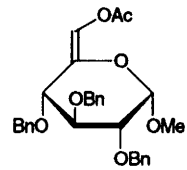
Considerable attention continues to be given to the synthesis of inositols. A multi-gram five-step route from *myo-* to *neo*-inositol which does not require chromatographic separations has been described,[107] and the *scyllo*-isomer can be made from the same starting material by treatment with Raney nickel in boiling water and preferential removal of unreacted starting material as an orthoester. From 20 g of the *myo*-compound the yield was 20%.[108]

Enantiomerically pure *myo*-inositol derivatives have been made from chiral dimethyl tartrate by chain extensions using methyl tolyl sulfoxide and LDA which gave an iditol 1,6-disulfoxide that was cyclized by an SmI_2-based

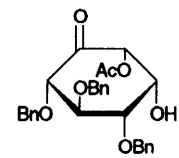
reaction.[109] Otherwise an *ido*-dialdose made from D-xylose has been similarly cyclized also to give chiral *myo*-inositol derivatives,[110] and the same group has made 2-*O*-α-D-galactopyranosyl-D-*chiro*-inositol from L-lyxose by a similar approach followed by glycosylation of a monohydroxy derivative.[111]



185

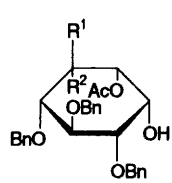


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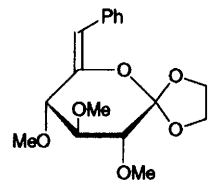


187

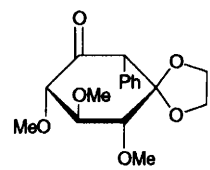
Palladium(II)-catalysed cyclization of 5-ene **186** gave compound **187** (49%) and three stereoisomers, and analogues derived from D-galactose and D-mannose afforded isomeric inososes,[112] the products affording selectively substituted chiral inositols with remarkable (and opposite) selectivities when reduced with sodium borohydride or tetramethylammonium triacetoxyborohydride. Compound **187**, for example, gave the *epi*- and *myo*-inositol derivatives **188** and **189**, respectively, in 83% yield and with >99% selectivity when reduced in these ways.[113] The method is therefore of appreciable value for the synthesis of selectivity substituted chiral inositol compounds as was illustrated by the preparation of 1-*O*-allyl-3,4,5-tri-*O*-benzyl-D-*myo*-inositol.[114] In related work the 6-*C*-phenyl derivative **190** was converted to the cyclohexanone **191** by treatment with $TiCl_4$ (the reagent being known to permit retention of the aglycon), but phenylmagnesium bromide gave the further product with Grignard reaction having occurred at the carbonyl group of **191**.[115]



188 R^1 = H, R^2 = OH
189 R^1 = OH, R^2 = H



190



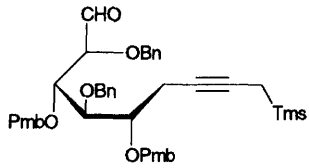
191

The alkene **186** lacking the acetoxy group reacts analogously with Ti(O-*i*Pr)Cl_3 to give the analogue of **187** without this group, but having retained the methyl group,[116] and the same alkene by Pd(II)-catalysed carbocyclization was used to make the carbaglucose epoxide cyclophellitol.[117]

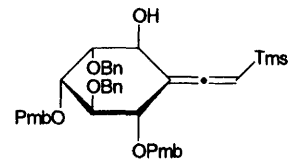
2-Deoxy-*scyllo*-inosose synthase (an enzyme used biosynthetically in the preparation of 2-deoxystreptamine) cyclized 2-deoxy- and 3-deoxy-D-glucose 6-phosphates to dideoxyinososes, but the 4-deoxy-isomer was not a substrate.[118]

A new approach to inositols from sugars is exemplified by the conversion of the D-glucose-derived alkyne **192** which was ring-closed with acid to the allene **193** and hence oxidized to 2,3,6-tri-*O*-benzyl-*myo*-inositol.[119]

Several inositol syntheses have depended on initial biological oxidation of

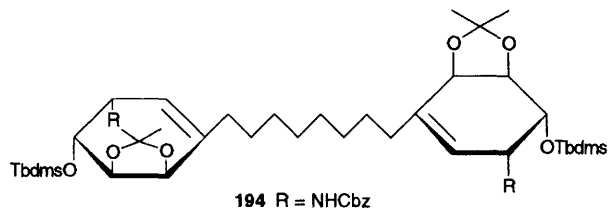


192

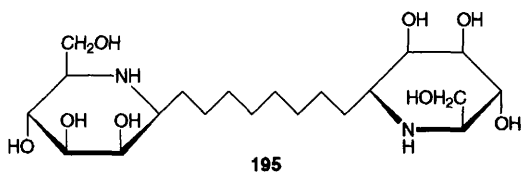


193

aromatic compounds, bromobenzene having been elaborated to *muco*- and L-*chiro*-inositol *via* conduritol derivatives[120] and to compound **194** which was then oxidatively ring-opened and converted into the bis-deoxymannonojirimycin compound **195** which was active against some glycosidases.[121] Chlorobenzene was the starting material for another synthesis of 1-O-allyl-3,4,5-tri-*O*-benzyl-D-*myo*-inositol.[114]

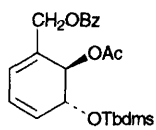


194 R = NHCbz

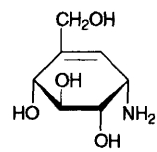


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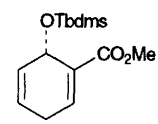
Dihydrobenzenes have also been used to make deoxyinositols and related compounds, 1,4-cyclohexadiene giving access to racemic 1,4/2,5-cyclohexanetetraol in high yield,[122] and all of the cyclohexane diepoxides and cyclohexene epoxides were made from the (−)-quinic acid-derived **196**.[123] Racemic and (+)-valienamine **197** were elaborated from the Diels-Alder product **198**.[124]



196



197



198

Enes to have been used as starting materials are cyclohexene (D-*chiro*-inositol and *muco*-quercitol),[125] a 3,4-*O*-isopropylidene-cyclohexene 3,4,6-triol (1-deoxy-*myo*-inositol and 1-deoxy-*neo*-inositol)[126] and a corduritol (inosamines).[127] 3-Acetoxycyclohexene has been converted into racemic conduritol acetates by iterative hydroxyiodinations.[128]

The carbaglycosylamine 2-*epi*-validamine (racemic) has been made from a Diels-Alder-derived bicyclo[2.2.2.]octane derivative,[129] and Vogel's group have made selectively *O*-substituted conduritols from an oxygenated bicyclo[2.2.1]-heptane compound and hence the *pseudo*-glycoside **199** and its enantiomer which are orally active antithrombotic agents. Surprisingly, the illustrated compound was the more potent.[130,131]

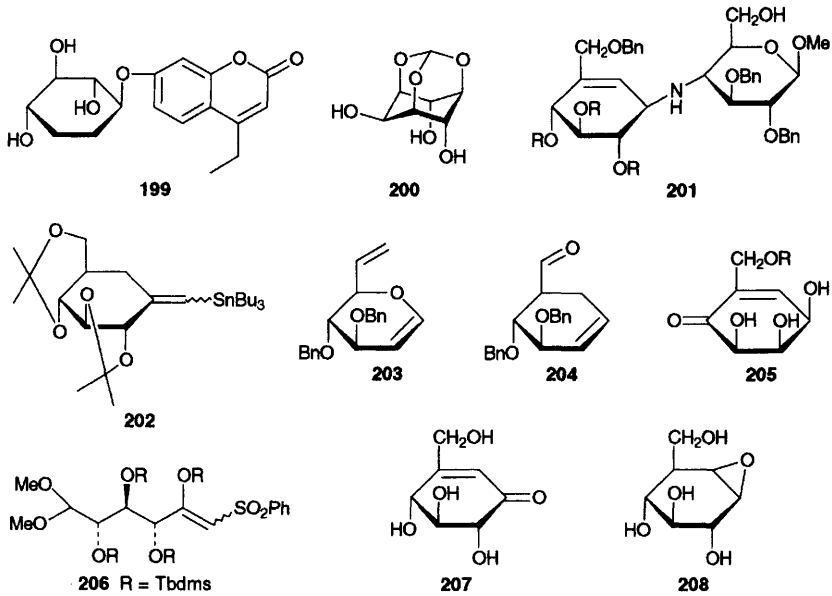
In the area of *O*-substituted inositol derivatives the *myo*-inositol orthoformate **200** has been used to make several selectively *O*-protected esters[132,133] and ethers,[134] and from the analogous orthopivaloate the 1D- and 1L-enantiomers of 1,2,3,5/4 cyclohexanepentaol were derived.[135] Vasella and colleagues have continued their study of hydrogen-bonding factors in derivatives of orthoesters like **200** – in particular a compound with an axial fluorine atom in place of one of the axial hydroxyl groups. Selective glycosylation occurred at the remaining axial hydroxyl group which is less strongly H-bonded and more acidic.[136]

D-1,2-Dideoxy-1,2-difluoro-*myo*-inositol 3,4,5,6-tetrakisphosphate and its L-enantiomer have been made as analogues of *myo*-inositol tetrakisphosphate, the halogen atoms being introduced in two steps.[137] Two papers have appeared on various inositol derivatives bearing purinyl substituents.[138,139] Compound **201** (R = Bn), a diastereomer of methyl acarviosin, has been made by use of the inosamine and a 4-*O*-triflylgalactoside,[140] and β-glucocerebrosidase inhibitors were made by di-*N*-substituting the unprotected inosamine unit of **201**.[141] Other amino derivatives of inositols are noted in Chapter 19.

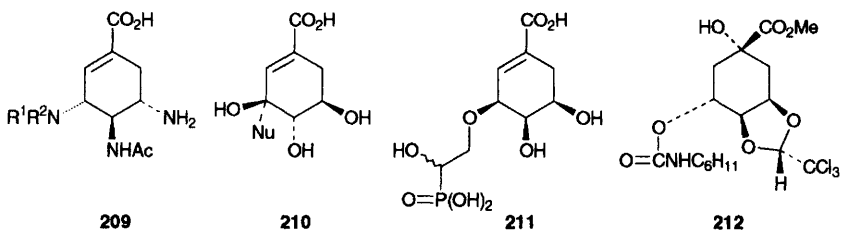
2.3 Carbasugars. – In the area of carbasugars carba-β-D-glucopyranose and -galactopyranose have been made by a method involving radial cyclizations of *O*-protected 1,2,6-trideoxy-6-methylene-hept-1-ynitol derivatives to lead *e.g.* to product **202** (in the D-glucose case) which was ozonized and reduced.[142] The Claisen rearrangement represented by **203**→**204** allows access to carba-β-D-glucose and -α-D-mannose,[143] and the latter (and a carba-methyl taloside isomer) has also been accessed by Baeyer-Villiger oxidation of a 2,3,5-trihydroxy-7-oxobicyclo[2.2.1]heptane derivative.[144] Compound **205** (R = MeCH=CHCO), (−)-glyoxalase inhibitor I, has been made following a Lewis acid-catalysed cyclization of compound **206**,[145] and gabosine I (**207**), a *Streptomyces* product and one of several biologically active carbasugar compounds, was synthesized by ring closure ($CrCl_2$, $NiCl_2$, DMF) of 2,3,4,6-tetra-*O*-benzyl-5-bromomethylene-5-deoxy-D-*xylo*-hexose.[146]

A further synthesis of (+)-cyclophellitol (**208**) depended upon a Grubbs' catalyst cyclization of D-xylose-based methyl 4,5,6-tri-*O*-benzyl-2,3,7,8-tetradeoxy-3-*C*-vinyl-L-*gulo*-oct-7-enonate.[147] A trisphosphate based on carba-D-glucose is noted in Section 2.5.2.

2.4 Quinic and Shikimic Acid Derivatives. – In the field of quinic and shikimic acid chemistry several derivatives have been made – particularly in the search for specific enzyme inhibitors. From the former, some compounds (**209**, R^1, R^2 = H, alkyl) were derived which displayed inhibition of influenza neuramini-



dase,[148] **210** (Nu = CH_2CO_2Et, CH_2SO_2Ph, allyl, H) were evaluated as dihydroquinase inhibitors,[149] and **211** was a good inhibitor of 3-deoxy-D-*manno*-2-octulosonate 8-phosphate synthase.[150] 2-Bromo and -fluoro-2-deoxyquinic acid and 3-dehydroquinic acid have been reported,[151] and the carbamate **212** and the corresponding 1,2-unsaturated analogue have been made directly from the corresponding methyl quinate and methyl shikimate, respectively.[152]



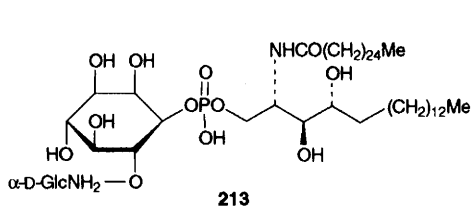
2.5 Inositol Phosphates. – Appreciable work continues in this area, and a review has appeared on the application of lipases to the synthesis of *myo*-inositol phosphates.[153]

2.5.1 Monophosphates. *Myo*-inositol 1,2-cyclic phosphate has been prepared on a multigram scale by use of a whole cell culture of *Bacillus subtilis*,[154] and a phosphodiester has been made with the phosphate linking *myo*-inositol (through O-1) to fluorescein (required for continuous assay of a phospholipase).[155] A related compound was made to link *myo*-inositol with

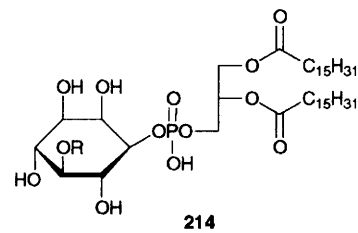
o-(3-hydroxypropyl)phenol, the latter being condensed in the form of the cyclic phosphate.[156]

Ceramide compound **213** was made as an intermediate in GPI-anchor biosynthesis.[157] By use of a differentially substituted analogue of alkene **186** Peng and Prestwich have made the phosphatidyl-D-*myo*-inositol **214** (R = H) as well as the further phosphate **214** (R = PO_3H_2).[158] Closely related work has given an analogue of this bisphosphate with a phosphate ester at O-4, a sulfur atom linking the glycerol to the phosphate and myristoyl (C_{14}) in place of the palmitoyl (C_{16}) residues.[159] Other closely similar work has afforded an analogue with a fluorescent 2′-naphthyl group at the end of a long chain glycerol substituent.[160] Phosphonate derivative **215** of the 3-deoxyinositol had three times the cancer cell growth inhibitory effect of the corresponding phosphate.[161]

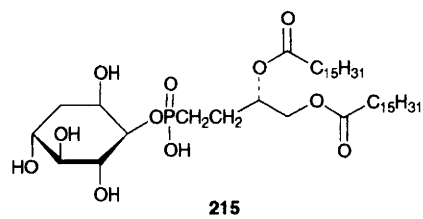
6-Amino-3,5,6 trideoxy-*myo*-inositol 1-phosphate and the *N*-methyl analogue are both substrates for inositol monophosphatase.[162]



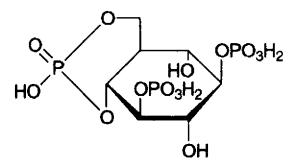
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2.5.2 Phosphates with more than one ester substituent. Phospatidyl phosphates (which are bisphosphate derivatives) are mentioned above,[158,159] and other work has yielded phosphatidyl 3- and 4-phosphates.[163]

All regioisomers of *myo*-inositol bisphosphate have been described,[164] and the 2,6-substituted compound has been independently made.[165]

The following *myo*-inositol trisphosphates have been reported: 1,4,5-,[166] 1,3,4-,[167] 5-deoxy-5,5-difluoro-1,2,6-[168] and compound **216** (which is a conformationally restricted analogue of inositol trisphosphate; it acts as an agonist of platelet Ins P_3 receptor).[169] The 'microscopic acid-base properties' of D-*myo*-inositol 1,2,6-triphosphate analogues (differing in configuration, or having a ring carbon atom replaced by O or N) have been studied by potentiometry or ^{13}P NMR titrametric methods.[170] Inositol phosphatidyl bisphosphates to have been synthesized are the 3,4-bisphosphate (distearoyl ester),[171] the 3,5-bisphosphate (dipalmitoyl diester),[172] 4,5-bisphosphate (dibutanoyl ester)[173] and a 2-deoxy-2-fluoro analogue of the last of these.[174]

In the group of *myo*-inositol tetrakisphosphates the following have been made: 1,2,4,5-,[175] 1,3,4,5-,[176,177] and the 1- and 2-deoxy derivatives of *myo*-inositol 3,4,5,6-tetrakisphosphate have also been described.[178]

1-Phosphatidyl-D-*myo*-inositol 3,4,5-, 3,4,6-, 3,5,6- and 4,5,6-trisphosphates have been made with palmitoyl glycerol ester groups,[179] and specific attention has been paid to the 3,4,5-trisphosphate having one arachidonic acid ester group bound to the glycerol.[180] A related study described compounds having shorter chain acids in place of the arachidonic acid.[181]

In the pentakisphosphate series the *myo*-inositol compounds having O-3 or O-6 unsubstituted have been described.[182]

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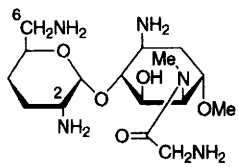
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19
Antibiotics

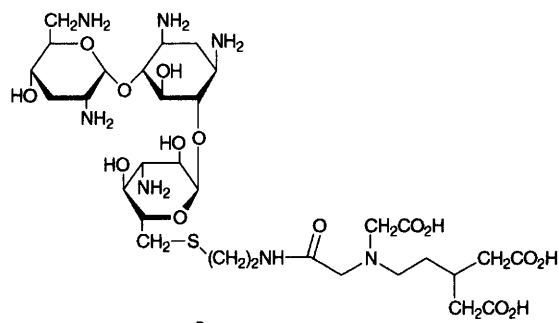
1 Aminoglycosides and Aminocyclitols

Shorter and more efficient routes have been described for the synthesis of sannamycin-type aminoglycosides, such as 6-des(*N*-methyl)sannamycin A (**1**) and its 2-*epi*-analogue (see Vol. 29, p. 252 for earlier work).[1]

All four regiospecifically *N*-bromoacetylated derivatives of neamine have been prepared as potential affinity inactivators of aminoglycoside-3′-phosphotransferase type IIa, an enzyme responsible for bacterial resistance against aminoglycoside antibiotics.[2] These compounds were used to identify Glu-3 and Asp-23 as being in the active site of the enzyme.[3] The conformation in which lividomycin binds to the active site of aminoglycoside-3′-phosphotransferase type IIIa has been studied by NMR spectroscopy and by molecular modelling.[4]



1



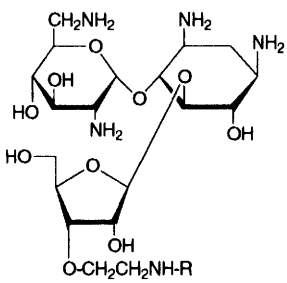
2

Recent advances in knowledge of RNA-aminoglycoside interactions have been reviewed, with a discussion of the importance of electrostatic interactions, and of a recognition model suggesting three-dimensional electrostatic complementarity.[5] The importance of electrostatic effects has been supported by the synthesis of 6″-amino-6″-deoxykanamycin A, 5″-amino-5″-deoxyneomycin B and 6″-amino-6″-deoxytobramycin by modification of the antibiotics, and the demonstration that addition of the extra amino group enhances RNA binding.[6] Neomycin B has been shown to accelerate the hydrolysis of the phosphodiester unit of ApA more effectively than a simple unstructured diamine,[7] whilst the formation of Cu(II) complexes of neomycin B and of

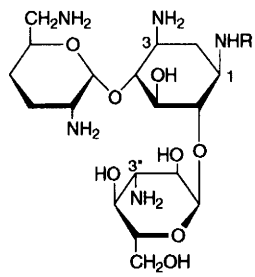
Carbohydrate Chemistry, Volume 32
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kanamycin A leads to much enhanced cleavage of DNA at physiological pH and temperature.[8] The EDTA derivative **2** derived from tobramycin has been prepared, and converted into Fe^{2+} and Fe^{3+} complexes. These materials were tested for their ability to inhibit the hammerhead ribozyme HH16; the RNA affinity differed from that of the parent antibiotic and was dependent on the oxidation state of the chelated metal ion.[9] In order to probe the importance of ring IV (the 2,6-diamino-2,6-dideoxy-β-L-idopyranose unit) in neomycin B, the analogues **3** and **4**, in which this unit is replaced by a flexible chain, were prepared by semisynthesis from neamine, using an amino-to-azide transformation (Vol. 30, p. 149) for 'protection' of the amino groups. The analogues of neomycin B in which the 2‴-amino-group and both the 2‴- and 6‴-amino-functions in ring IV were replaced by hydroxy-groups were also made. Binding results indicated that the positive charge presented on the L-idose ring is necessary for specific binding *in vitro*, but both **3** and **4** had activity in liquid culture assay comparable with neomycin B.[10]

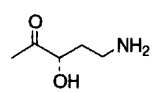
Enzymic acetylation of arbekacin (**5**) and of amikacin occurs at N-3″, whilst dibekacin (**6**) and kanamycin, lacking the acyl group at N-1, undergo acetylation at N-3.[11] Coupling of dibekacin with the appropriate acid (Chapter 16) has given rise to the derivatives **7** (both epimers).[12] Neomycin B has been converted into a derivative in which each amino group is replaced by an isonitrile, and various metal carbene complexes of this were prepared.[13]



3 R = H
4 R = -(CH$_2$)$_3$NH$_2$

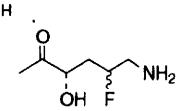


5 R =



6 R = H

7 R =



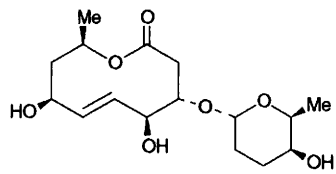
The substrate specificity of 2-deoxy-*scyllo*-inosose synthase, the first enzyme in the biosynthesis of 2-deoxystreptamine, has been investigated by the synthesis of 2-, 3- and 4-deoxy analogues of D-glucose-6-phosphate. The 2- and 3-deoxycompounds were transformed by the enzyme into 2,4- and 2,5-dideoxy-*scyllo*-inosose respectively, but 4-deoxyglucose-6-phosphate was not a substrate, since it lacks the hydroxy group that is oxidized to a ketone during the action of the enzyme.[14] It has been demonstrated by ^{15}N-labelling studies that glutamate is the primary source of the nitrogen of acarbose.[15]

Periodate cleavage of the non-reducing *N*-acetylglucosamine unit in allosamidin gave a dialdehyde which could be used to make biotin-allosamidin conjugates, which retained the strong chitinase inhibitory activity of allosamidin itself. One of the conjugates was immobilized through streptavidin in an optical biosensor system.[16]

A new synthesis of racemic 2-*epi*-validamine, a constituent of validamycin A, is mentioned in Chapter 18.

2 Macrolide Antibiotics

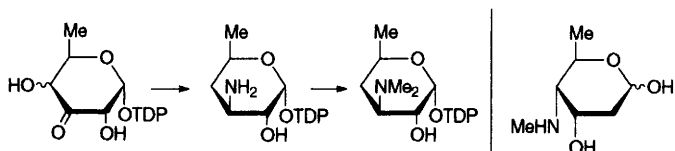
The 10-membered lactones decarestrictine B and D, inhibitors of cholesterol biosynthesis, have been glycosylated with deoxysugars found as constituents of angucycline antibiotics, to give hybrid antibiotics such as **8**. The glycosylations involved the use of glycals, which were activated for coupling in a variety of ways.[17]



8

Leucomycin analogues have been prepared which have a 3-hydroxy group, and with a 4-*O*-acyl-α-L-cladinose as the terminal sugar of the disaccharide. 4″-*O*-Butyryl-3″-*O*-methylleucomycin V showed good therapeutic effects in mice.[18]

Studies on the biosynthesis of desosamine using blocked mutants of the methymycin-producing *Streptomyces venezuelae* have provided good evidence that, in the conversion of intermediate **9** into **10** (Scheme 1), deoxygenation at C-4 precedes the transamination which introduces the 3-amino group.[19] It was also shown that deletion of the gene (Des VI), which causes blockage of the conversion of **10** into TDP-desosamine (**11**), led to the formation of a methymycin analogue with an *N*-acetyl sugar (3-acetylamino-3,4,6-trideoxy-D-*xylo*-hexose).[20] The results[19,20] indicate that the product of Des VII, responsible for coupling the sugar to the macrocycle, can accept modified substrates.



9 **10** **11** **12**

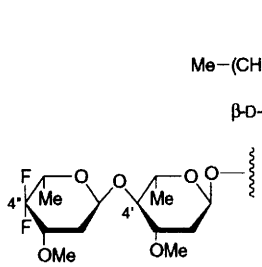
Scheme 1

A new aminosugar, 2,4,6-trideoxy-4-*N*-methylamino-D-*ribo*-hexose (**12**), termed vicenisamine, has been found as a constituent of the antitumour macrocyclic lactam vicenistatin.[21]

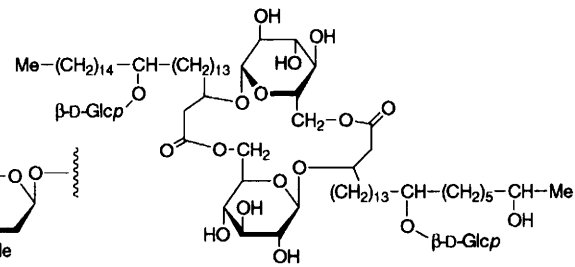
It has been shown that erythromycin C exists as a 4:5 mixture of the 9-ketone and the 12,9-hemiacetal in aqueous solution at room temperature.[22]

A modified avermectin has been prepared, containing a difluorinated disaccharide **13**, and the derivative with one sugar unit, difluorinated at C-4′, was also made. These compounds displayed good antiparasitic activity.[23]

A new antiherpetic agent from a strain of *Streptomyces microflavus* has been named fattiviracin A1 and assigned structure **14**. This compound is related to the cycloviracins (Vol. 26, p. 212), but with differences in the lengths of the sidechains and the nature of the appended sugar.[24]



13

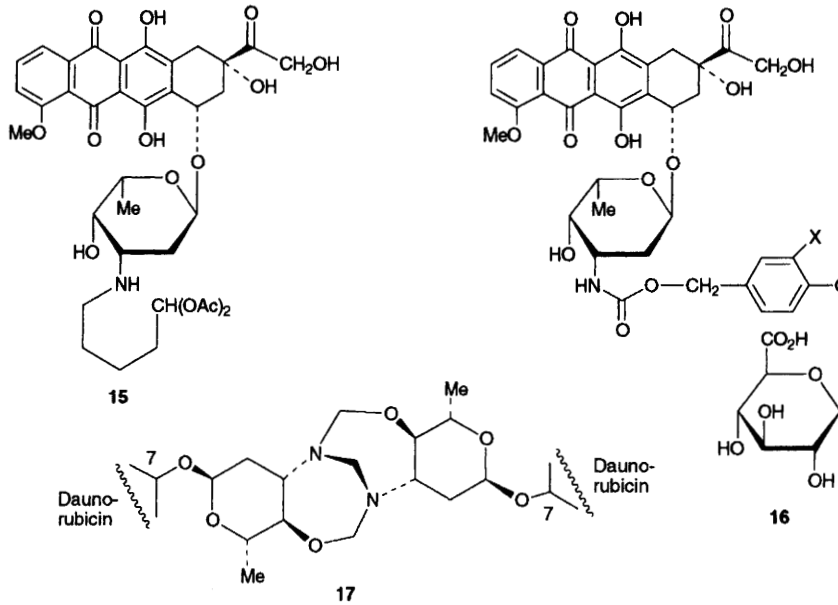


14

3 Anthracyclines and Other Glycosylated Polycyclic Antibiotics

Reductive amination of doxorubicin has led to potent analogues such as **15**, which can give rise to iminium ions by hydrolysis under biological conditions.[25] In a search for candidates for antibody-directed enzyme prodrug therapy (ADEPT), the doxorubicin derivatives **16** (X = Cl, F, NO_2) were prepared by a sequence in which an appropriately-substituted *p*-hydroxybenzaldehyde was coupled with protected glucuronic acid, followed by borohydride reduction and linkage to doxorubicin *via* the *p*-nitrophenyl carbonate. Of these compounds, which are activated by β-glucuronidase, the nitro-derivative **16** (X = NO_2) was selected for clinical trials. Isomers in which the glucuronoside unit was *ortho*- to the carbamate link were also made.[26] Following from previous work on doxoform and daunoform (Vol. 31, Chapter 19, ref. 18), it has now been shown that 4′-epi-doxorubicin reacts with formaldehyde to give a compound ('epidoxoform') of structure **17**, which was hydrolytically more stable than doxoform and which had improved antitumour activity compared with epidoxorubicin.[27]

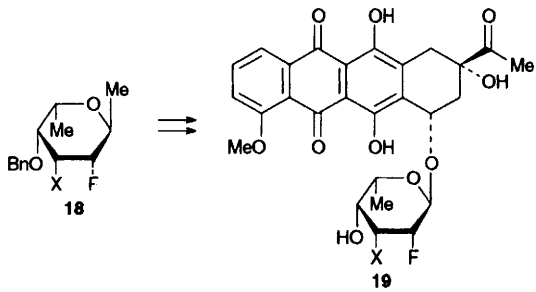
The fluorosugar **18** was used to prepare various glycosyl donors which were coupled with daunomycinone to give 2′-fluoro-daunorubicin analogues such as **19** (X = H, F, I), although the couplings proceeded with poor stereoselectivity.[28] Daunorubicin has been converted into 4′-deoxy-4′-iodo-4′-epi-daunorubicin, prepared as a potential cancer radiotherapeutic agent, by a sequence involving



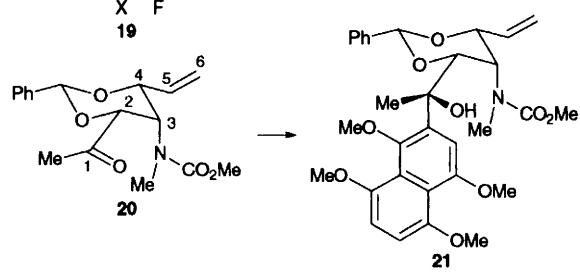
displacement of a triflate with iodide ion.[29] Some 9-fluoroanthracyclinones have been coupled with L-fucose,[30] and 9-fluoro-9-deoxy-4-demethoxydaunorubicinone has been prepared and coupled with daunomycin to give a mixture of stereoisomers of the daunorubicin derivative.[31]

In an approach to the assembly of the *C*-glycoside unit present in the anthracycline antibiotics nogalamycin and menogarol, the protected ketose **20** was prepared from di-*O*-isopropylidene-D-glucose (glucose carbons numbered). Reaction with organolithium compounds then gave the adduct **21** and a simpler compound with a dimethoxybenzene ring, in which the newly-created chiral centre was that appropriate for the targets. Reduction of **21** with $LiAlH_4$ introduced the *N,N*-dimethyl group of the antibiotics.[32]

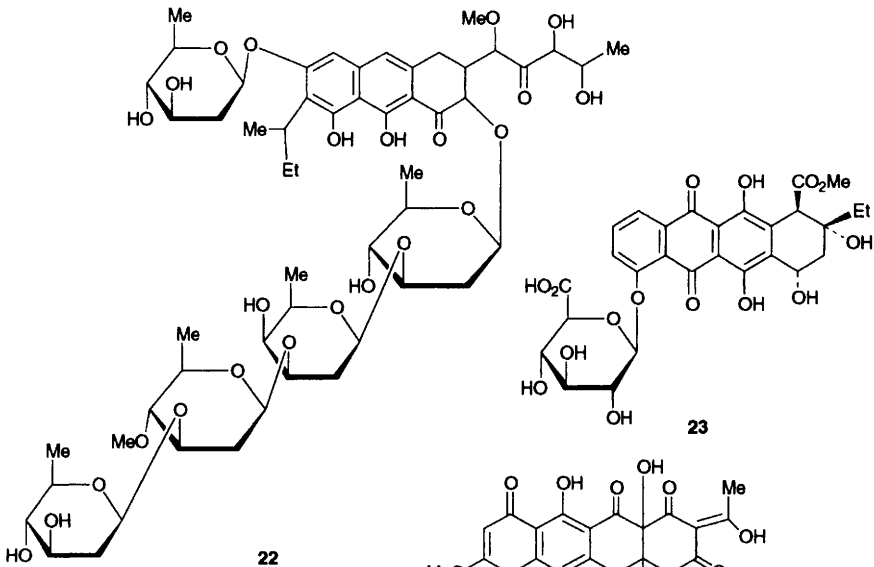
Studies on the binding of chromomycin A_3 to DNA have shown that the DNA duplex unwinds by around 12° when the antibiotic binds, presumably due to intercalation.[33] The structure of UCH 8, a new antitumour antibiotic of the aureolic acid family, isolated from a *Streptomyces* strain and related to chromomycin, has been determined as **22**, with a tetrasaccharide consisting of oliose and 4-*O*-methylolivose, as well as two olivose units.[34] Other *Streptomyces* species have been found to produce 4-*O*-(β-D-glucopyranouronosyl)-ε-rhodomycinone (**23**)[35] and polyketomycin (**24**), containing the sugars amicetose and L-axenose.[36] Another new antitumour antibiotic is FD-594, which has a pyrano[4′,3′:6,7]naphtho[1,2-*b*]xanthone core, to which is attached the trisaccharide β-D-oleandrose-(1→4)-β-D-olivose-(1→4)-β-D-olivose.[37] A series of tyrosine kinase inhibitors, termed hibarimycins, and isolated form a *Microbispora rosea* subspecies, have a common aglycon, a dimeric naphthylnaphthoquinone, and differ in the attached sugars, all of them containing 4-*C*-acetyl-2,3,6-trideoxyhexopyranosyl units.[38]



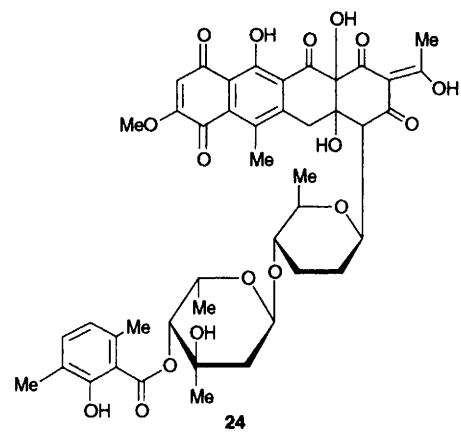
18 **19**



20 **21**



22 **23**

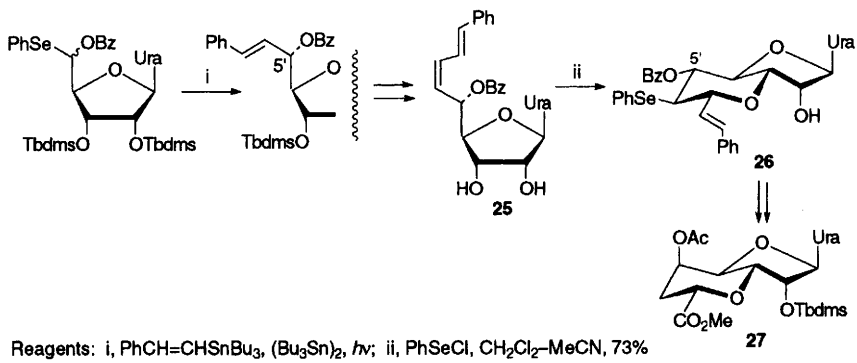


24

4 Nucleoside Antibiotics

An efficient route has been described for the synthesis of cordycepin (3′-deoxyadenosine), starting from di-*O*-isopropylidene-D-glucose, initial deoxygenation at C-3 being followed by nucleoside formation and removal of C-6′ by treatment with periodate-borohydride.[39]

In a new approach to octosyl acids and related compounds (Scheme 2), the diol **25** was produced with stereocontrol at C-5′, using a Wittig reaction with cinnamylidene triphenylphosphorane to give predominantly the *cis,trans*-isomer shown. Selenocyclization of **25** gave the product **26** in good yield, the same product being obtained from the *trans,trans*-isomer of **25**, and thus implying that the seleniranium ion intermediate derived from **25** can undergo isomerization before intramolecular capture. Subsequent manipulations, including inversion of configuration at C-5′, then gave the fully-protected octosyl acid **27** (a derivative of nikkomycin Sz).[40]

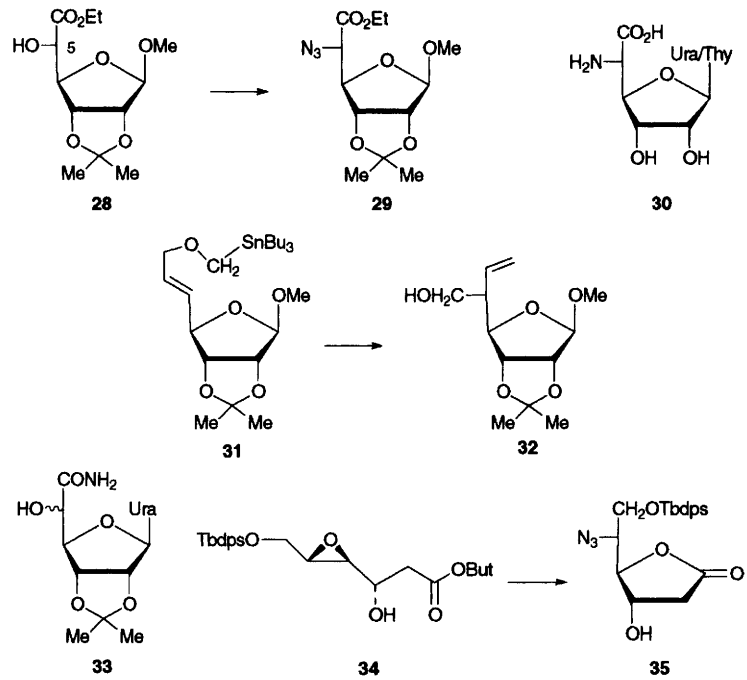


Reagents: i, $PhCH{=}CHSnBu_3$, $(Bu_3Sn)_2$, *hν*; ii, PhSeCl, CH_2Cl_2–MeCN, 73%

Scheme 2

A number of papers have discussed syntheses of the polyoxins, with particular emphasis on the stereoselective establishment of the configuration at C-5′. Thus, the ester **28** was produced as the major epimer by addition of (1-ethoxyvinyl)lithium to the C-5 aldehyde, followed by ozonolysis. A double inversion sequence then gave the azide **29**, convertible into thymine and uracil polyoxin C (**30**).[41,42] The same group has also described a route to the aminoacid units needed for the synthesis of polyoxins J and L.[43] Others have used the Wittig-Still rearrangement of **31** induced by treatment with BuLi to give the hydroxymethyl-branched system **32** with reasonable stereocontrol; the *Z*-isomer of **31** gave exclusively **32**. Oxidation of the hydroxymethyl group, a Curtius rearrangement and further manipulations then led to a protected form of thymine polyoxin C (**30**, Base = Thy).[44] The diastereomeric mixture **33** of α-hydroxyamides was prepared from 2′,3′-*O*-isopropylideneuridine by oxidation, cyanohydrin formation, and reaction with hydrogen peroxide. After acetylation, diastereoselective enzymic hydrolysis could be carried out to give the L-*talo*-epimer of **33**, and similar chemistry was carried out starting from adenosine and inosine.[45] The 2′-deoxy-analogue of thymine polyoxin C has

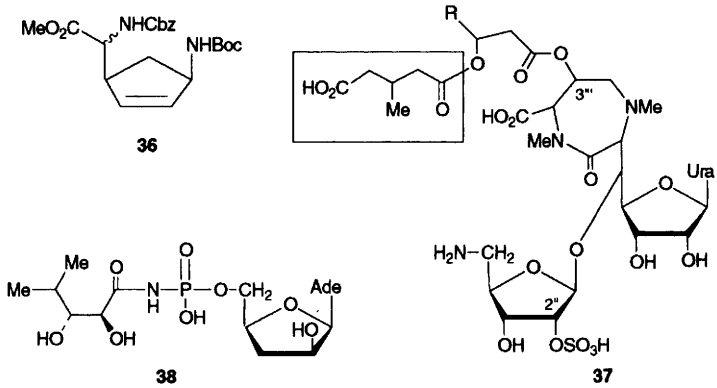
been made from the previously-known enantiopure epoxy-alcohol **34**, which on treatment with azide, followed by TFA, gave the lactone **35**. This was converted to the target nucleoside (2′-deoxy form of **30**, Base = Thy) by a sequence which involved a reasonably stereoselective formation of the base–sugar linkage.[46] The carbocyclic analogue of uracil polyoxin C has been made in racemic form *via* the intermediate **36**, from which the pyrimidine ring was built, **36** being prepared from the allylic acetate by organopalladium chemistry.[47]



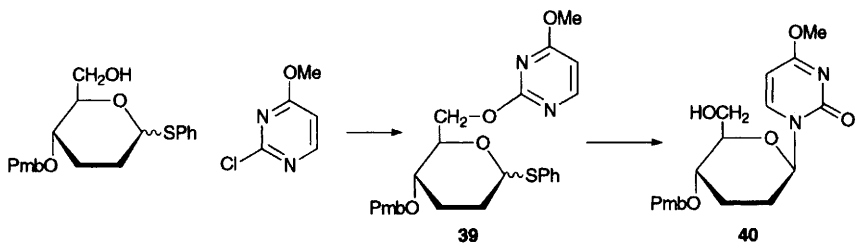
As regards other carbocyclic nucleoside antibiotics, a stereocontrolled route to (−)-neplanocin involves a lipase-mediated kinetic resolution to generate a highly enantiopure cyclopentene derivative, onto which the adenine unit was linked at a late stage using a Mitsunobu reaction.[48] A synthetic approach to carbocyclic sinefungin has also been described.[49]

New types of liposidomycins have been isolated and identified, leading to a classification of these antibiotics into four types: type I compounds have structures **37**; in type II compounds the boxed six-carbon unit is missing, with an enoate at C-3‴; type III systems lack the 2″-*O*-sulfate of **37**, whilst type IV compounds lack both the sulfate and the C-6 substituent.[50]

The synthesis of the antibiotically-active part **38** of agrocin 84 has been achieved for the first time using phosphoramidite methodology, and with the hydroxy groups of the dihydroxyacid unit protected as Tbdms ethers, permitting their release under conditions which did not induce N-to-O phosphoryl migration.[51]



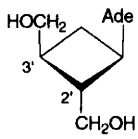
The intramolecular glycosylation shown in Scheme 3 was used to prepare the 2′,3′,6′-trideoxyhexopyranosyl nucleoside **40**, related to amicetin and other antibiotics of that class, and which was obtained in 89% yield from **39**.[52]



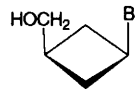
Reagents: i, NaH, DMF; ii, $(MeS)SMe_2.BF_4$, MS 4A, MeCN; iii, NaOH aq.

Scheme 3

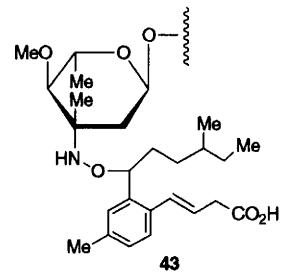
In the area of oxetanocin and its analogues, compounds related to 7-deazaguanine oxetanocin have been reported, with structural modifications at C-3′, and lacking the hydroxymethyl group at C-2′.[53] An asymmetric synthesis of cyclobutanones has been used to prepare the carbocyclic analogue of oxetanocin (cyclobut-A, **41**).[54] When the di-*O*-dibenzoyl derivative of (−)-cyclobut-A (**41**) was treated with lipase MY, a high yield could be obtained of the product selectively debenzoylated at the 3′-hydroxymethyl group, and the same regioselectivity was found in the hydrolysis of di-*O*-benzoyl carbocyclic oxetanocin T by the same lipase. A different lipase (lipase type XIII) effected kinetic resolution of racemic di-*O*-acetyl cyclobut-A by carrying out selective deacetylation of the 2′-hydroxymethyl group of the 'unnatural' enantiomer.[55] The pyrimidine derivatives **42** (B = Ura, Thy, Cyt) have been prepared, introducing the bases (Ura, Thy) by Mitsunobu reactions, and making the cytosine analogue using a standard Ura-to-Cyt transformation by Reese's method.[56]



41



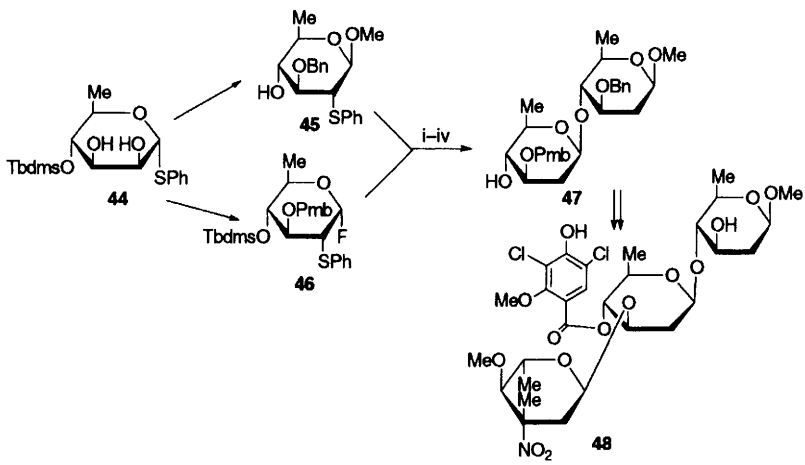
42



43

5 Miscellaneous Antibiotics

In the area of oligosaccharide antibiotics, the Schering group have determined the structure of Sch 49088, a compound of the everninomycin class with a hydroxylaminoether sugar **43**, named everhydroxylaminose, replacing the evernitrose unit of everninomycin.[57] Nicolaou's group have reported a synthesis of the acylated trisaccharide constituting the ABC fragment of everninomycin (Scheme 4). The two building blocks **45** and **46** were both made from the same precursor **44**, using a 1,2-transposition of the SPh group on treatment with DAST (Vol. 20, p. 26); after stereoselective formation of the disaccharide **47**, acylation and attachment of an evernitrose unit (prepared by a novel route), again in a stereoselective manner, gave the trisaccharide **48**.[58]



Reagents: i, $SnCl_2$; ii, Raney Ni, ; iii, BnBr, NaH, Bu_4NI; iv, TBAF

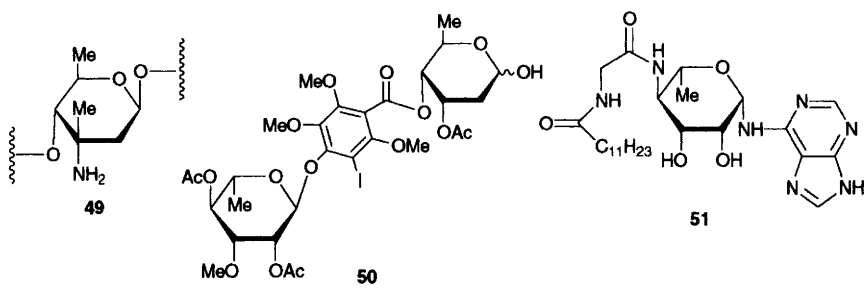
Scheme 4

Two new heptadecasaccharide antibiotics have been isolated from a new species of *Saccharithrix*, and shown to be effective against multi-drug resistant gram positive bacteria. These compounds, named saccharomycins A and B, have *N*-(3,4-dihydroxycinnamoyl)taurine as aglycone, with the oligosaccharide linked to O-4; saccharomycin A has five D-fucose units, four 4-*epi*-vancos-

amines, two units each of L-rhamnose and digitoxose, and four units of a new branched aminosugar **49** named saccharosamine, all the sugars being linked in a linear array with the exception of one of the 4-*epi*-vancosamine units, which forms a one-sugar branch. Saccharomycin B has one rhamnose unit replaced by another digitoxose.[59]

An analogue **50** of the BCD part of the carbohydrate domain of calicheamicin γ_1^I, in which the sulfur atom has been replaced by oxygen, has been prepared by a route in which the fucosylated aromatic ring was first assembled, and then linked to the B-ring.[60]

New semisynthetic glycopeptide antibiotics have been prepared by enzymic removal of the acyl groups of teicoplanin, followed by reductive alkylation to give mono- and di-alkylated compounds at the two possible glucosamine units.[61] Two families of conformations, differing in the position of the vancosamine substituent, were observed for vancomycin, by NMR and molecular dynamics calculations. In contrast, aglycovancomycin adopts only one conformation in solution. The conformations of vancomycin and aglycovancomycin differ in the alignment of the amide protons which participate in the hydrogen-bonding network with the cell-wall precursor and in the orientation of the aromatic rings relative to the backbone. Insight is thus provided into a possible role for glycosylation on the activity of vancomycin.[62]

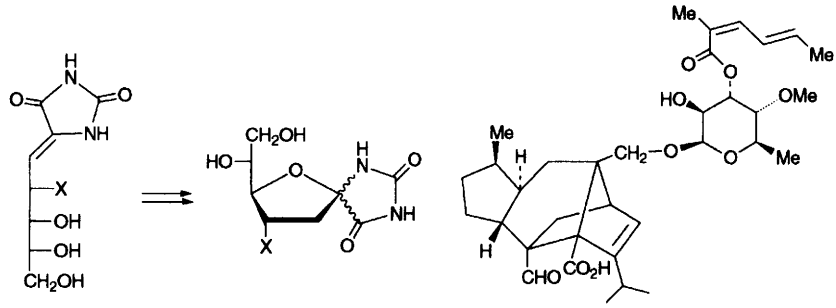


The L-rhamnose analogue **51** of spicamycin has been prepared and found to have high cytotoxicity towards human myeloma cells. In the synthesis, an azide group was positioned at C-4 of methyl 2,3-*O*-isopropylidene-α-L-rhamnoside by a double inversion procedure; after hydrolysis, the glycosylamine underwent reaction with 4,6-dichloro-5-nitropyrimidine to give in moderate yield an adduct from which the purine ring could be elaborated prior to attachment of the side-chain.[63]

Two new streptothricin-type compounds, A-53930-A and -B, have been isolated from a strain of *Streptomyces vinaceusdrappus*; they have a carbamoyl group on O-6 of the D-gulosamine unit, as opposed to the O-4 carbamoyl group of other stroptothricins.[64]

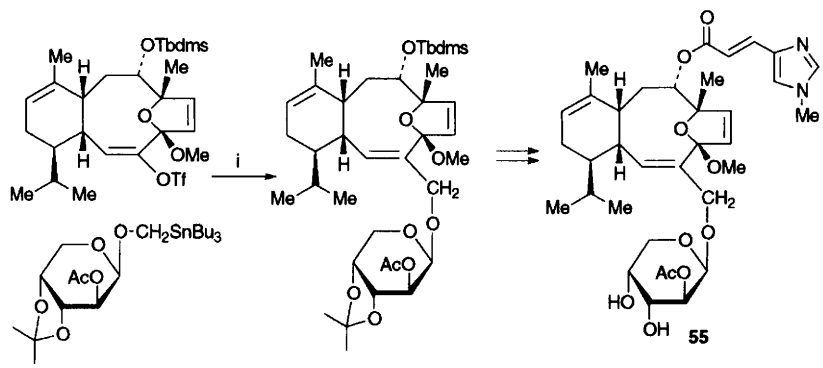
Analogues **53** (X = H, OH, both anomers at C-2) of hydantocidin have been prepared by selenocyclization (PhSeCl) of the Wadsworth-Emmons products **52**, followed by reductive removal of the phenylselenyl group.[65]

The glycosylated diterpene GR 135402 (**54**), from *Graphium putredinis*,



52 **53** **54**

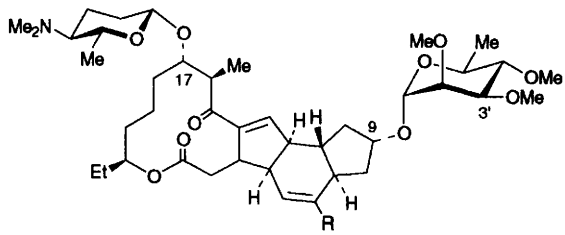
inhibits protein synthesis in *Candida albicans* but not in rabbit reticulocytes. The structure contains the sugar unit 6-deoxy-4-*O*-methyl-β-D-altropyranose (sordarose).[66] Various other similar esters have also been isolated from a strain of the same microorganism.[67] A review has been given on synthetic approaches to the potent antitumour agent eleutherobin (**55**),[68] and Danishefsky's group have reported a total synthesis of eleutherobin in which the D-arabinose unit is put in place in a novel fashion using the Stille coupling indicated in Scheme 5. The stereoisomer containing an L-arabinose unit (*neo*-eleutherobin) was also made, and served to demonstrate unequivocally that the natural product contained the D-sugar.[69] A simpler analogue has been prepared of the sesterterpene aleurodiscal, an antifungal antibiotic in which a secondary alcohol function is glycosylated with a β-D-xylopyranosyl unit.[70]



Reagent: i, $Pd(PPh_3)_4$

Scheme 5

In the insecticidal compounds spinosyn A and D (**56**, R = H and Me respectively), the forosamine unit at C-17 can be selectively removed by hydrolysis under mild conditions. The tri-*O*-methyl-L-rhamnose unit could be removed from spinosyn A under more vigorous conditions, but decomposition occurred for spinosyn D. Spinosyns J and L, which are the 3′-*O*-demethyl derivatives of spinosyns A and D, could be oxidized to give a ketone, permitting removal of the sugar at C-9 by β-elimination.[71]



56

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20
Nucleosides

1 General

A review on protein radicals in enzyme catalysis includes a discussion of ribonucleotide reductases, discussing the use of nucleotide analogues in probing the mechanism of Class 1 ribonucleotide reductases.[1] The chemistry of neutron capture therapy has been reviewed, the discussion including structures in which a carborane is linked in various ways to a nucleoside, nucleotide or dinucleotide.[2]

A comprehensive paper from Eschenmoser's laboratory concludes the extensive study of hexopyranosyl-(6′→4′)-oligonucleotide systems carried out by this group over recent years ('Why Pentose- and not Hexose-Nucleic Acids?').[3]

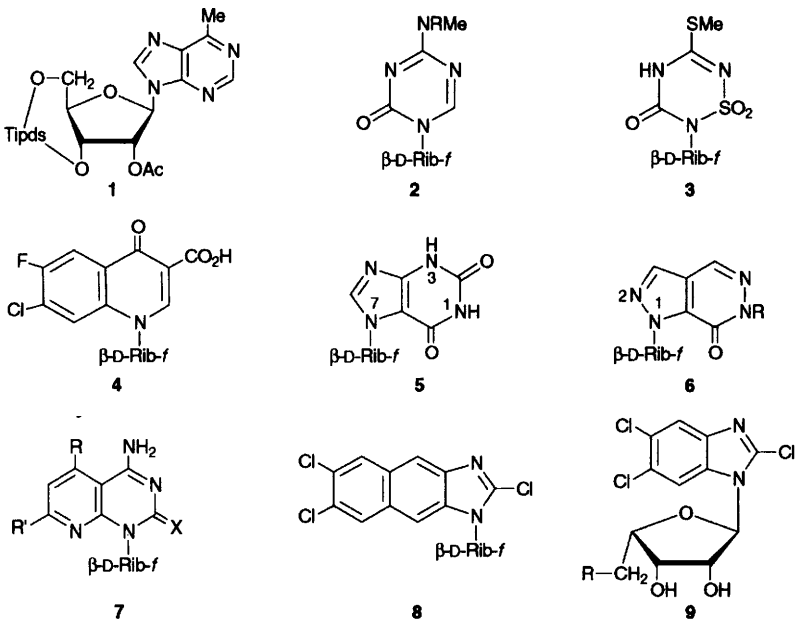
2 Synthesis

8-Fluoroadenosine has been prepared by enzymic hydrolysis of its 2′,3′,5′-tri-*O*-acetyl derivative, chemical hydrolysis of which leads to defluorination.[4] Chemical transglycosylation from the corresponding hypoxanthyl nucleoside has been used to prepare the 6-methylpurine riboside **1**, which was subsequently converted to the 2-deoxynucleoside.[5] Various 6-substituted-5-azacytidines have been prepared by reaction between tri-*O*-benzoyl-β-D-ribofuranosyl isocyanate and acylguanidines,[6] and N^4-methyl- and N^4,N^4-dimethyl-5-azacytidines (**2**, R = H, Me) have been made similarly, or by displacement of a 4-methoxy-substituent.[7] Other 1,3,5-triazine nucleosides have been prepared by base–sugar condensation,[8] as has the thiatriazin-3-one 1,1-dioxide nucleoside **3** and the glucopyranosyl analogue,[9] and some nucleosides of halogenated quinolone carboxylic acids such as **4** and its 2′-deoxy-analogue.[10] 7-β-D-Ribofuranosylxanthine (**5**) has been made for the first time by Vorbrüggen-type coupling of bis-(pivaloyloxymethyl)xanthine, and some 1-alkyl derivatives were similarly prepared.[11] N^3-Alkylxanthine-7-β-D-ribofuranosides have also been made by base–sugar coupling.[12]

β-D-Ribofuranosyl derivatives of 6-substituted pyrazolo[3,4-*d*]pyridazin-7-ones (**6**, where the N^2-isomers were also obtained in most cases),[13] 4-amino-5,7-disubstituted-pyrido[2,3-*d*]pyrimidin-2-ones and -thiones (**7**, X = O or S)

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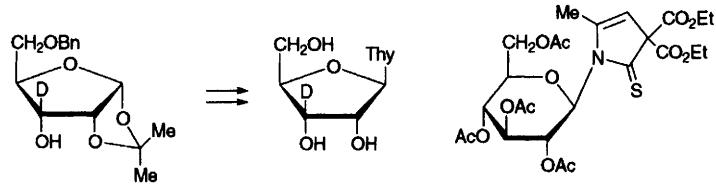
and similar 2,4-diones,[14] 8-aza-adenine (N^7- and N^8-regioisomers being obtained, the former being converted into oligonucleotide building blocks),[15] and substituted 2*H*,6*H*-dipyrazolo[3,4-*b*:3′,4′-*d*]pyridin-3(5*H*)-ones[16] have been prepared by condensation methods. The stretched analogue **8** of the antiviral benzimidazole nucleoside TCRB has been similarly prepared,[17] as have the β-D-ribofuranosides of 6,7-dichloroimidazo[4,5-*b*]quinoxalin-2-one and some other 2-substituted compounds,[18] α-D-, α-L- and 5-deoxy-lyxofuranosyl analogues of TCRB such as **9** (R = OH, H)[19] and the α-L-arabinofuranosyl analogue of TCRB.[20]



An improved synthesis of β-D-arabinofuranosylcytosine (ara-C) has been reported.[21]

As an alternative to stereocontrolled reduction of a 3′-ketonucleoside (Vol. 31, Chapter 20, Scheme 1), the 3′-deuteriated nucleoside **11** was made from the sugar **10**, which was produced by highly diastereoselective reduction of the corresponding 3-one; deoxygenation can be carried out at C-2′ if required.[22] Other workers have developed routes for making ribonucleosides labelled with deuterium at any or all of C-3′, C-4′ and C-5′ (monodeuteriated stereorandomly); the deuterium is incorporated into glucose or ribose derivatives prior to nucleoside formation, and use of $^{13}C_6$-glucose thus leads to $^{13}C_5$-nucleosides with the appropriate deuterium labels as well.[23] A subsequent paper from the same group presents methods for inserting deuterium at C-5 of ribose derivatives with reasonable stereocontrol, thus giving access to nucleosides stereoselectively *R*- or *S*-deuteriated at C-5′, with other ^{2}H- or ^{13}C-labels as required.[24]

β-D-Gluco- and galacto-pyranosyl nucleosides have been prepared from

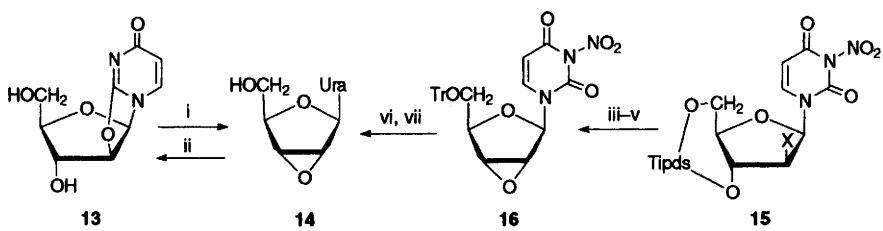


10 **11** **12**

3-cyano-2-pyridone and the 2-thione,[25] and also from versions of these compounds with a saturated carbocyclic ring annulated at C-5 and C-6.[26] The *N*-glucosyl thiolactam **12** was prepared by reaction of the glucosyl isothiocyanate with the enolate of diethyl (2-oxopropyl)malonate, followed by cyclodehydration.[27]

3 Anhydro- and Cyclo-nucleosides

A report from Reese's laboratory has described for the first time the isolation of 2′,3′-anhydrouridine (**14**), long postulated as a reaction intermediate, by treatment of the 2,2′-anhydro-nucleoside **13** with NaH in DMSO (Scheme 1). The process is readily reversed as indicated.[28] Other workers have also made **14** from the *N*-nitro-uracil derivative **15** (X = I) (see Section 5 for the synthesis of this) as indicated in Scheme 1. Unlike **14** itself, the *N*-nitroderivative **16** and the product of detritylation are quite stable.[29]



13 **14** **16** **15**

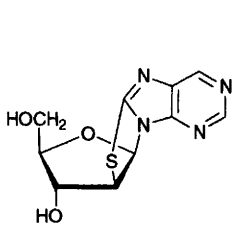
Reagents: i, NaH, DMSO; ii, Et_3N, MeOH; iii, TBAF, AcOH, THF; iv, TrCl, Py; v, Bu^{t}OK, DMF; vi, TFA; vii, H_2, Pd/C, MeOH

Scheme 1

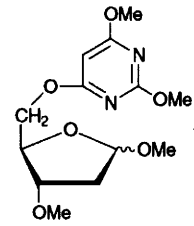
2,2′-Anhydro-β-D-lyxofuranosylthymine has been prepared by reaction of 2′-*O*-tosyl-3′,5′-di-*O*-benzoyl-β-D-xylofuranosylthymine with sodium benzoate and then deprotection with NaOMe in MeOH.[30] The 8,2′-*S*-cyclopurine nucleoside **17** has been made by an impoved route, involving an intramolecular Mitsunobu reaction of an adenosine-8-thione, followed by deamination.[31]

The mechanism by which 2,3′-anhydro-2′-deoxy-pyrimidine nucleosides are formed by dehydration using *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine has been investigated, and 3′,5′-bridged intermediates were proposed.[32]

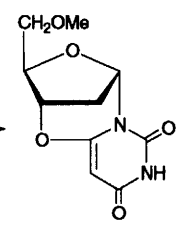
When **18** was treated with BCl_3 at low temperature, followed by warming to RT, the 6,3′-anhydro-compound **19** was isolated in ~40% yield, the structure of



17



18

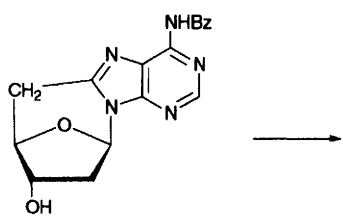


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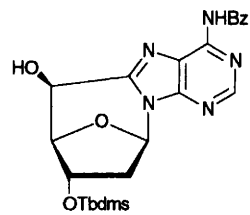
19 being confirmed by crystallography. A mechanism was proposed involving intramolecular transfer of the base to O-3′ *via* a spiro-intermediate, followed by cyclization.[33]

The cyclonucleoside **20** was obtained by photolysis of N^6-benzoyl-2′,5′-dideoxy-5′-phenylthioadenosine in triethylphosphite, and was converted stereoselectively into **21** by Matsuda's method (see Vol. 12, p. 166), involving oxidation at C-5′ using SeO_2. This cyclonucleoside was then incorporated into oligodeoxynucleotides, where it was found that the phosphate links involving the cyclonucleoside were relatively stable to enzymic hydrolysis, but the cycloA-T pairing was less stable than a normal A-T pair.[34]

Some references to the use of anhydronucleosides in the synthesis of other types of nucleoside can be found later in this chapter.



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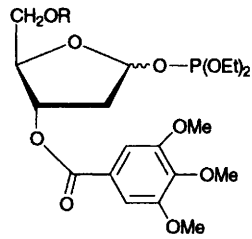


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4 Deoxynucleosides

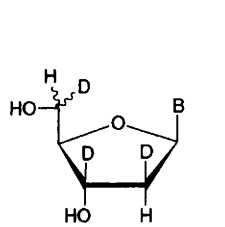
Glycosylation of silylated pyrimidine bases with deoxyribosyl phosphites of type **22** gives 2′-deoxynucleosides with high β-selectivity.[35] Iodocyclization of D-arabinal, followed by radical reduction and thiocarbamoylation, gives a [2.2.1] bicyclic acetal well suited for the stereoselective synthesis of pyrimidine β-2′-deoxynucleosides.[36]

Routes have been devised for the synthesis of 2′-deoxyribonucleosides triply-labelled with deuterium as indicated in **23**; the isotope at C-2′ was predominantly (~85%) in the *pro-S* position as shown, whilst the label was much more evenly distributed between the two positions at C-5′. The deuteriated deoxynucleosides were incorporated into a dodecamer for use in NMR studies of oligonucloetide conformation.[37] Thymidine has been converted in five steps into 4′-deuteriothymidine.[38]

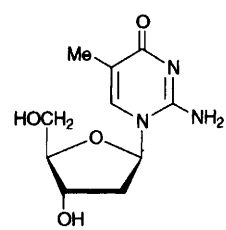


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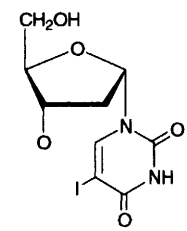
Some improvements have been reported in the synthesis of 5-methyl-2′-deoxyisocytidine (**24**) by reaction of 2,5′-anhydrothymidine with ammonia, and 2′-deoxyisoguanosine derivatives were also prepared using radical deoxygenation; suitably protected phosphoramidites were also described.[39] The α-anomer **25** predominated when the silylated base was treated with 2-deoxy-3,5-di-*O*-toluoyl-α-D-*erythro*-pentofuranosyl chloride in the presence of *p*-nitrophenol and pyridine; subsequently, **25** was converted into 2′-deoxy-5-(propyn-1-yl)-α-uridine which was incorporated into oligonucleotides.[40] Some 6-aza-5-substituted-2′-deoxyuridines, some of which are competitive inhibitors of HSV-1 thymidine kinase, have been made by base–sugar condensation,[41] as has the non-polar isostere **26** of deoxyadenosine (the regioisomer was also formed), which was incorporated into a dodecamer.[42] Similar condensations were used to make 2′-deoxyribonucleosides of various 6-alkoxypurines,[43] 7-deazapurines,[44] and 7-halogenated-8-aza-7-deazaguanines such as **27**, where the use of NaH in MeCN in the couplings also gave the N^2-regioisomers without dehalogenation (see Vol. 31, p. 272),[45] and in all these cases building blocks for oligonucleotide synthesis were also described. The 6-methyl-isoxanthopterin nucleoside **28**, various derivatives and a protected phosphoramidite have been made by glycosylation,[46] as have 2′-deoxyribosides of thieno[3,2-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidines.[47]



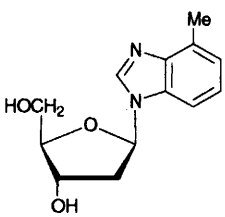
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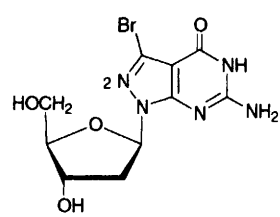
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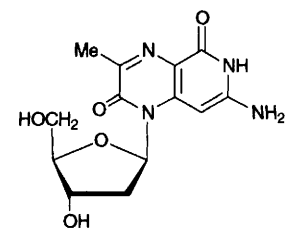
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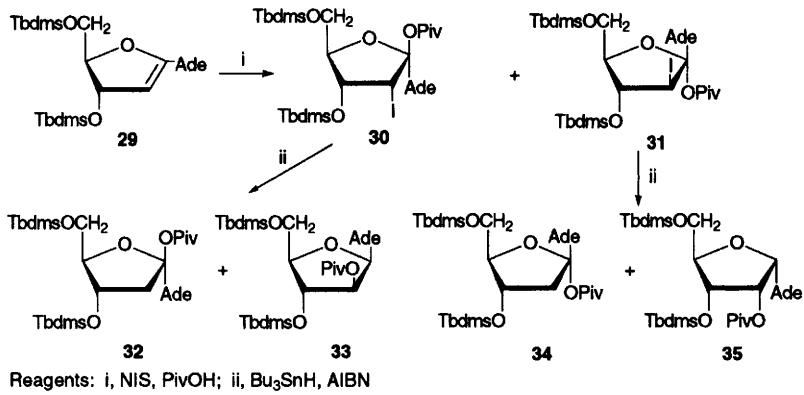
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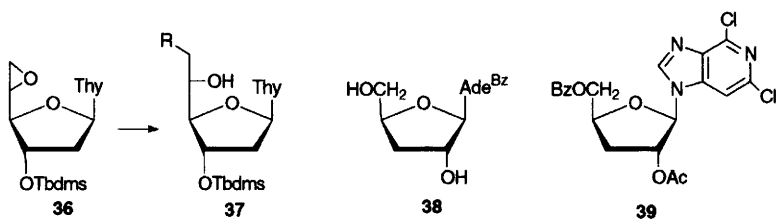


Scheme 2

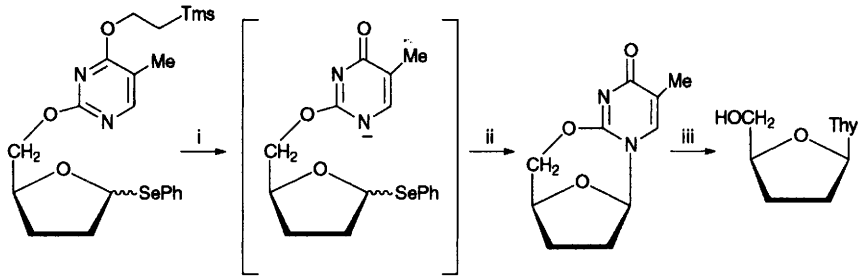
Reaction of the unsaturated adenosine derivative **29**, for which an improved synthesis is detailed, with NIS and pivalic acid gives a mixture of the two *trans*-adducts **30** and **31** (see Scheme 2). When these were separately subjected to radical deiodination, they gave the unstable 2′-deoxygenated derivatives **32** and **34**, together with the β-D-arabino- and α-D-ribo-nucleoside products **33** and **35** of radical rearrangement (see Vol. 29, pp. 268–9). Use of higher concentrations of tributylstannane gave predominantly the deoxygenated products.[48]

When the epoxide **36**, produced as the major diastereomer by epoxidation of the alkene, was treated with various nucleophiles, the chain-extended thymidines **37** (R = OMe, NH_2, CN, Br) were obtained. The compound **37** (R = $CH{=}CH_2$) and its epimer were also prepared by addition of allylmagnesium chloride to the 5′-aldehyde. These compounds were converted into 5′-*O*-dimethoxytritylated 3′-*O*-phosphoramidites (see also Vol. 30, p. 274).[49]

Benzoylated cordycepin **38** has been made from di-isopropylidene glucose *via* the 3-deoxycompound, and used to incorporate cordycepin into oligonucleotides. This route enables this to be done without using expensive cordycepin itself.[50] An acid-catalysed fusion method was used to produce **39** regioselectively, and this was converted to various 3′-deoxy-3-deazaadenosine derivatives.[51]



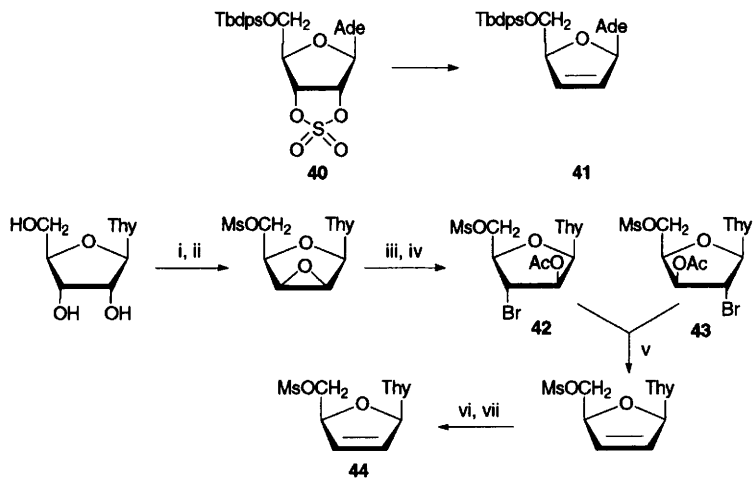
5′-Deoxy- and 2′,5′-dideoxy-6-thiopurine nucleosides have been prepared by enzymic glycosyl transfer from the thymine or hypoxanthine nucleosides to the thiopurine bases, with the 1-phosphosugar being formed *in situ*.[52]



Reagents: i, TBAF; ii, AgOTf; iii, NaOH

Scheme 3

In the area of 2′,3′-dideoxycompounds and the related 2′,3′-enes, 3′-deoxythymidine has been prepared by the intramolecular process outlined in Scheme 3.[53] 2′,3′-Dideoxy-adenosine and -inosine have been made by catalytic hydrogenolysis of the 2′,3′-dimesylates in the presence of a resin in the bicarbonate form,[54] whilst 5′-*O*-silylated didehydro-dideoxy-compounds have been prepared by reduction of the 2′,3′-dimesylates, 2′,3′-cyclic sulfates or cyclic phosphates with sodium naphthalenide, as in the case of the conversion of **40** to **41**.[55] A new route to d4T (**44**) is indicated in Scheme 4. This method



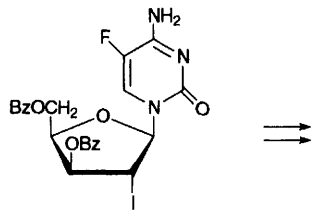
Reagents: MsCl, *N*-methylmorpholine; ii, NaOH aq.; iii, HBr, MeOH; iv, AcBr, CH_2Cl_2; v, Zn-Cu, MeOH; vi, $PhCO_2Na$, DMF; vii, $BuNH_2$

Scheme 4

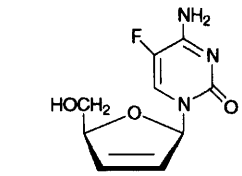
gives the product without contamination by thymine, and a key feature is thought to be the *trans*-orientation of the bromide and acetoxy groups in **42** and **43**, whereas in an earlier route where Zn/Cu-induced elimination is used to make the alkene (Vol. 23, pp. 138–9), these substituents are *cis* (D-*ribo*-), so that *trans*-elimination of bromide and thymine can compete.[56] A similar zinc-mediated elimination applied to **45**, itself made by NIS-induced addition of the

silylated base to the glycal, was used to make the d4 analogue **46** of 5-fluorocytidine (for the enantiomer, see Vol. 31, p. 273).[57]

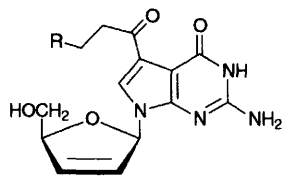
Elimination procedures have also been used to make the d4 compounds **47** (R = CH_2NH_2, CN, CO_2Me, $CONH_2$) which are nucleoside analogues of the phosphatidylinositol kinase inhibitors echiguanine A and B,[58] some d4 derivatives of 5-alkoxymethyluracil nucleosides,[59] the isoinosine derivative **48** (X = N) and the 7-deazacompound **48** (X = CH),[60] and the d4 derivative of 5-*o*-carboranyluridine, its α-anomer and the enantiomers of these.[61] Some fluorinated d4 compounds are mentioned in the next section.



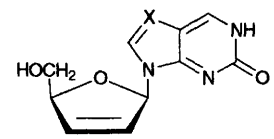
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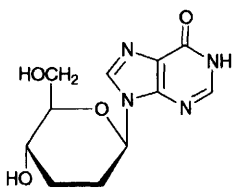


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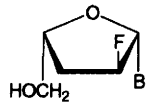
A number of 2′,3′-dideoxyhexopyranosyl nucleosides such as **49** have been prepared in connection with studies on hexopyranosyl oligonucleotides and homo-DNA.[3]



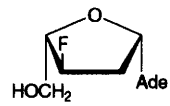
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5 Halogenonucleosides

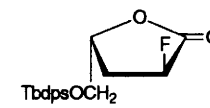
The β-L-compound **50** (B = Ade) has been prepared by base–sugar condensation, after which fluorine was introduced by a double-inversion process. The 3′-fluorocompound **51** was also reported.[62] In an alternative approach to compounds of type **50**, the α-fluorolactone **52** was prepared by stereoselective electrophilic fluorination of the enolate using *N*-fluorodibenzenesulfonimide [$(PhSO_2)_2NF$]; subsequent reduction with DIBAL and nucleoside formation



50

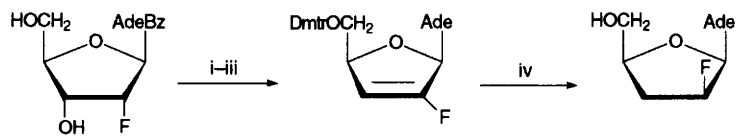


51



52

then gave **50** (B = Thy, 5-F-Ura, 5-F-Cyt) with some stereoselectivity in favour of the β-anomers. The enantiomers of **50** (B = Ura, Cyt, Thy, 5-F-Ura, 5-F-Cyt) were also prepared starting from the enantiomeric lactone, made from L-glutamic acid.[63] The anti-HIV agent β-FddA (**55**) has been prepared from the known fluoronucleoside **53**, available from ara-A, as outlined in Scheme 5.[64] Other workers have made the thymine analogue of **54** by a procedure in which reduction of the fluorolactone **56** preceded nucleoside formation.[65]

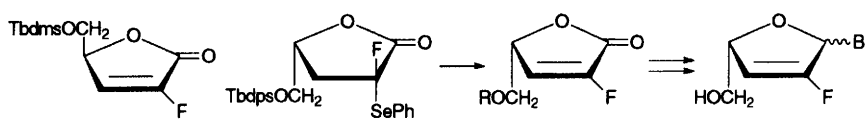


53 **54** **55**

Reagents: i, DmtrCl, Py, Et_3N; ii, MsCl, Py, Et_3N; iii, NaOH, EtOH; iv, H_2, Pd/C

Scheme 5

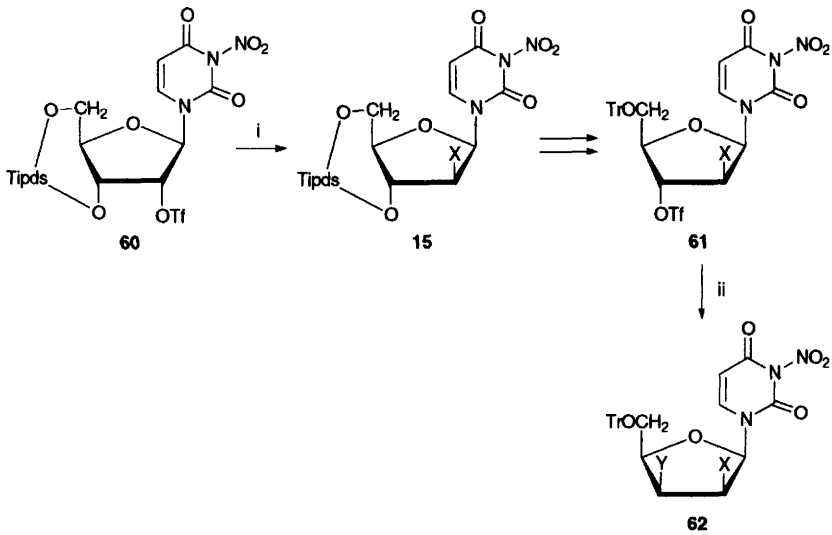
Fluorinated nucleosides similar to the intermediate **54** in Scheme 5, but in the enantiomeric series, have been described. Thus, the lactone **57**, again produced by fluorination of the enolate of the α-phenylselenyl-lactone with $(PhSO_2)_2NF$, was subjected to selenoxide elimination to give **58** (R = Tbdps), followed by reduction and nucleoside formation leading to **59** (both anomers, B = Ade, Thy, 5-F-Cyt, 5-I-Ura). The β-anomer, B = 5-F-Cyt, had the best antiviral activity.[66] Meanwhile, another group have described the synthesis of both anomers of **59** (B = Ade, Hypoxanthine) by a sequence also involving the lactone **58** (R = Tbdms), but in which this compound was made by a sequence involving a Horner-Emmons reaction on isopropylidene-L-glyceraldehyde.[67]



56 **57** **58** **59**

The triflate **60**, which is notably stable, can be prepared from 3′,5′-*O*-Tipds-uridine by treatment with triflic anhydride in pyridine–chloroform for short times, followed by trapping with trifluoroacetyl nitrate. This triflate can be used (Scheme 6) to make the 2′-deoxy-2′-halonucleosides **15** (X = Cl, Br, I), convertible into the triflates **61** (X = Cl, Br), which again show no tendency to form anhydronucleosides. The 2′,3′-dideoxy-2′,3′-dihalo-β-D-lyxofuranosyl-nucleosides **62** (X = Cl, Y = Br, Cl; X = Br, Y = Cl) can then be prepared.[29]

The 8-substituted analogues **63** (X = Br, OH, SH) of 3′-deoxy-3′-fluoroadenosine have been reported, the fluorine being inserted into 8-bromoadenosine

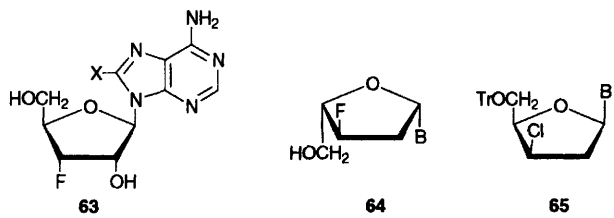


Reagents: i, Bu_4NX, toluene; ii, Bu_4NY, toluene

Scheme 6

by a double inversion sequence,[68] and the β-L-3′-fluoronucleosides **64** (B = Thy, Ura, Cyt, 5-Me-Cyt) have been described; they were converted into 5′-triphosphates which inhibited hepatitis B virus DNA polymerases.[69] A full account has been given of the formation of the chlorinated nucleosides **65** (B = Ade, Cyt, Thy) using tris-(2,4,6-tribromophenoxy)dichlorophosphorane to effect chlorination with inversion of configuration, and the same reagent was used to make some 5′-chloro-5′-deoxynucleosides (see Vol. 26, p. 233).[70]

The synthesis and antiviral activity of some 2′-fluorohexopyranosyl nucleosides has been reported.[71]



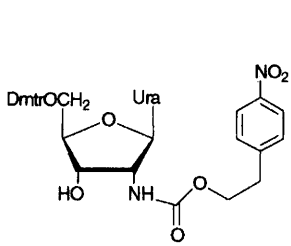
Some branched-chain fluorinated nucleosides are discussed below in Section 8, and some further examples of halogenated unsaturated nucleosides are mentioned in Section 9.

6 Nucleosides with Nitrogen-substituted Sugars

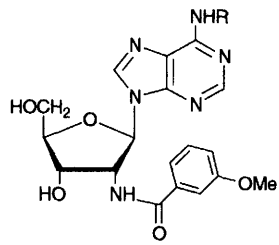
A report from Pfleiderer's laboratory describes syntheses of suitably-protected derivatives of 2′-amino-2′-deoxynucleosides and their phosphoramidites for incorporation into oligonucleotides. The uracil derivative **66** was made

through ring-opening of a 2,2′-anhydronucleoside with azide ion, and was used to make a guanine derivative by transglycosylation.[72] Some modified nucleosides , including 2′-azido-2′-deoxycompounds, were prepared from 5,6-disubstituted uridines, 5-substituted cytidines and cytidine by nucleophilic substitution reactions in alkaline or neutral medium.[73]

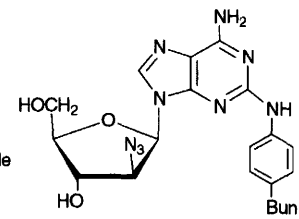
In connection with studies on inhibitors of trypanosomal glyceraldehyde-3-phosphate dehydrogenase, in which **67** (R = H) is a lead compound, a series of other amides of 2′-amino-2′-deoxyadenosine have been made by direct acylation of the nucleoside on a polymeric support.[74] Other workers have also reported other amides related to **67**, R = H, and some N^6-substituted derivatives; the compound **67**, R = Bn, had good inhibitory activity.[75] The azidonucleoside **68** has been prepared starting from 2′,3′,5′-tri-*O*-acetyl-2-iodoadenosine; the 5′-triphosphate of **68** showed strong selective inhibition of calf thymus DNA polymerase α.[76]



66

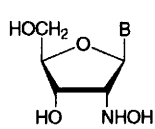


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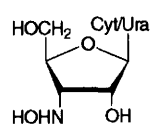


68

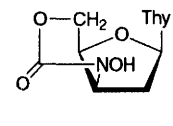
There have been reports on the synthesis of the 2′-deoxy-2′-hydroxyamino pyrimidine nucleosides **69** (B = Cyt, Ura), using variants on the chemistry reported in Volume 30, p. 277. The cytidine analogue has good antitumour activity.[77,78] The adenosine analogue **69** (B = Ade) has also been made, using intramolecular displacement of a mesylate at C-2′ of a D-*arabino*-compound to introduce the hydroxylamino group, and the 3′-hydroxylamino-compounds **70**, and their 2′-deoxy analogues, have been prepared from 3′-keto-compounds *via* oximes.[78] 2′,3′-Dideoxy-3′-hydroxylamino thymine nucleosides have been converted into *N*-hydroxy-ureas and -carbamates, such as in the bicyclic case **71**.[79]



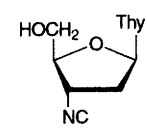
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70



71



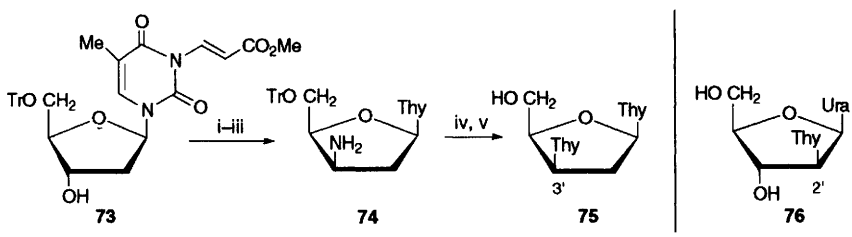
72

Both enantiomeric forms of 3′-azido- and 3′-amino-3′-deoxyadenosine have been prepared, starting from the mono-isopropylidene derivatives of either D- or L-xylose, introducing azide by displacement with inversion at C-3 and then forming the adenine–sugar link at a late stage.[80] AZT analogues in which the base is a 5-alkoxyalkyluracil have been reported,[59] and a kinetic study has

been reported on the reaction of 5′-*O*-benzoyl-2,3′-anhydrothymidine with dimethylammonium azide.[81] The azido-function in 5′-*O*-trityl-AZT has been converted in a one-pot reaction into the *t*-butyloxycarbonylamino-group by treatment with trimethylphosphine followed by Boc-ON, and aqueous work-up,[82] whilst the isocyanide **72** has been made from the corresponding *N*-formylamino compound by dehydration using the Burgess reagent methyl (carboxysulfamoyl)triethylammonium inner salt.[83]

When the thymidine derivative **73** was treated with an azide source under Mitsunobu conditions, the presence of the methoxycarbonylvinyl group prevented anhydronucleoside formation so that clean inversion was observed. After reduction and deprotection on nitrogen, the aminonucleoside **74** was converted to the novel type of analogue **75** bearing two thymine units. The 3′-epimer of **75** was also made, and so were **76** and its 2′-epimer; in the synthesis of **76**, the methoxycarbonylvinyl group was again used, so that azide could be inserted at C-2′ of 3′,5′-Tipds-uridine with inversion of configuration.[84]

The 'nucleoside dimer' **77** has been prepared by cycloaddition of an AZT derivative and tri-*O*-acetyl-*N*-propargyluridine, and a similar adduct was formed using tri-*O*-acetyl-5′-ethynyluridine.[85]



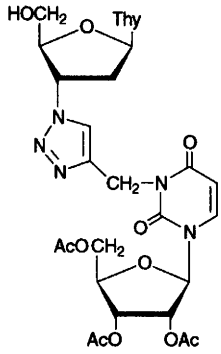
Reagents: i, DEAD, $(PhO)_2PON_3$, Ph_3P; ii, $SnCl_2$, PhSH, Et_3N; iii, pyrrolidine; iv, MeO-CH=CONCO; v, H_2SO_4, dioxan

Scheme 7

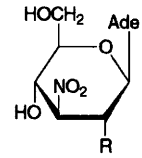
A number of compounds of type **78** (R = various amines, SMe, SPh, H) have been made by methods similar to those used previously for uracil analogues (Vol. 30, p. 278).[86]

5′-Amino-5′-deoxythymidine has been prepared from thymidine in two steps, the first being a Mitsunobu reaction with tetrachlorophthalimide as the nucleophile, since use of phthalimide itself did not prevent 2,5′-anhydronucleoside formation. The product was used to make peptide-DNA hybrids.[87] 5′-Amino-5′-deoxythymidine has been converted into the bio-isostere **79**, designed to mimic the conformation of thymidine 5′-triphosphate when the triphosphate unit is coordinated to a magnesium ion. A similar analogue of d4T was also prepared.[88] Various amides of type **80** have been made, as has the corresponding phthalimide, for evaluation against trypanosomal glyceraldehyde-3-phosphate dehydrogenase (see also ref. 75 above).[89] A paper relating to the conformation of 5′-amino-5′-deoxyuridine is mentioned in Chapter 21.

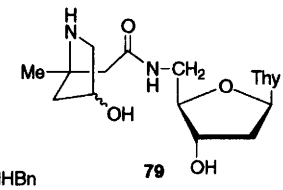
The aziridine **81** has been prepared by displacement of a 5′-tosylate; this compound was made as an analogue of *S*-adenosylmethionine which is



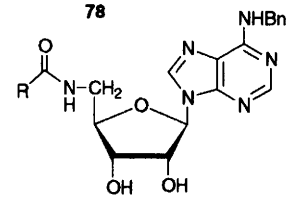
77



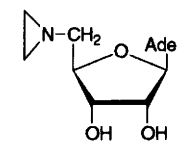
78



79



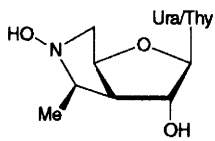
80



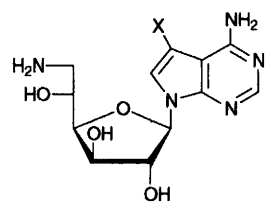
81

capable of reaction with a nucleophile to give transfer of the whole unit of **81**, rather than just a methyl group, to the nucleophile. Indeed, a bacterial DNA methyltransferase catalysed the linkage of **81** to the amino-group of an adenine base in a double-stranded DNA segment.[90]

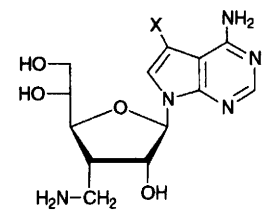
The bicyclic nucleosides **82** and their epimers α- to nitrogen have been prepared from the sugar units (see Chapter 14); UV irradiation of these gave the *N*-oxyl radicals, for which ESR data were reported.[91] The pyrrolo[2,3-*d*]pyrimidine nucleosides **83** and **84** (X = CN and $CONH_2$), with the chromophores of toyocamycin and sangivamycin, have been prepared from di-isopropylidene-D-glucose.[92]



82



83



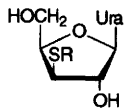
84

7 Thio- and Seleno-nucleosides

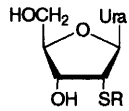
An annual review on the synthesis of thiols, selenols, sulfides, selenides and their oxidized forms includes a number of cases from the nucleoside area.[93]

When 2,2′-anhydrouridine (**13**) was treated with excess sodium hydride, followed by EtSH or $PhCH_2SH$, the 3′-thiocompounds **85** (R = Et, Bn) were produced, presumably through the intermediacy of the 2,3′-anhydrocompound **14** (see Scheme 1). However, if the thiolate was initially prepared from NaH and either EtSH or $PhCH_2SH$, followed by addition of **13**, then the 2′-thiocompounds **86** (R = Et, Bn) were obtained instead, by direct attack on **13**.[28]

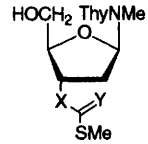
When the xanthate **87** was treated with lauroyl peroxide in benzene, the 3′-



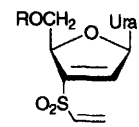
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86



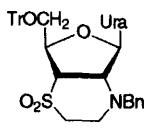
87 X = O, Y = S
88 X = S, Y = O



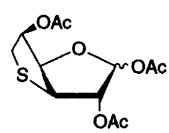
89

thionucleoside **88** was obtained. A bimolecular mechanism was proposed in which a deoxygenated sugar radical attacked **87** at sulfur, followed by a further expulsion of the sugar radical from oxygen.[94]

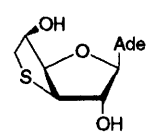
The unsaturated sulfones **89** (R = H, Tr) have been prepared by a double elimination from a D-*arabino*-precursor. Reaction with various amines then gave either bicyclic products such as **90** or the products of addition just to the exocyclic alkene; the product of reaction of the exocyclic double bond of **89** with the anion of dimethyl malonate was also described.[95] Treatment of **91** with N^6-benzoyladenine and $SnCl_4$ in acetonitrile gave after deprotection the 3′,6′-epithionucleoside **92**, and the uracil analogue was similarly prepared. In an experiment in which moist $SnCl_4$ was used, the rearranged product **93** was obtained, the structure being confirmed by X-ray analysis; a mechanism involving episulfonium ion intermediates was proposed.[96] The spirocyclic compound **94**, made because of its similarity to TSAO-T, has been prepared by condensation of the 3′-ketonucleoside with L-cysteine, and further manipulation of the relevant diastereomer, but it did not have anti-HIV activity.[97]



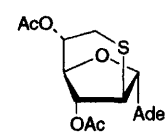
90



91

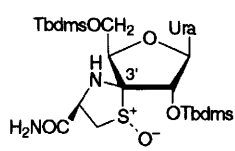


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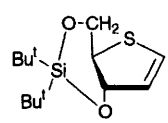


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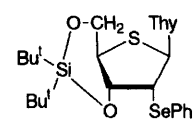
There has been continued activity in the area of 4′-thionucleosides ('sulfur-in-ring' compounds). In a stereoselective route to 2′-deoxy-4′-thionucleosides, various silyl-protected 4-thio furanoid glycals such as **95** were prepared; condensation with silylated pyrimidines in the presence of PhSeCl gave products such as **96** with high β-selectivity, and subsequent reduction



94



95

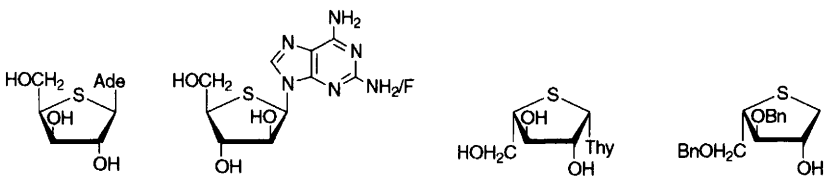


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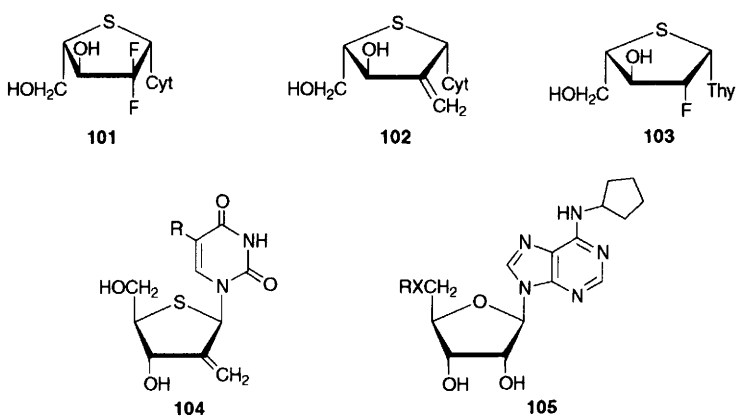
(Bu_3SnH, Et_3B, O_2) gave the 2′-deoxycompounds.[98] An efficient synthesis of the 4′-thioanalogue of BVDU has been described (see Vol. 25, p. 254 for earlier work), giving the β-anomer in 35% overall yield from 5-(2-bromovinyl)uracil.[99] A study has been reported of the acid stability of 2′-deoxy-4′-thiouridine and

its 5-fluoro- and 5-alkyl-derivatives; cleavage of the *N*-glycosidic bond competes with the reversible isomerization of the furanose (4′-thio) and pyranose (5′-thio) forms, confirmed by isolation of the pyranose forms of the parent compounds.[100] Periodate oxidation of 2′-deoxy-5-ethyl-4′-thiouridine gave mostly (5:1) the *R*-sulfoxide, which underwent base-catalysed exchange with D_2O at C-4′, predominantly (2.1:1) with retention of configuration. Reduction of the sulfoxide with TmsBr-TFA then gave the starting 4′-thionucleoside labelled with deuterium at C-4′.[101] 2′-Deoxy-4′-thionucleosides in the L-series, with both purine and pyrimidine bases, and with both α- and β-stereochemistry, have been prepared by condensation procedures.[102]

The D-*xylo*-analogue **97** of 4′-thioadenosine has been prepared by a base–sugar condensation with some β-selectivity.[103] There has been a further report on the synthesis of 4′-thioarabinofuranosylpurines **98** and the guanine analogue,[104] whilst the approach used previously in the enantiomeric series (see Vol. 31, p. 276) has now been applied to the synthesis of the L-4′-thionucleosides **99** and the cytidine analogue.[105] The tetrahydrothiophene **100** has been



prepared from D-xylose by a sequence involving inversion of configuration at C-4; this could then be used to make L-4′-thionucleosides; oxidation of **100** and difluorination of the ketone by DAST, followed by attachment of the base using sila-Pummerer-type chemistry similar to that used earlier for the enantiomeric series (Vol. 30, p. 281), led to **101** and the α-anomer. Oxidation and Wittig reaction led after attachment of the base to **102** and its anomer.[106] Treatment of **100** with DAST gave the fluoroderivative with retention, which could be converted to **103**, the 4′-thioanalogue of the anti-hepatitis B agent



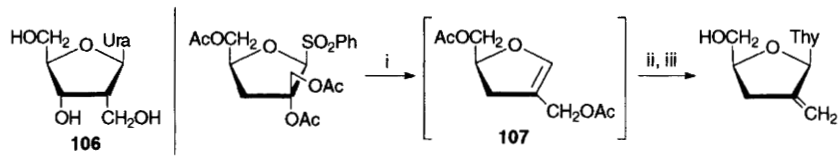
L-FMAU.[107] Sila-Pummerer glycosylation was also used to make a series of 5-substituted uracil derivatives **104**, related to the antineoplastic agent DMDC.[108]

Uracil nucleosides have been converted into their 5′-deoxy-5′-phenylthio- or -phenylselenyl-derivatives by treatment with either diphenyldisulfide or diphenyldiselenide and [bis(trifluoroacetoxy)iodo]benzene.[109] 5′-Substituted adenosine analogues of type **105** (X = S or Se) have been prepared as high-affinity partial agonists for the adenosine A_1 receptor.[110]

8 Nucleosides with Branched-chain Sugars

A review has appeared on the asymmetric synthesis of *C*-branched nucleoside analogues.[111]

An efficient synthesis of 2′-homouridine (**106**) has been developed, which uses as a key step an ene-reaction carried out on a known 2′-*C*-allyl-2′-deoxycompound (Vol. 27, pp. 253–4). The branched-chain compound **106** was incorporated into a dinucleoside monophosphate (with a normal 3′,5′-link), which was found to be resistant to ribonuclease and to undergo chemical hydrolysis about 2000 times more slowly than UpU.[112] Two new routes have been reported for the preparation of 2′,3′-dideoxy-2′-*C*-methylene nucleosides, both starting from α-D-isosaccharino-γ-lactone; in one of these (Scheme 8) the



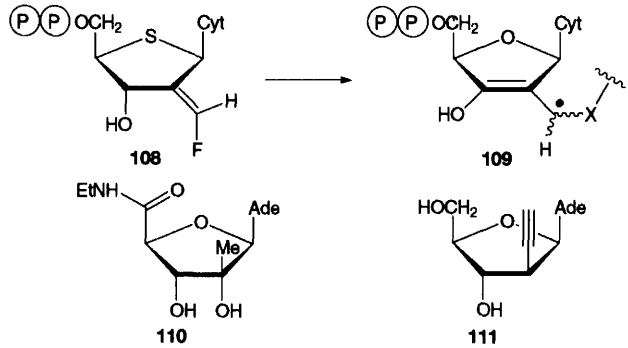
Reagents: i, SmI_2; ii, silylated Thy, $Pd_2(dba)_2$, PPh_3; iii, NH_3, MeOH

Scheme 8

intermediate **107**, produced by reductive samariation, was not isolated but subjected to palladium-catalysed linkage to the base, to give predominantly the β-anomer.[113]

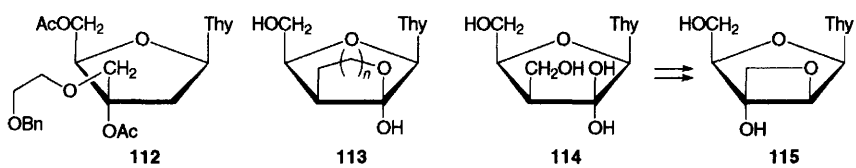
The diphosphate **108** of the antitumour agent (*E*)-2′-deoxy-2′-difluoromethylenecytidine is a stoicheometric inhibitor of ribonucleoside diphosphate reductase. Studies with **108** labelled at the exocyclic position with deuterium have led to the demonstration that a radical intermediate is involved in the inactivation of the enzyme.[114] Further work with **108** labelled at the exocyclic position with ^{13}C has led to ESR evidence in favour of an enzyme-bound non-fluorinated allyl radical of type **109** being produced.[115]

Some 2′-*C*-methyl analogues of selective adenosine receptor agonists have been prepared, and the *N*-ethylamide **110** was made by oxidation at C-5′.[116] The 2′-deoxy-2′-*C*-ethynyl compound **111** has been made by a method similar to one used earlier in the pyrimidine series (Vol. 28, p. 276); it was incorporated into oligonucleotides which showed enhanced thermal stability in duplexes



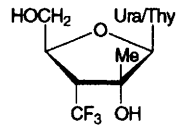
with complementary DNA, but decreased stability with RNA.[117] The anti-tumour activity of 3′-*C*-ethynyl-uridine and -cytidine (Vol. 30, pp. 284–5) has led to the synthesis of various related 3′-*C*-substituted derivatives, along with 2′-*C*-ethynyl- and 3′-deoxy-3′-*C*-ethynyl-compounds.[118]

A range of other C-3′-alkylated thymidines have also been reported, including the compound **112**, made from a known sugar (Vol. 29, pp. 192–3), and 3′-*C*-methyl- and -azidomethyl-thymidine; the same paper also describes the incorporation of 3′-(3-hydroxypropyl)thymidine, made from earlier-reported intermediates (Vol. 31, p. 277), into oligonucleotides.[119] This chemistry can be adapted to prepare the bicyclic hemiacetals **113** (n = 1,2).[120] The same group have also described the [3.2.0]bicyclonucleoside **115**, made by cyclization of **114**; incorporation of 13 units of **115** into a 14-mer oligothymidylate gave enhanced thermal stability in duplexes with both complementary ssRNA and ssDNA.[121] Various potential prodrugs derived from 1-[2′,3′-dideoxy-3′-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]cytosine, such as esters and urethanes, have been described,[122] and a report from Benner's laboratory discusses the synthesis of intermediates for the preparation of sulfur-linked oligodeoxynucleosides.[123]

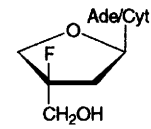


The 3′-deoxy-3′-trifluoromethyl nucleosides **116** have been made by base–sugar condensation; the 2′-deoxycompound was prepared by standard deoxygenation, and the d4 analogue by elimination.[124] 3′-Fluoro-apionucleosides **117** have been made in an enantioselective route from isopropylidene-D-glyceraldehyde, and the β-anomers were also obtained.[125] The same precursor was also used to make the cyclopropane-fused compounds **118**, in which the base–sugar link was made with fair β-selectivity using an α-glycosyl chloride.[126]

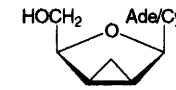
As regards compounds branched at C-4′, when **119** (Scheme 9), made using the method of Giese's laboratory (Vol. 28, p. 275), was treated with large



116

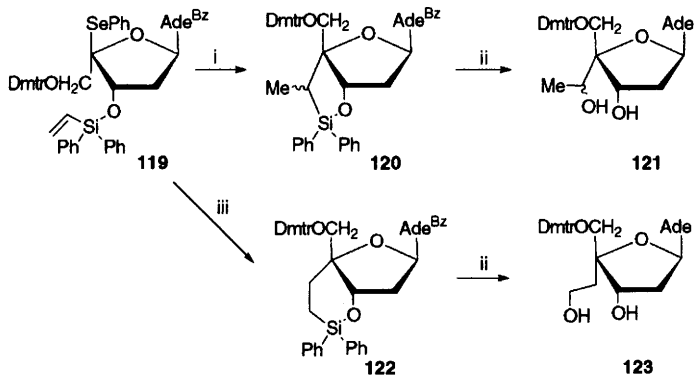


117



118

amounts of Bu_3SnH, the 4′-branched product **121** was obtained after oxidative desilylation. Use of limited amounts of Bu_3SnH gave an isomeric product **123**. It seems likely that a bicyclic radical is initially formed by 5-exo-cyclization, and that this at high stannane concentrations abstracts a hydrogen atom to give **120**, whilst at low concentrations of Bu_3SnH, the initial radical rearranges to the precursor of **122**.[127] Similar chemistry was also carried out in the thymidine series, and the derived product **124** was incorporated into oligonucleotides which formed only slightly destabilized duplexes with complementary DNA or RNA.[128]

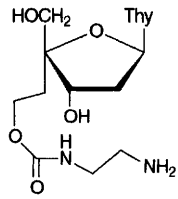


Reagents: i, Bu_3SnH (high concn.), AIBN; ii, H_2O_2, KF, $KHCO_3$; iii, Bu_3SnH (low concn.), AIBN

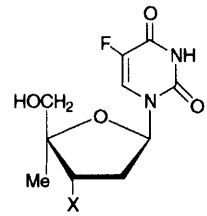
Scheme 9

The 3′-azido- and 3′-fluoro-4′-methyl-compounds **125** (X = N_3, F) have been prepared, together with their α-anomers, by a method in which the sugar unit was assembled enantioselectively using asymmetric epoxidation.[129] An efficient route has been reported for the synthesis of 4′-α-carboxy-nucleosides, in which the intermediate **126** was prepared from dimethyl-L-tartrate and then elaborated into a unit which could be linked to bases to give products **127** (B = Thy, Cyt^{Ac}, Gua^{Ac}, Ade^{Bz}), suitable for incorporation into oligonucleotides.[130] The 4′-*C*-trifluoromethyl-nucleoside **128** has been prepared from the appropriate sugar unit (Chapter 14), and was converted into the 2′-deoxy- and 2′,3′-dideoxy-compounds, and into the d4 analogue; some work was also reported in the purine series.[131]

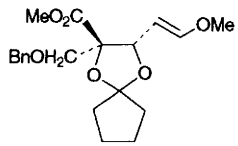
There have been a number of significant publications concerning 2′-*O*, 4′-*C*-methylene ribonucleosides, predominantly from Wengel's laboratory (but see Vol. 31, p. 279 for an earlier paper from elsewhere). These compounds of type **130**, where the furanose ring is fixed in an *N*-type conformation, can be



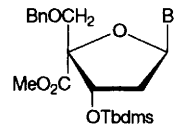
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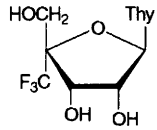
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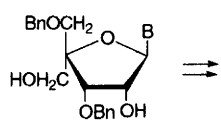


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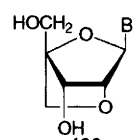


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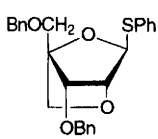
prepared by selective tosylation of diols **129** followed by treatment with NaH and deprotection. When incorporated into oligodeoxyribonucleotides [termed locked nucleic acids (LNA)], the duplexes between LNA and either complementary DNA or RNA sequences had very substantial increases in thermal stability (up to +8 °C per modification),[132,133] and Imanishi's group have reported similar findings for oligodeoxynucleotides incorporating **130** (B = Ura, Cyt).[134] Improved synthetic routes have subsequently been described for **130** (B = Thy), in which the tosylation is done before base–sugar coupling, and for **130** (B = Ade).[135] It has been found that a 9-mer oligoribonucleotide (a ribo-LNA) comprising three units of **130** (B = Thy) and six ribonucleosides also gave duplexes with either complementary RNA or DNA sequences which had unprecedented thermal stability, and which was largely destroyed by one mismatch.[136] Condensation of the bicyclic thioglycoside **131** with silylated thymine, with NBS as activator, led with some stereoselectivity to the α-nucleoside **132**, a precursor for α-LNA.[137] Conversion of **129** (B = Thy) into a disulfonate, and reaction of this with benzylamine, gave after deprotection the imino-linked analogue **133** (R = H). A similar route was used to make the sulfide **134**.[138] A later paper has given more detail of the synthesis of **133** (R = H, Me), and described the incorporation of both of these into oligodeoxy-



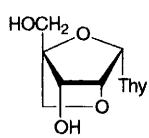
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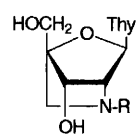
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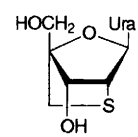
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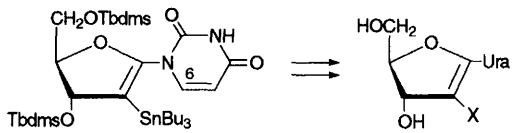


134

nucleosides which again displayed high affinity towards complementary DNA or RNA sequences.[139]

9 Nucleosides of Unsaturated Sugars and Uronic Acids

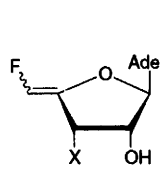
The 2′-stannylated alkene **135** was produced by stannyl migration when the 6-tributylstannyl compound, itself produced by metallation and quenching with Bu_3SnCl (see Vol. 28, p. 281), was treated with lithium tetramethylpiperidide. Reaction of **135** with NCS, NBS or iodine gave after deprotection the alkenyl halides **136** (X = Cl, Br, I), whilst carbon substituents could be introduced by Stille couplings on either **135** or the protected form of **136** (X = I), to give **136** (X = Ph, Bn, Me, CH_2=CH).[140] A paper discussing a reaction of 1′-alkenyl nucleosides in which the base is lost is mentioned in Chapter 13, and 2′,3′-didehydro-2′,3′-dideoxyfuranosyl systems (d4 compounds) are discussed above in Section 4 together with their saturated analogues.



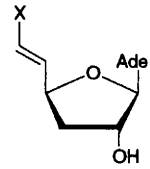
135 **136**

In further work on the inhibition of *S*-adenosyl homocysteine (SAH) hydrolase, Borchardt, Robins and co-workers have prepared the fluoroalkenes **137** (X = H, F, Cl), the alkenyl fluoride being introduced using methods previously developed (Vol. 28, p. 274), and also the 3′-deoxy-haloalkenes **138** (X = F, Br, I), where again the key functionality was produced by application of methods used earlier (Vol. 28, p. 272). These compounds, unlike the structures with the 3′-OH present, were not substrates for the hydrolytic activity of SAH hydrolase.[141] The carbocyclic compounds **139** (X = F, I) have also been prepared, both isomers of the iodo-compound and the *trans*-fluoride proving to be strong mechanism-dependent inhibitors of SAH hydrolase.[142] The dibromoalkenes **140** (X = Br) and **141** have been made either by bromination-dehydrobromination sequences from previously-known compounds (see Vol. 28, p. 272), or, in the case of **140** (X = Br), by Wittig-type reaction on a protected 5′-aldehyde, an approach also used for the bromofluoroalkene **140** (X = F, both isomers). The dibromo-compounds were irreversible inhibitors of SAH hydrolase.[143] Further interesting analogues reported are the haloalkynes **142** (X = Cl, Br, I); the chloro- and bromo-compounds were prepared by coupling adenosine with the haloalkynyl sugars (Chapter 13), whilst the iodo-compound came from a protected form of **140** (X = Br) by treatment with BuLi followed by NIS and $AgNO_3$. The mechanisms by which these compounds inhibit SAH hydrolase were discussed, but the iodo-compound behaved differently from the chloro- and bromo-analogues.[144]

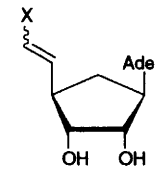
Ribonucleoside 5′-carboxylic acids have been prepared by oxidation of the



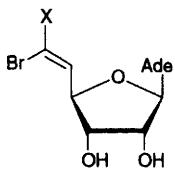
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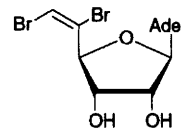
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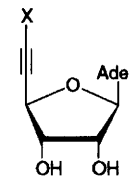
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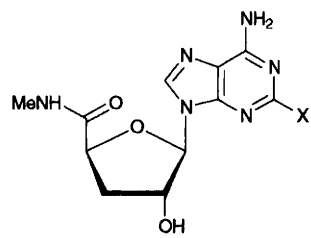


141



142

nucleosides using the nucleoside oxidase from *Stenotrophomonas maltophilia* (FERM BP-2252). The enzyme will accept ribonucleosides of unnatural bases and also carbocyclic compounds such as aristeromycin, and it has been immobilized and used on a preparative scale.[145] The uronamides **143** (X = Cl, H) have been made by base–sugar condensation, and the analogous 2′-deoxycompounds were also described.[146]



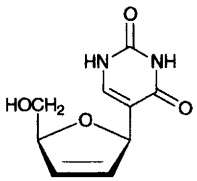
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10 *C*-Nucleosides

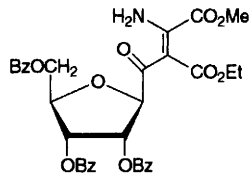
An extensive review has appeared on the chemistry of *C*-nucleosides with condensed heterocyclic bases, including formycin and its analogues.[147] The tautomeric situation for pseudouridine in basic solution has been investigated using NMR techniques. The pK_a values of the NH bonds at positions 1 and 3 were measured as 9.3 and 9.6 respectively, so that for the monoanion, the N^1 anion population was 64%, as compared with 36% for the N^3 anion.[148] Pseudouridine has been converted into its d4 analogue (**144**) using the Corey-Winter procedure; on hydrogenation of the 5′-*O*-Tbdms derivative, allylic hydrogenolysis occurred as well as alkene reduction, to give after deprotection (*S*)-5-(4,5-dihydroxypentyl)uracil, which occurs in the nucleic acid of a bacteriophage.[149]

Reaction of 2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide with ethyl bromoacetate in a Blaise reaction, followed by acid hydrolysis, gave a β-keto-ester

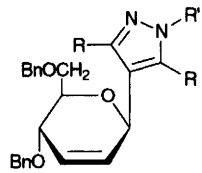
which on reaction with ethyl cyanoformate led to **145**. This could be converted to pyrazole and pyrimidine *C*-nucleosides by condensation with hydrazine derivatives and with acetamidine respectively.[150] In the pyrazole area, 3-β-D-ribofuranosylpyrazole-1-carboxamide has been prepared from known intermediates,[151] and 4-*C*-glycosylpyrazoles of type **146** have been made from 2-glycosyl-1,3-diketones.[152] Reaction of 2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide with 1-aza-2-azoniaallene salts of type **147**, followed by debenzoylation, gave 1,2,4-triazoles **148**, and the β-D-galactopyranosyl case was also described. The presence of the *t*-butyl group, which can be eliminated as isobutene, is necessary to obtain a neutral product.[153] 1,3-Dipolar cycloadditions of ethyl 3-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α- and -β-D-ribofuranosyl)-propiolate with various exocyclic and endocyclic heterocyclic ylides gave a range of *C*-nucleoside analogues including 2-(β-D-ribofuranosyl)pyrrolo[1,2-*a*]pyridines and pyrazolo[2,3-*a*]pyridines[154] and similar reactions with endocyclic heterocyclic azomethine ylides gave 3-(β-D-ribofuranosyl)pyrroles.[155]



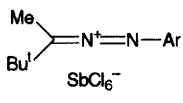
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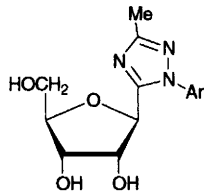
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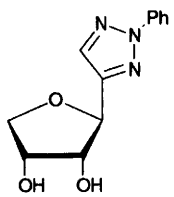


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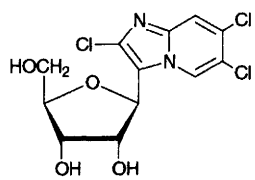


148

Cyclization of the appropriate triazole bearing tetrahydroxybutyl substituents of D-*ribo*- and D-*arabino*- configuration, using tosyl chloride in pyridine, led to the β-D-erythrofuranosyltriazole **149** and the α-anomer respectively.[156] There has been a report extending previous work on pyrazine-*C*-nucleosides (Vol. 30, pp. 286–7) to the synthesis of pyrazinoic acid derivatives.[157] Townsend's group have made the TCRB analogue **150** by a novel approach in which an aldehyde group on the heterocycle underwent a Wittig reaction with a chiral ylide, and the sugar ring was then elaborated stereoselectively, *via* the d4 derivative.[158] A paper on *C*-mannosylindoles is mentioned in Chapter 3.



149

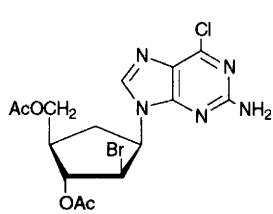


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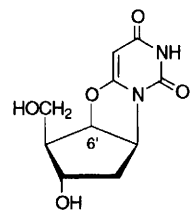
11 Carbocyclic Nucleosides

A review has been published on carbocyclic adenosine analogues as inhibitors of SAH hydrolase, and hence as antiviral agents.[159] A review on the application of enzymes and whole cells in synthesis mentions examples, mainly kinetic resolutions, of relevance in the preparation of carbocyclic nucleosides.[160]

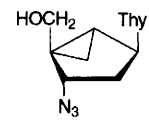
A route to 2′-deoxy-carbocyclic nucleosides involves the formation of 2′-bromo-2′-deoxy-compounds such as **151** by regio- and stereo-selective addition of NBS in acetic acid to the 2′-alkene in the presence of silver acetate, followed by radical debromination.[161] A conformationally-restricted analogue **152** of 2′-deoxy-carbocyclic uridine has been prepared as a racemate by ring opening of an epoxide with uracil, inversion of configuration at C-6′, and then oxidative cyclization. The cytosine analogue was also prepared, but neither compound was active in antiviral tests.[162] In an interesting study, Marquez and co-workers have prepared the AZT analogues **153** and **154** from previously reported diols (see Vol. 31, pp. 282–3). These have locked conformations, corresponding to the $_2$E (*N*)- and $_3$E (*S*)-conformations of AZT. Both were converted to their triphosphates, and it was found that the 'northern' triphosphate of **153** inhibited HIV reverse transcriptase with equal potency to AZT triphosphate, but that **154** triphosphate was inactive, indicating the conformational preference ('northern', similar to A-form DNA) displayed by the reverse transcriptase, even if nucleoside kinases required to form the triphosphate *in vivo* may have a preference for a 'southern' conformation.[163]



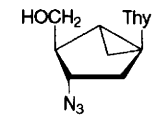
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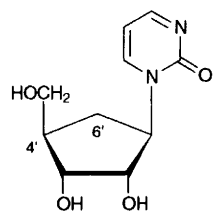


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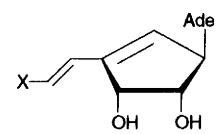


154

The carbocyclic analogue **155** of the cytidine deaminase inhibitor zebularine has been prepared, as have the 4′,6′-ene (neplanocin-type analogue) and the 4′,6′-methano-compound.[164] One-pot oxidations [$Ba(MnO_4)_2$] and Wittig reactions of neplanocin have led to the chain-extended compounds **156** (X = CO_2Et, CN).[165] Some chain-extended halovinyl derivatives of aristeromycin were mentioned above[142] in the context of related structures.

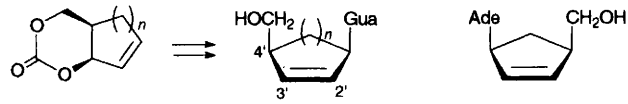


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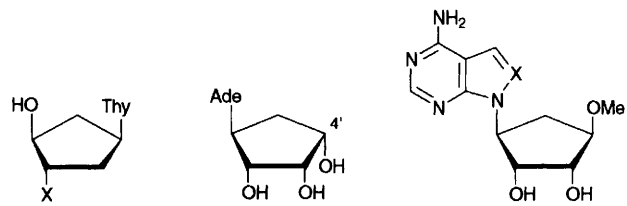
There have been further reports on the synthesis of carbocyclic analogues of 2′,3′-didehydro-2′,3′-dideoxynucleosides. The chiral cycloalkenes **157** (n = 1,2), made using enzymic kinetic resolution, can be converted using Pd(0) chemistry into carbovir (**158**, n = 1), its homologue, and some related compounds.[166] Other workers have also used Pd(0)-induced coupling of nucleobases with allylic acetates to make racemic carbovir and related species.[167] The L-enantiomer **159** has been prepared, as has the 6-mercaptopurine analogue, by a



157 **158** **159**

sequence in which Mitsunobu coupling of 6-chloropurine to an allylic alcohol was a key step.[168] The 2′-fluoro-[169] and 3′-chloro-substituted[170] derivatives of carbovir (**158**, n = 1) have been prepared as racemates from 2-azabicyclo[2.2.1]-hept-5-en-3-one. 4′-α-Alkylated derivatives of carbavir have been made by a sequence in which the asymmetric alkylation of a β-ketoester was a key step.[171] Racemic homologues of carbovir (CH_2-Gua replacing Gua), and compounds with other bases, have been prepared from norbornadiene.[172]

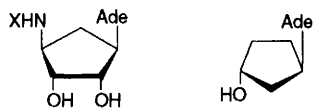
A range of nor-analogues of carbocyclic nucleosides have been reported. The compounds (±)-**160** (X = OH, N_3, SPh) have been made from opening of an epoxide,[173] the epimer **161** of (+)-5′-nor-aristeromycin, its 4′-deoxy-analogue, and the 4′-ene have been described,[174] as have the *O*-methylated compounds **162** (X = CH, N) and the adenosine analogue.[175] 5′-Amino-5′-



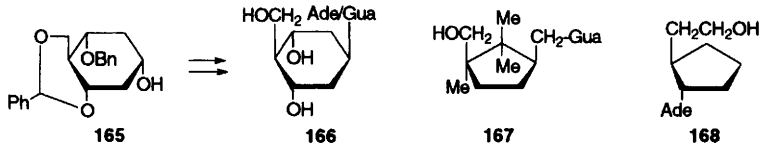
160 **161** **162**

deoxy-5′-noraristeromycin (**163**, X = H) has been prepared from an intermediate previously used in this area (Vol. 27, p. 267),[176] and the hydroxylamine **163** (X = OH), together with some related compounds, have been reported.[177] The inhibitor **164** of tumour necrosis factor-α has been prepared enantioselectively by a procedure involving enzymic resolution of a cyclopentene derivative.[178]

(*R*)-(−)-Carvone has been converted in a number of steps into **165**, which



163 **164**



165 **166** **167** **168**

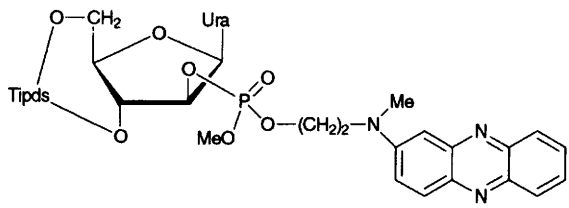
was used to make the cyclohexyl nucleosides **166**.[179] Further analogues of type **167** have been reported,[180] as has the 'carbocyclic α-L-dideoxyhomonucleoside' **168**.[181]

Some alkenyl carbocycles were discussed in Section 9 above. Some phosphates of carbocyclic nucleosides are mentioned in the next section, some cyclopropyl nucleoside analogues in Section 15, and some carbocyclic analogues of oxetanocin in Chapter 19.

12 Nucleoside Phosphates and Phosphonates

A review on boron-containing oligonucleotides discusses both species which have internucleosidic boranophosphate links and those with a carboranyl unit either linked to the phosphate unit or on the nucleobase.[182] An overview has been given of the synthetic methods available to prepare nucleoside analogues containing P–F bonds, covering phosphofluoridate, phosphorofluoridothioate and phosphorofluoridodithioate mono- and di-esters.[183]

12.1 Nucleoside Mono- and Di-phosphates, Related Phosphonates and Other Analogues. – Phenazine units have been tethered to D-arabinofuranosyl- and D-xylofuranosyl-uracil units through phosphate links, as in the case of **169**, and

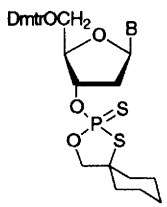


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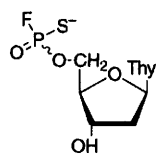
these were then incorporated into oligodeoxynucleotides for studies of duplex stability and fluorescence properties.[184] An improved synthesis of 2′-deoxy-L-cytidine-3′-phosphate has been reported.[185] Although we do not routinely report the preparation and use of nucleoside phosphoramidites, we note that the use of *O*-allyl phosphoramidites has been developed to permit the incorporation of base-sensitive heterocycles into oligonucleotides,[186] and it has been shown that problems involved in incorporation of tertiary alcohols (branched-chain nucleosides) into oligonucleotides can be reduced if the coupling time to produce the phosphite is prolonged, and if subsequent oxidation is carried out with *t*-butyl hydroperoxide rather than iodine–water–

pyridine, since use of the latter conditions cause partial elimination of the tertiary alkyl group.[187]

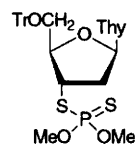
Direct procedures have been reported for the synthesis of the 3′-thiophosphates of 2′-deoxy- and 2′,5′-dideoxy-adenosine, and the 5′-thiophosphate of 2′-deoxyadenosine was also prepared.[188] In an improvement of the oxathiophospholane approach to phosphorothioate oligonucleotides, the diastereoisomers of the spirocyclic 1,3,2-oxathiaphospholanes **170** were easily separated, and then used in the diastereoselective preparation of oligodeoxyribonucleoside phosphorothioates and chimeric PS/PO systems.[189] Opening of monocyclic oxathiophospholanes by fluoride ion, which occurred in a non-stereoselective manner, led to the synthesis of 2′-deoxynucleoside-3′-*O*- and -5′-*O*-phosphorofluoridothioates. In the case of **171**, the absolute configurations of the diastereoisomers could be determined by the use of snake venom phosphodiesterase.[190] An interesting route to the *S*-nucleosidyl-phosphorodithioate **172** involves the reaction of 5′-*O*-trityl-2,3′-anhydrothymidine with *O,O*-dimethyl dithiophosphate, and by use of a 3′-*O*-dithiophosphoryl nucleoside as the nucleophile, the 3′,3′-dinucleoside **173** could be obtained.[191]



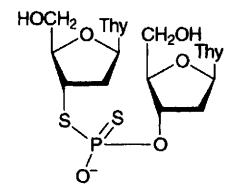
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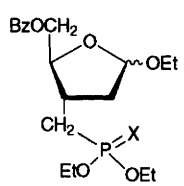


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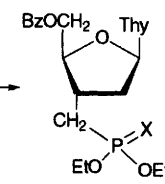
When the phosphonothioate **174** (X = S) (Vol. 29, pp. 198–9) was treated with silylated thymine in the presence of a Lewis acid, the β-nucleoside **175** (X = S) was formed with good selectivity. It was argued that this reflected intramolecular participation by the sulfur, since the phosphonate **174** (X = O) reacted in a much less stereoselective manner, although **175** (X = O) could be prepared from the sulfur analogue by oxidation with MCPBA.[192]

Bisphosphates of 2′- and 3′-deoxyadenosine derivatives, with substituents at C-2 and N-6, have been prepared and found to be potent agonists at $P2Y_1$ receptors.[193]

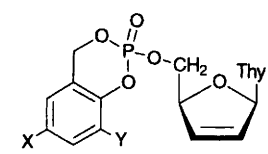
There has been a review on prodrugs of bioactive nucleoside-5′-phosphates, concentrating on species which give lipophilicity for transport, and from which the 5′-phosphate can be liberated by chemical or enzymatic means *in vivo*.[194] In



174

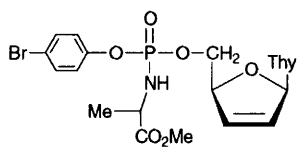


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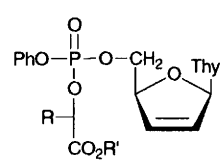


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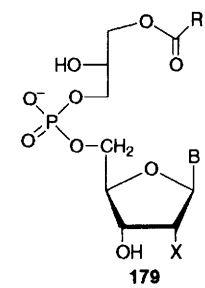
this area, there have been fuller reports on cyclosaligenyl (*cyclo*Sal) derivatives of the monophosphates of d4T (**176**)[195] and AZT,[196] and the bis-*S*-acetyl-2-thioethyl (SATE) prodrug (see Vol. 30, p. 294) of β-L-2′,3′-didehydro-2′,3′-dideoxy-5-fluorocytidine 5′-monophosphate has been reported.[197] The *p*-bromophenyl-compound **177** has been shown to undergo enhanced hydrolysis as compared with the non-brominated species,[198] and previous work on phosphoramidates of d4T (Vol. 30, p. 294) has been extended to the synthesis of lactate and glycolate derivatives **178** (R = Me, H; R′ = Me, Et), but these were inactive as antiviral agents.[199] The 5′-mono-and di-phosphates of 2′-azido-2′-deoxy-uridine and -cytidine have been prepared; the diphosphates are inhibitors of ribonucleoside diphosphate reductase, and in studies with permeabilized cells, it was found that the first phosphorylation of the nucleosides was rate-limiting in the activation.[200] This led to the preparation of the bis(pivaloyloxymethyl) ester of 2′-azido-2′-deoxy-uridine 5′-monophosphate, which was an effective prodrug.[201]



177



178



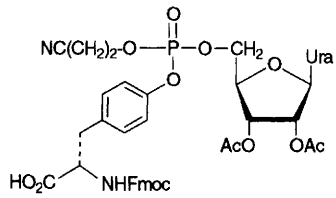
179

Lysophosphatidylnucleosides of type **179** (R = C_4–C_{15}, X = H, OH) have been assembled in a combinatorial manner, the acylation of the glycerol unit being carried out enzymically at a late stage.[202]

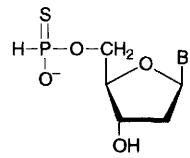
In work on the synthesis of nucleopeptides, the uridylated tyrosine **180** was prepared, and converted into a pentapeptide on a solid support. This pentapeptide was then linked in a solution-phase coupling to another heptadecapeptide to give a nucleopeptide fragment from the poliovirus genome.[203] Other workers have reported the preparation of nucleopeptide fragments using enzymes to deprotect selectively the *C*-terminal carboxylates, the nucleobases, and the 3′-hydroxy groups of 2′-deoxyribose residues.[204]

Syntheses of thymidine-5′-phosphorofluoridothioate and -phosphorodithioate have been reported,[205] and unprotected 2′-deoxynucleoside 5′-*H*-phosphonates and 5′-*H*-phosphonothioates (**181**) have been described, and converted by reaction with sulfur into phosphorothioates and phosphorodithioates respectively.[206]

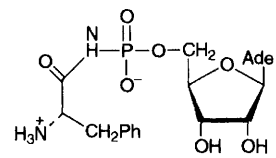
An improved procedure has been developed for the preparation of acyladenylates from AMP and carboxylic anhydrides,[207] and a good route has been reported for the synthesis of *N*-acyl phosphoramidate analogues of aminoacyl adenylates, the phenylalaninyl example **182** being one of those made, as were the valyl and prolyl cases; the key step involves reaction of an adenosyl 5′-



180



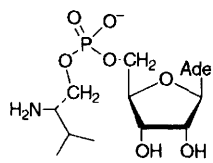
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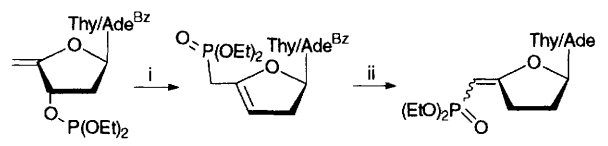
182

phosphoramidite with an *N*-protected amino amide, followed by oxidation at phosphorus, but careful attention to protecting groups was needed to ensure good yields.[208] The leucinol adenylate **183** has been prepared, and converted into short peptides such as Pro-Met-Leucinol-AMP, analogues of aminoacyl adenylates which can be delivered using peptide permeases.[209]

In an approach to 4′-unsaturated 5′-phosphonates, the phosphites **184** underwent photochemical single electron transfer rearrangement (Scheme 10) to give allylic phosphonates **185**. These could be isomerised to the vinylic species **186**, where the *E*-isomer was the thermodynamic product.[210]



183

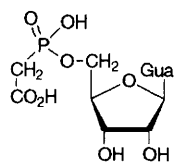


184 **185** **186**

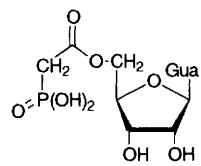
Reagents: i, 1,4-dicyanonaphthalene, hv; ii, NaOMe, MeOH (B = Ade^{Bz}) or NH_4OH (B = Thy)

Scheme 10

The reagent 2-(4-nitrophenyl)ethyl methylenebis(phosphonate) has been developed as an effective reagent for the conversion of 3′-*O*-acetyl-2′-deoxynucleosides[211] and 2′,3′-*O*-isopropylidene ribonucleosides[212] into their 5′-methylenebisphosphonates. A series of enzymically-stable analogues of GDP have been reported, including the methylenebis(phosphonate), the imidodiphosphate, the 5′-*O*-malonate half-ester, and the phosphonates **187** and **188**.[213]



187



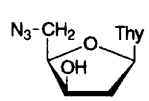
188

Similar analogues of CDP have also been prepared, designed to inhibit sialyl transfer, as does CDP itself.[214] Mycophenolic acid is a potent inhibitor of IMP dehydrogenase,with its carboxyl group positioned at the space occupied by the phosphoryl group of the nicotinamide mononucleotide; the isopropylidene derivative of adenosine 5′-methylenebis(phosphonate) has now been used

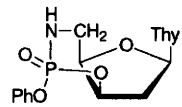
to prepare a methylene-linked analogue of mycophenolic adenine dinucleotide.[215]

12.2 Cyclic Monophosphates and Their Analogues. – A route has been developed for the preparation of oligonucleotides terminated with a 2′,3′-cyclic phosphate unit, involving a thiophosphate linker to the solid support, from which the oligonucleotide can be released oxidatively, with formation of the cyclic phosphate at the 3′-terminus.[216] The 3′,5′-Tipds-derivative of 2′-homouridine (**106**)[112] has been converted into its 2′,3′-cyclic phosphate with a six-membered ring.[217]

When the *threo*-compound **189** was treated with triphenyl phosphite at 100 °C, the cyclic phosphoramidate **190** was formed. When the same procedure was applied to the *erythro*-epimer of **189** (5′-azido-5′-deoxythymidine), the major product was the 5′-diphenylphosphoramidate of the 2,3′-anhydronucleoside, the formation of which could be rationalized as occurring by cyclization of a cyclic intermediate with 5-co-ordinate phosphorus. Under the same conditions, AZT gave just the *N*-diphenylphosphoryl derivative of 3′-amino-3′-deoxythymidine.[218]



189

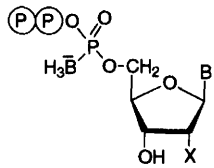


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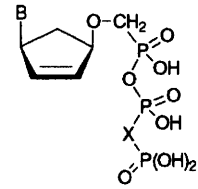
12.3 Nucleoside Triphosphates and Their Analogues. – Syntheses of 3′-deoxyadenosine-2′-triphosphate and 2′-deoxyadenosine-3′-triphosphate have been described; the products were examined as potential phosphate donors for various nucleoside kinases.[219] A range of 5-substituted 2′-deoxyuridine-5′-triphosphates have been prepared, and used as substrates for thermostable DNA polymerases, hence making DNA libraries containing the modified structures.[220] Also described are 5′-triphosphates of various 'universal' deoxynucleosides (*i.e.* containing bases which do not discriminate between natural bases opposite them in a duplex), including as bases 3-nitropyrrole and 5-nitroindole.[221]

An improved method has been developed for the preparation of 2′-deoxy-5′-(α-P-borano)triphosphates of nucleosides (**191**, X = H), involving reaction of a cyclic triphosphate with a borane-amine complex, followed by hydrolysis,[222] and the method can also be applied in the ribonucleotide series (**191**, X = OH).[223] A route has been described for the preparation of the 5′-(α,β-imido)triphosphate of N^2-(*p*-*n*-butylphenyl)-2′-deoxyguanosine, an inhibitor of B family DNA polymerases.[224]

A review has been published on some routes to deoxynucleoside triphosphate analogues in which one or more phosphonate units are present,[225] and the analogues **192** (X = CH_2, CHF, CF_2) of nor-carbovir triphosphate ('non-natural' enantiomer) have been synthesized (see also Vol. 28, p. 291 and Vol. 30, pp. 295–6), the CF_2 analogue being a potent inhibitor of HIV reverse transcriptase.[226]



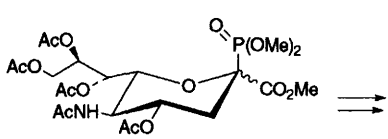
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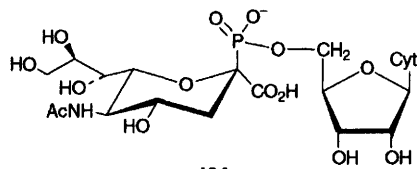
192

A route has been developed for the synthesis of hydrolase-resistant phosphonate analogues of diadenosine-5′,5″-P^1,P^3-triphosphate (Ap^3A),[227] and transmembrane transport of ATP has been facilitated by the synthesis of cholesteryloxycarbonyl-ATP, in which O-3 of cholesterol is linked to the ψ-phosphate of ATP though a carbonate group.[228]

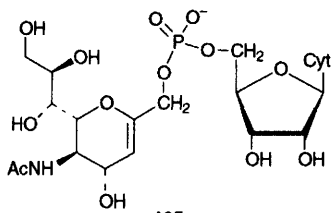
12.4 Nucleoside Mono- and Di-phosphosugars And their Analogues. – A number of reports from Schmidt's laboratory describe elegant work on inhibitors of sialyl transferase. The phosphonate **193** and its α-anomer were produced by reaction of a glycosyl phosphite with dimethyl trimethylsilyl phosphite in the presence of TmsOTf. After separation, the β-anomer was converted to the phosphonate analogue **194** of CMP-Neu5Ac, the attachment of the nucleoside using a Mitsunobu reaction between 2′,3′-di-*O*-acetyl-*N*-acetylcytidine and the phosphonate monoester. The α-anomer of **194** was also made, and some earlier work by others (Vol. 30, p. 293) was shown to be in error.[229] The transition state analogue **195** for α(2→6) sialyltransferase has been prepared,[214] and CMP-quinic acid has been synthesized and shown to be a potent inhibitor of rat liver α(2→6) sialyltransferase.[230] Both diastereomers of **196** (Ar = Ph, 2-furyl) have been prepared and shown to be good



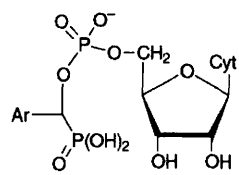
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194



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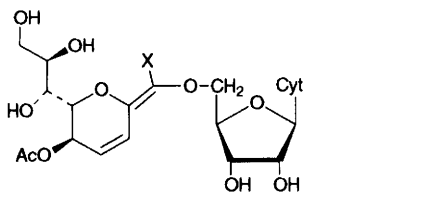


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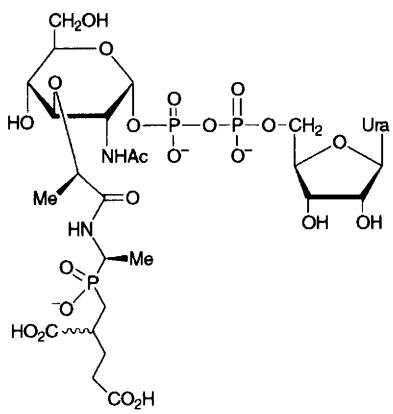
sialyltransferase inhibitors.[231] The phosphonate **197**, incorporating design features of other inhibitors, has also been made[231] from intermediates used in earlier work, based on the finding that **198** was a good inhibitor[214] (see also Chapter 17).

An improved route to TDP-L-rhamnose has been reported,[232] and GDP-L-galactose, GDP-3-deoxy-L-galactose and GDP-3,6-dideoxy-L-galactose have been prepared from the sugars (Chapter 16) as analogues of GDP-L-fucose.[233] An enzymic method has been used to prepare TDP-6-deoxy-4-keto-D-glucose, a common intermediate in the biosynthesis of deoxysugars, on a gram scale.[234]

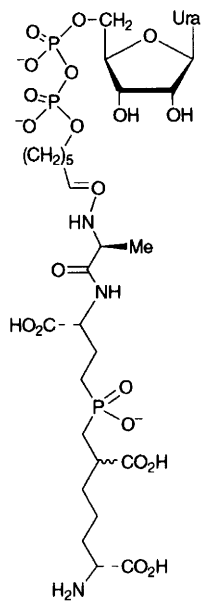
A notable achievement by workers at Lilly has been the first synthesis of the 'Park nucleotide', UDP-*N*-acetylmuramic acid with a pentapeptide [L-Ala-D-Glu(γ)-L-Lys-D-Ala-D-Ala] attached. The preformed peptide unit was coupled to an α-dibenzyl phosphate of *N*-acetyl muramic acid, after which debenzylation and coupling to uridine 5′-phosphomorpholidate completed the synthesis.[235] A group at Merck have described the synthesis of the phosphinate **199** as a potential inhibitor of Mur D, the enzyme in peptidoglycan biosynthesis that attaches D-glutamic acid to UDP-Mur*N*Ac-L-Ala, and indeed **199** proved effective (IC_{50} <1nM).[236] Similarly, earlier work (Vol. 30, pp. 295–6) in which the *N*-acetyl muramyl unit is replaced by a pentamethylene chain has now been extended to the synthesis of the phosphinate **200**, designed to inhibit the enzyme Mur E, which attaches *meso*-diaminopimelate to UDP-Mur*N*Ac-L-Ala-D-Glu.[237]



197 X = PO_3H^-
198 X = H



199

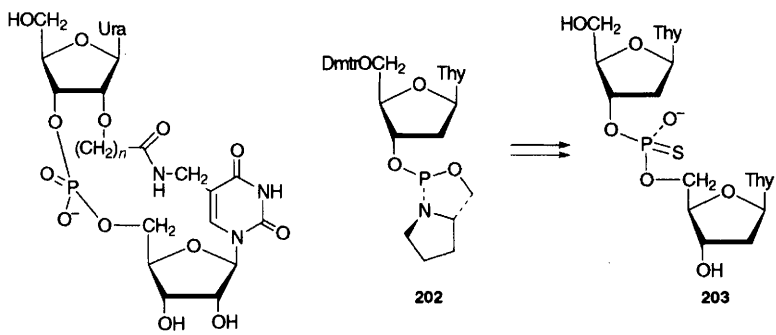


200

12.5 Dinucleotides and their Analogues. – *12.5.1 3′→5′- Linked systems.* The two cyclic diuridine monophosphate derivatives **201** (*n* = 0, 1) have been prepared as models for the U-turn structure of certain tRNAs and hammerhead ribozymes, in which an intramolecular hydrogen bond is thought to exist

between O-3′ of a uridine unit and the side-chain of an adjacent 5-methylaminomethyluridine. In the synthesis, the phosphate link was established at a late stage, after assembly of the amide or urethane linkage.[238]

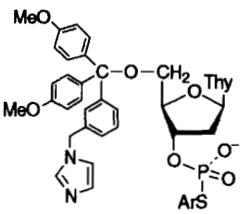
There has been interest in the diastereoselective synthesis of dinucleotide phosphorothioates. A full account has been given of the route to these compounds developed in Just's laboratory, using a chiral auxiliary derived from D-xylose (see Vol. 30, pp. 290–291). However it should be noted that the original stereochemical assignments have been revised, with the auxiliary derived from D-xylose giving dithymidine phosphorothioate of S_P-chirality, whilst the enantiomeric auxiliary was used to make the R_P-phosphorothioate.[239] An account has also been given of a less successful approach to the diastereoselective synthesis of internucleosidic phosphorothioates also investigated in the same laboratory.[240] Meanwhile, other workers have reported the use of prolinol as an auxiliary. The oxazaphospholidine **202**, derived from L-prolinol, on reaction with CPG-linked thymidine, followed by sulfurization, removal of the chiral auxiliary and Dmtr group, and disconnection from the support gave dithymidine phosphorothioate predominantly (9:1) of S_P-chirality (**203**).[241] This method has been extended to the diastereoselective preparation of dinucleotide phosphorothioates of 2′-*O*-methyl-ribonucleosides, which were then incorporated into oligonucleotides.[242] In an alternative approach, *S*-aryl phosphorothioates of type **204**, with a protecting group at O-5′ which is functionalized with an imidazole, gave, on coupling with 3′-*O*-benzoyl thymidine, derivatives of dithymidine phosphorothioate which were predominantly (~85:15) of S_P-chirality.[243]



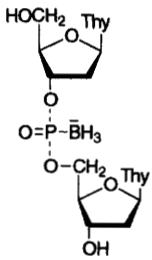
The 2-(diphenylmethylsilyl)ethyl group, which has been employed for the protection of P–O and P–S groups in the synthesis of phosphorothioates, can be removed without the undesired formation of phosphodiesters by the use of tetrabutylammonium fluoride.[244] Earlier work (Vol. 29, p. 287) on the synthesis of phosphorothioate analogues of nucleotides by the phosphotriester approach, using 3′-(*S*-2-cyanoethyl) phosphorothioates as intermediates, has now been extended to the preparation of an octadeoxyribonucleoside heptaphosphorothioate in solution.[245]

The synthesis of the separable diastereoisomers of dithymidine boranophos-

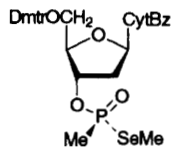
phate has been reported, involving the interaction of a bis-thymidinyl 2-cyanoethyl phosphite with borane-dimethyl sulfide, followed by deprotection.[246] Use of a chiral auxiliary [(*S*)-3-hydroxy-4-(2-indolyl)butyronitrile; see Vol. 31, pp. 288–9 for the use of this in making dinucleoside phosphorothioates diastereoselectively] in place of 2-cyanoethanol gave a stereoselective synthesis of the S_P-diastereomer **205**.[247]



204



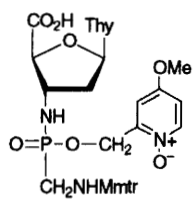
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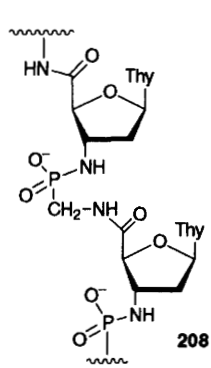
206

The diastereomers of dithymidinyl methylphosphonate have been prepared in a suitable form for building into oligonucleotides by reaction of thymidine derivatives with $MePCl_2$, and separation of the isomers, which were incorporated into DNA hairpin loops.[248] A diastereoselective synthesis of the R_P-isomers of 2′-deoxy-dinucleoside methylphosphonates has been developed, relying on kinetic resolution of 3′-methylphosphonamidites when they react with 2′-deoxy-3′-*O*-Tbdps-nucleosides in the presence of a substituted imidazole.[249] The S_P-phosphonoselenolate **206** has been prepared and a nucleophilic substitution at phosphorus was carried out with 3′-*O*-acetyl-N^4-benzoyl-2′-deoxycytidine to give, with inversion of configuration, the S_P-isomer of di-2′-deoxycytidine-(3′,5′)-methanephosphonate.[250]

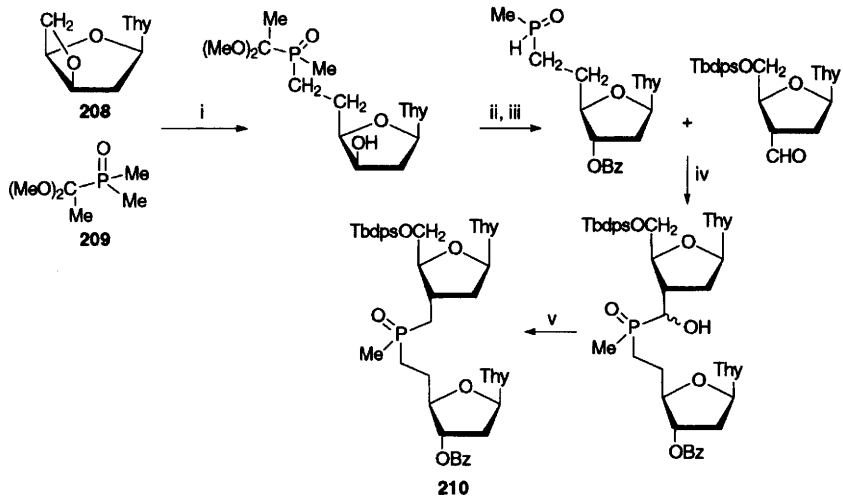
Oligonucleotides of type **208** have been prepared by linking together monomer **207**, forming the amide bonds, using solid-phase methods; the building block **207** was made from AZT by oxidation at C-5′, followed by reduction of the azide and coupling to the protected α-aminophosphonate.[251] Oligonucleotide analogues containing phosphine oxide units have been prepared from the building block **210**, itself made as indicated in Scheme 11 from



207



208



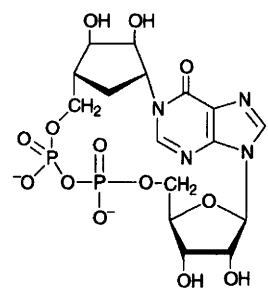
210

Reagents: i, **209**, BuLi, then **208**,then $BF_3.Et_2O$; ii, $PhCO_2H$, DEAD, PPh_3; iii, TmsCl, MeOH; iv, DBU; v, radical deoxygenation

Scheme 11

the oxetan **208** and the functionalized phosphine oxide **209**. The incorporation of **210** gave lower T_m values in hybridization studies.[252]

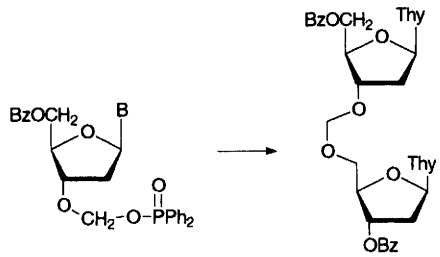
12.5.2 5′→5′- Linked systems. NAD analogues incoporating the *C*-nucleosides furanfurin, thiophenfurin (Vol. 29, p. 283) and selenophenfurin (Vol. 31, pp. 280–281) have been prepared as inhibitors of IMP dehydrogenase.[253] The inosine analogue **211** of cyclic ADP-ribose, with a carbocyclic ring to stabilize the most labile bond in the natural product, has been synthesized. The pyrophosphate link was formed at a late stage, and it was necessary to place a bromine at C-8 of the inosine ring for cyclization to occur, this substitution presumably forcing the conformation about the glycosidic bond into the required *syn*-orientation.[254] Under certain conditions, the cyclization of the brominated precursor led not to the expected product with an 18-membered ring, but gave instead a 36-ring dimer.[255]



211

13 Oligonucleotide Analogues with Phosphorus-free Linkages

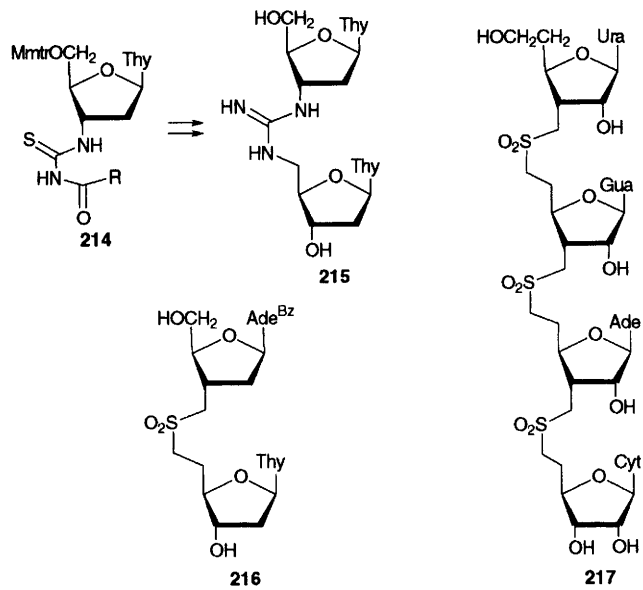
In a new variant on routes to oligodeoxynucleotide analogues with formacetal linkages, phosphinates **212** have been used to prepare dimers of type **213** by reaction with a 3′-*O*-benzoylated 2′-deoxynucleoside in the presence of TmsOTf. These could be incorporated into oligonucleotides using standard



212 **213**

procedures.[256] There has been a fuller and expanded account of the preparation of dinucleotide analogues linked by a sulfamide group (see Vol. 31, pp. 292–3).[257] Acylated thioureas **214** (R = Me, OAllyl, OCH_2CCl_3) could be converted to *N*-acylated carbodiimides which on reaction with 5′-amino-5′-deoxythymidine, followed by deprotection, gave the guanidine-linked system **215** which will carry a positive charge at physiological pH (for other guanidine links with strongly electron-withdrawing substituents on nitrogen, see Vol. 26, pp. 236–7 and Vol. 27, p. 252).[258]

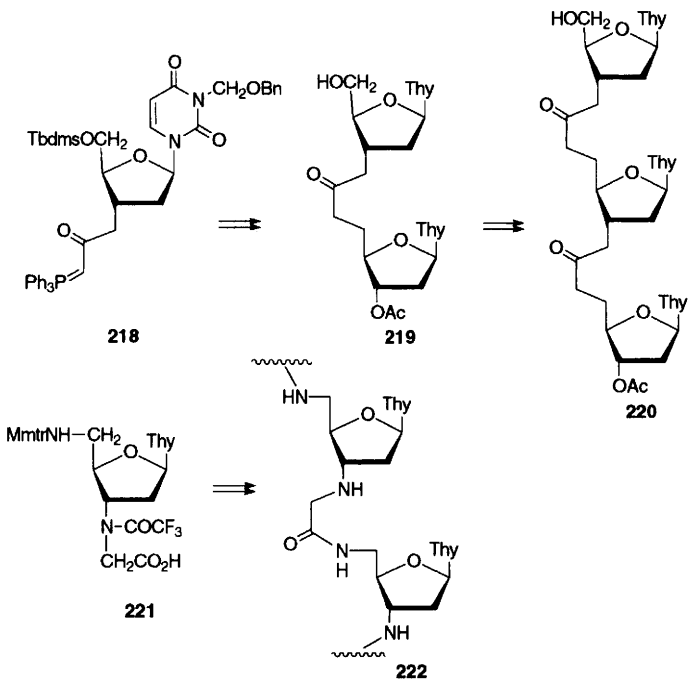
Further work has been reported on sulfone links. The dinucleotide analogue **216** has been prepared and incorporated into an oligonucleotide designed to



214 **215** **216** **217**

mimic the distortion that occurs when DNA is bound to certain restriction enzymes, and the modified oligonucleotides were indeed inhibitors.[259] Also, earlier routes (Vol. 30, p. 298) developed in this area have been used to prepare the non-ionic tetranucleotide **217**. This could be tritiated by exchange α- to the sulfones, and the tritiated compound was found to be distributed rapidly in mice, and to be excreted intact.[260]

In work on all-carbon chains, the phosphorane **218** was prepared from a 3′-allyl-3′-deoxy-thymidine derivative (Vol. 23, p. 218), and used in a Wittig reaction with a thymidine-5′-aldehyde, followed by reduction, to make the 'dimer' **219**; oxidation of **219** at the primary alcohol, and further reaction with **218** then led to the 'trimer' **220**.[261,262]

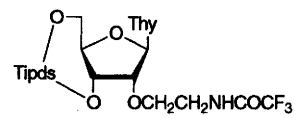


The building block **221** has been prepared and used in solid-phase synthesis to produce oligonucleotide analogues containing the five-atom link as in **222**.[251] A neutral, phosphorus-containing link (phosphine oxide) was mentioned above.[252]

14 Ethers, Esters and Acetals of Nucleosides

14.1 Ethers. – The 2′-*O*-alkylated nucleoside **223** has been prepared, using alkylation with ethyl bromoacetate followed by subsequent transformations. It was incorporated into oligodeoxynucleotides to give, after removal of the trifluoroacetyl groups, positively-charged species which bound to the phos-

phate backbone of double-stranded DNA to give a triplex with an increase in T_m of around 3.5 °C per modified unit.[263] It has been shown that condensation of a trichloroacetimidate derived from 2-*O*-methyl-3,5-*O*-Tipds-D-ribose with silylated pyrimidines gives the α-nucleoside as major product, in contradiction of earlier claims (Vol. 28, p. 294).[264] 1-Deaza-3′-*O*-methyladenosine, which has a *syn*-conformation in both the solid state and in solution, has been prepared as the major isomer obtained by methylation using diazomethane in the presence of $SnCl_2$.[265]



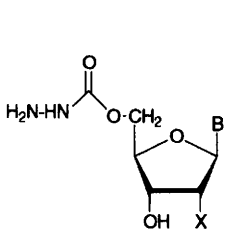
223

The 9-phenylxanthyl (pixyl) group could be removed in high yield from 5′-*O*-pixylthymidine (the only nucleoside or carbohydrate example) by photolysis in aqueous acetonitrile.[266] In the area of silyl ethers, the 1,1,3,3-tetraisopropyl-3-[2-(trityloxy)ethoxy]disiloxan-1-yl (TES) group has been advocated for the protection of O-5′ during solid-phase RNA synthesis; it can be removed by fluoride ion and is thus readily compatible with the use of THP ethers to protect O-2′.[267] The desilylation of 2′,3′-*O*-isopropylidene-5′-*O*-Tbdms-uridine has been carried out under neutral conditions using LiCl in DMF including a little water. Tbdms groups can be removed selectively in the presence of Tbdps ethers, although this selectivity was not applied in carbohydrate or nucleoside examples.[268] Potassium *t*-butoxide in DMF at room temperature has been used to desilylate a number of nucleoside Tbdms and Tbdps ethers.[269]

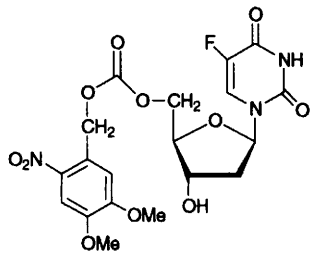
14.2 Esters. – There has been a report on the attachment of deoxynucleosides, unprotected on nitrogen, to solid supports through 3′-*O*-succinyl spacers, for use in oligonucleotide synthesis by an *H*-phosphonate method (Vol. 31, p. 288).[270] Additionally, model studies for the detachment of succinyl-anchored oligodeoxynucleotides under basic conditions have been reported.[271] Reaction of adenosine, AMP, various oligonucleotides and *E. coli* $tRNA^{Val}$ with isatoic anhydride led predominantly to 3′-*O*-anthaniloyl esters, which in the latter cases are models of aminoacyl-tRNA.[272] Selective 3′-*O*-benzoylation of uridine has been reported, using the dibutyltin oxide method.[273] Reaction of nucleoside 5′-vinyl carbonates with hydrazine leads to carbazoyl nucleosides of type **224** (X = H, OH), and similar 3′-carbazoyl derivatives were made in the 2′-deoxy-series, the vinyl carbonates being prepared by enzymic acylation (Vol. 27, p. 266).[274] The carbonate **225** has been developed as a photoactivated prodrug for 5-fluorodeoxyuridine.[275] Standard methods have been used to prepare 5′-*O*-(*O*-benzyl-L-seryl-L-valyl)- and 5′-*O*-(L-valyl-*O*-benzyl-L-seryl)-uridine as potential inhibitors of UDP-glucuronosyl transferase.[276] The 5′-*O*-myristoyl, and some functionalized myristoyl, esters of 2′,3′-dideoxy-3′-fluorothymidine have been made as potential bifunctional prodrugs, which could inhibit myristoyl transferase as well as reverse transcriptase.[277] A tetraaza-

macrocycle has been attached to AZT by spacer arms coupled to O-5′ by ester links.[278]

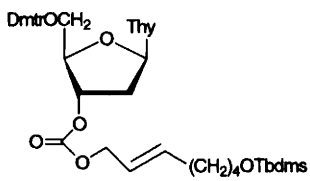
3′-*O*-Allyloxycarbonylthymidine can be deprotected electrochemically, and *O*-allyl groups on internucleotidic phosphates can be similarly removed.[279] Nucleosidyl allyl carbonates such as **226** have been prepared and linked to solid supports, and optimal procedures for their cleavage from the resin using Pd(0) reagents have been developed.[280]



224



225

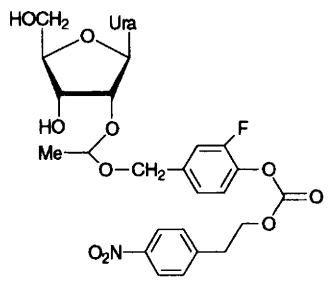


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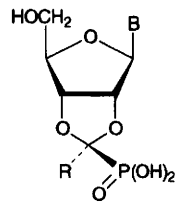
14.3 Acetals and Glycosides. – By reaction of the 3′,5′-*O*-Tipds derivative with the appropriate vinyl ethers, a large series of 2′-acetals of uridine were prepared. The example **227** was adjudged to contain a protecting group very suitable for solid-phase oligonucleotide synthesis, since it is stable under conditions for removal of a dimethoxytrityl group, but under basic conditions used for removal of phosphate and nucleobase protection, it undergoes elimination to give a 3-fluoro-4-hydroxybenzyl group, and the acetal is now very acid-labile.[281]

Various 2′,3′-*O*-alkylidene derivatives of adenosine have been prepared by reaction with aldehydes in the presence of triethyl orthoformate and $ZnCl_2$,[282] and the 2′,3′-*O*-isopropylidene derivative of *S*-adenosylmethionine has been described.[283]

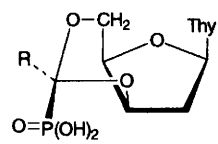
There has been a very extensive account of the preparation of 2′,3′-*O*-phosphonoalkylidene derivatives of type **228** (R = H, Me, Ph) by the reaction of nucleoside 2′,3′-orthoesters with diethyl chlorophosphite, followed by deprotection. The *S*-epimers shown predominated.[284] The related 3′,5′-*O*-phosphonoalkylidene compounds **229** were similarly prepared, again with



227



228

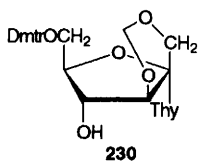


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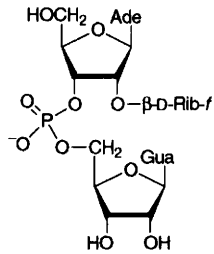
S-chirality dominating, and in several of the reported cases, the group R was a short alkyl chain with a functional group at the terminal position.[285]

The methylene acetal **230** has been prepared; it and the corresponding methylcytosine nucleoside were incorporated into oligonucleotides by *H*-phosphonate methods, but the resultant structures did not form duplexes.[286]

Glycosylation of 3′,5′-*O*-Tipds-ribonucleosides with tri-*O*-benzoyl-β-D-ribofuranosyl acetate in the presence of $SnCl_4$ has given rise to 2′-*O*-(β-D-ribofuranosyl)-nucleosides. In the adenosine case, the ribosylated nucleoside was further converted into the ribosylated dinucleotide **231**.[287] Ribosylation of



230

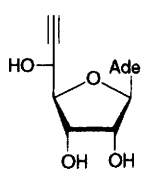


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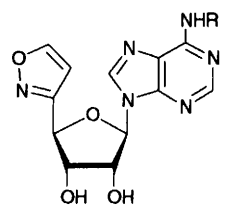
pyrimidine nucleosides at O-5′ has similarly been carried out,[288] but in the purine series trisaccharide nucleosides were also formed, which was ascribed to the nucleoside disaccharide also acting as a glycosyl donor under the conditions of reaction. This problem could be avoided by using isopropylidene protection, instead of acyl groups, for the secondary alcohol functions of the purine nucleoside during reaction with tri-*O*-benzoyl-β-D-ribofuranosyl acetate.[289]

15 Miscellaneous Nucleoside Analogues

The chain-extended alkynyl nucleoside **232**, a selective and potent ligand for the P_3 purinoceptor-like protein, was obtained as the major diastereomer through a Grignard reaction.[290] 2′-*O*-Amino-ribonucleosides of uracil and adenine have been prepared by reaction of *arabino*-triflates with *N*-hydroxyphthalimide, followed by deprotection, Mitsunobu inversions having been ineffective. The products were incorporated into hammerhead ribozymes *via* phosphoramidite methods.[291] The isoxazole nucleosides **233** (R = OMe, 3-iodobenzyl) have been prepared as potential adenosine A_3 receptor ligands by



232



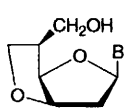
233

a sequence involving cycloaddition of Tms-acetylene to a ribose-derived nitrile oxide, followed by base–sugar linkage. The isoxazole was designed as an isosteric replacement for the amide units in known agonists.[292]

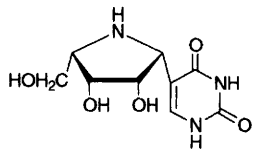
The bicyclic deoxynucleoside analogues **234** (B = Thy, Cyt, Ade) have been prepared from 1,4:3,6-dianhydro-D-glucitol in a sequence in which the key steps were introduction of a hydroxymethyl group at C-5 through olefination-hydroboration, glycal formation, iodo-glycosylation and radical de-iodination.[293]

The L-*lyxo*- 'N-in-ring' *C*-nucleoside **235**, and an imidazole analogue, have been prepared from 2,3-*O*-isopropylidene-D-ribose; in the course of this work it became necessary to revise the structures of similar compounds reported earlier (Vol. 30, p. 230) as being of D-*ribo*- stereochemistry.[294]

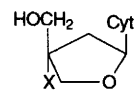
Various racemic 3′-fluoro-apiosyl pyrimidine nucleosides such as **236** (X = F) have been described,[295] as have the azido- and amino-compounds **236** (X = N_3, NH_2), along with the adenosine analogues.[296] The racemic alkene **237**, related to d4T, has also been reported, and found to have anti-cytomegaloviral activity.[297]



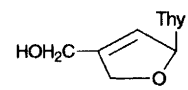
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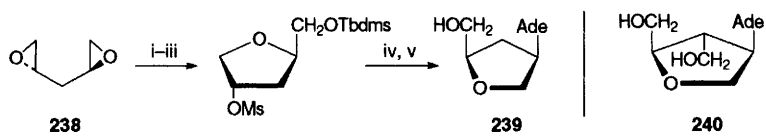


236



237

In the area of iso-dideoxynucleosides, the chemistry outlined in Scheme 12 has been used in a new route to iso-ddA (**239**), and an adaptation of this sequence was used to make the thio-analogue of **239** and its uracil nucleoside. The diepoxide **238** is accessible from D-ribonolactone (*Tetrahedron*, 1989, **45**, 7161) or in other ways.[298] A route has also been developed to the hydroxymethyl-substituted compound **240**, which can be regarded as a methylene-expanded analogue of oxetanocin, its thymine analogue, which showed moderate anti-HIV activity, and the enantiomer of **240**.[299] The exo-methylene

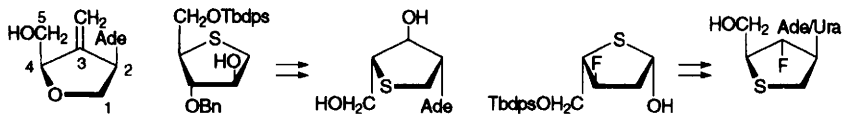


238 **239** **240**

Reagents: i, H_2O, NaOH; ii, TbdmsCl; iii, MsCl; iv, adenine, 18-C-6, K_2CO_3; v, TBAF

Scheme 12

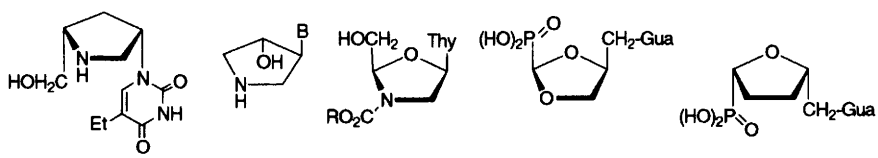
compound **241** has also been prepared, along with the inosine and guanosine analogues, from L-xylose (sugar carbons indicated), the bases being introduced by Mitsunobu inversions.[300] The cyclic sulfide **242**, prepared from D-glucose and used in earlier work on 4′-thionucleosides (Vol. 30, p. 281; Vol. 31, p. 276), has also been used to prepare thio-isonucleosides **243**, where the introduction of the bases used Mitsunobu reactions proceeding with inversion of configura-



241 **242** **243** **244** **245**

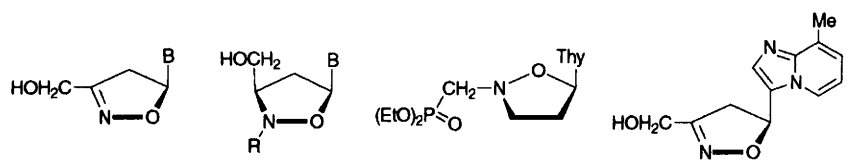
tion, presumed to be due to participation by sulfur.[301] In contrast, the conversion of the fluorinated L-*arabino*- compound **244** into the analogues **245** used two Mitsunobu reactions to install the bases, each proceeding with inversion of configuration.[302] The L-nucleoside analogue **246** has been prepared from 4-hydroxy-L-proline,[303] and the racemic analogues **247** (B = Ade, Thy, Ura) have been reported.[304] A related structure with an N-N base–'sugar' link is mentioned in Chapter 18.

A preliminary account has been given of an asymmetric route to 1,3-oxathiolane nucleoside analogues,[305] and oxazolidine systems **248** have been prepared, but not surprisingly deprotection of the nitrogen was not possible.[306] A new class of nucleoside analogues are the dioxolanyl phosphonic acids **249** and its enantiomer,[307] and the related compounds **250** and its diastereoisomer α- to phosphorus have also been made;[308] some of these species had good anti-HCMV activity.



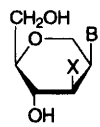
246 **247** **248** **249** **250**

A review has been given of routes to isoxazolinyl and isoxazolidinyl nucleosides of type **251** and **252**, but also discussing cases in which the heterocycle is fused to a conventional nucleoside framework.[309] An enantioselective route to compounds of type **251** (B = Ade, Cyt) uses an oxidative process on isoxazolidine nucleosides (see Vol. 31, pp. 297–8),[310] and **251** (B = Thy) has been made by cycloaddition of a nitrile oxide to 1-vinylthymine; the phosphonate **253** was also reported, made by nitrone cycloaddition.[311] Related *C*-nucleoside analogues such as **254**, and the species with the heterocycle and the CH_2OH group reversed, have also been described.[312] An enantioselective synthesis of **252** (B = Thy, R = Bn) has been reported, relying on a diastereoselective cycloaddition to a nitrone derived from isopropylidene-D-glyceraldehyde.[313]

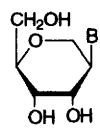


251 **252** **253** **254**

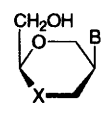
In the area of anhydrohexitol nucleosides, there have been reports of such systems (**255**, X = H) in which the base is one of a number of 5-substituted uracils, the 5-trifluoromethyl compound having anti-HSV activity; the conformational analysis of the thymine analogue is discussed in the next chapter.[314] 1,5-Anhydro-D-mannitol nucleosides (**255**, X = OH) with purine bases (Ade, Gua) have been reported, the base being introduced by displacement of a triflate (see Vol. 30, pp. 310–2 for earlier work on related pyrimidines);[315,316] the nucleoside analogues were incorporated into oligonucleotides, which were found to form less stable duplexes than were formed with the 3′-deoxy-systems.[316] There has been a brief report on the synthesis of the D-*altro*-analogues **256** (B = Ade, Gua, Ura, Cyt), where the base units were introduced by opening of an epoxide. An oligonucleotide composed of the uridine analogue formed a duplex which was more stable than one involving the equivalent 3′-deoxy-species (**255**, B = Ura, X = H).[317] The branched-chain systems **255** (X = CH_2OH, B = Ade, Thy) have also been reported; the base units were introduced into a branched-chain sugar (Chapter 14) by Mitsunobu inversion.[318,319] Levoglucosenone has been used as starting material to prepare the 'dideoxy'-analogues **257** (X = CH_2, B = Ade, Gua), which can be thought of as methylene-expanded 2′,3′-dideoxynucleosides,[320] and the dioxane analogues **257** (X = O, B = Ura, Thy, 5-F-Ura) have been described (see also Vol. 31, p. 298).[321]



255

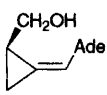


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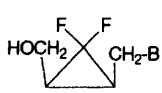


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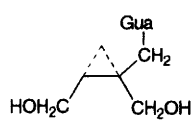
The cyclopropane **258** has been made as a racemate, as have the guanine analogue and the *E*-stereoisomers of these, with the *Z*-isomers showing good antiviral activity.[322] The *R*-enantiomer (**258**), termed 'synadenol', and the *S*-isomer have subsequently been separately prepared; both have antiviral effects, but these differed between viruses.[323] Racemic difluorinated cyclopropanes **259** (B = Cyt, Ura, Hx) have been prepared,[324] as have analogues such as **260**, where compounds in both enantiomeric series were made, the example illustrated (**260**) having the strongest anti-HSV activity, and being phosphorylated by HSV-1 thymidine kinase.[325] The cyclobutanes **261** (X = CH, N) have been reported, the heterocycles being elaborated from a chiral amine.[326]



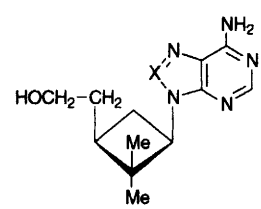
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16 Reactions

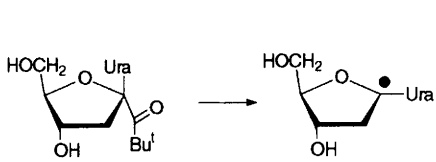
A review has been given of metal-assisted stacking interactions and their involvement in the facilitated hydrolysis of nucleoside 5′-triphosphates.[327] An issue of *Chemical Reviews* (1998, no. 3) is devoted to cleavage of RNA and DNA, including photocleavage by natural and synthetic reagents, and oxidative cleavage, in addition to enzymic methods. In particular, we note a discussion of the kinetics and mechanisms for cleavage and isomerization of the phosphodiester bonds of RNA by Brønsted acids and bases, discussing much kinetic work with simplified models of lower molar mass.[328]

In the presence of a ligand having two metal-binding sites, combinations of Fe(III) and either Zn(II) or Cd(II) catalyse the hydrolysis of ApA, and a mechanism was proposed involving synergistic co-operation between the two types of metal ion.[329] Methylation of UpA at C-3′ of the uridine unit increases the rate of hydroxide ion-catalysed hydrolysis by more than an order of magnitude, and the situation with 2′,5′-UpA is more complex, with the reaction order >1 with respect to hydroxide ion concentration. It was suggested that this possibly reflected the need for a dianion, with the monoanion having an intramolecular hydrogen bond.[330]

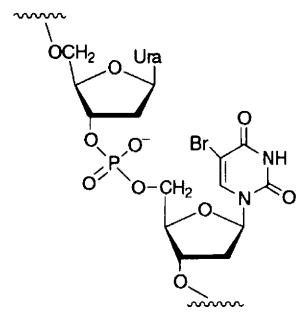
Various dialkyl esters of 5′-*O*-pivaloyl-uridin-3′-yl phosphate have been prepared, and the isomerization of the phosphotriester to its 2′-counterpart and the cleavage of the isomeric mixture to 2′- and 3′-phosphodiesters and the 2′,3′-cyclic phosphate was monitored by HPLC. The mechanisms of various partial reactions were discussed.[331] A study has also been made of the concurrent isomerization of various monoalkyl esters of uridine-3′-phosphate to the 2′-isomers and the formation of the 2′,3′-cyclic phosphate over a range of pH. The mechanisms of various partial reactions were evaluated by comparison with those of the corresponding phosphotriesters.[332]

The hydrolysis of thymidylyl(3′→5′)thymidine is accelerated in weakly acidic solution in the presence of Zr(IV) salts and complexes, including the complex with tris; the efficiency is similar to that of Ce(IV) compounds, but the zirconium species have the advantage of not being redox active.[333]

The C-1′ radical **263**, obtained by photolysis of the corresponding C-1′-pivaloyl compound **262** (Vol. 30, p. 304), has been studied by ESR and laser flash photolysis, and computationally.[334] An alternative route to **262** has also

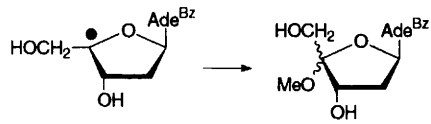


262 **263**



264

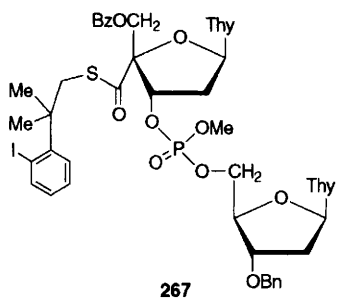
been described, involving addition of *t*-butyllithium to a nitrile, and the mechanism for the formation of 2-deoxyribonolactone by photolysis of **262** under aerobic conditions has been investigated by oxygen-labelling experiments, which provided evidence for two competing pathways.[335] Photolysis of deoxyoligonucleotides containing 5-bromouridine (part structure **264**) in the presence of oxygen also give rise to products which can be rationalized by formation of a C-5 radical which reacts with oxygen to give a peroxy radical, followed by abstraction of H-1′ of the adjacent uridine unit to give a C-1′ radical.[336] When the C-4′ radical **265** was generated in deoxygenated methanol (by photolysis of the phenyl selenide) in the presence of $Mn(OAc)_3$, the acetal **266** was formed. In the presence of oxygen, a peroxy radical was formed, for



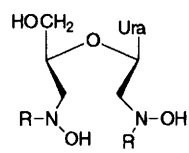
265 **266**

which ESR data was obtained. These results support the theory of Stubbe for the mechanism of DNA cleavage by bleomycin, in which it is proposed that oxidation of a C-4′ radical to a carbocation occurs in the presence of a metal salt, but oxygen does not do this.[337] Stannane reduction of **267** also generates a C-4′ radical, which expels the phosphate to give a radical cation, various decomposition products of which could be isolated.[338] A report has described studies of the mechanisms of degradation of 2′-deoxyguanosine on exposure in the solid state to heavy ions, where both sugar and purine radicals are involved.[339]

Seconucleosides have been prepared from some 1-(β-D-ribofuranosyl)-3-substituted-pyrazine-2-ones by treatment with periodate and borohydride,[340] and bis(hydroxylamines) of type **268** have been made by periodate cleavage of uridine, nitrone formation and reduction. The products oxidized in air to afford the corresponding aminoxy radicals, which were studied by ESR.[341]



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21
NMR Spectroscopy and Conformational Features

1 General Aspects

A review of a workshop on carbohydrate molecular modelling has appeared; eleven research groups have made a comparison and chemometric analysis of twenty molecular mechanics force fields and parameter sets applied to seven carbohydrate test cases.[1] The use of computational methods for the conformational analysis of carbohydrates has also been reviewed.[2] New approaches for calculating conformational equilibria by multiple-copy locally enhanced sampling (LES) have been reported; this technique has been applied to $\alpha \rightarrow \beta$ anomerization of glucose.[3]

Pulse sequences have been proposed for the measurement of long range heteronuclear $^{n}J_{CH}$ coupling constants; this approach has been applied to sucrose, for which accurate and efficient measurement of coupling constants has been obtained.[4] Three bond C–O–C–C coupling constants have been used to correlate molecular structure and conformation in a variety of ^{13}C-labelled mono- and di-saccharides.[5] Specifically ^{13}C-labelled pentoses have been used to accurately quantitate the ratio of cyclic and acyclic forms in aqueous solution.[6] Triply labelled monosaccharides have been examined by ^{13}C–^{13}C COSY-45, which provides information about the sign and magnitude of ^{13}C–^{13}C spin coupling. These experiments provided excellent support for the 'projection resultant rule', which predicts the magnitude and sign of $^{2}J_{C1-C2}$ values in such molecules.[7]

Generalized Karplus-like equations for vicinal $^{3}J_{HF}$ couplings have been proposed in connection with studies on monodeoxymonofluoronucleosides and the corresponding 2,2′-difluoro compounds.[8] The effect of ^{2}H and ^{13}C longitudinal (T_1) and transverse (T_2) relaxation parameters has been determined for the first time for stereospecifically deuterated nucleosides.[9] It has been reported that NMR spectroscopy can be used to determine the absolute configuration of tertiary alcohols substituted with methyl or methylene groups following derivatization as their fucofuranoside adducts.[10]

2 Acyclic Systems

The conformation of various 5-amido-pyrimidines, derived from aldonolactones and 4,5,6-triaminopyrimidine, have been investigated by ^{1}H NMR

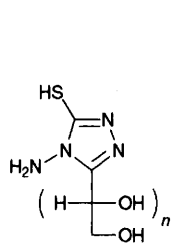
Carbohydrate Chemistry, Volume 32
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spectroscopy.[11] The synthesis and conformational analysis of *seco*-*C*-nucleosides **1** and their di-*seco*-analogues, *e.g.* **2**, derived from aldonolactones and diethyl galactarate, respectively, have been investigated.[12]

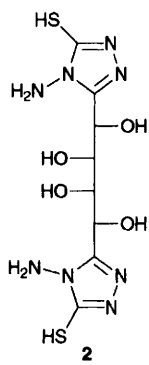
3 Furanose Systems

The synthesis, separation and NMR spectral analysis of methyl apiofuranoside **3** have been reported.[13] Malonate **4** and phosphonate **5**, **6** derivatives of 2-deoxyribose and 2-deoxy-2-fluoroarabinose have been synthesized and their conformations have been determined by NMR spectroscopy.[14] High resolution ^1H and ^{13}C NMR spectral data for β-D-glucofuranosidurono-6,3-lactone have been recorded.[15]

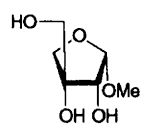
Computational studies coupled with X-ray data have been used to study the conformational behaviour of methyl 5-deoxy-α-D-ribofuranoside and its β-anomer.[16] The use of crystal structure data to analyse the furanose ring conformation in nucleosides and nucleotides has been reviewed.[17] Selectively deuterated nucleosides **7** and **8** have been synthesized and incorporated into oligo-DNA to help simplify overcrowded regions of the ^1H NMR spectrum and to enhance resolution and sensitivity.[18,19]



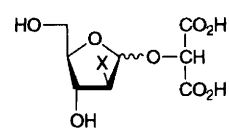
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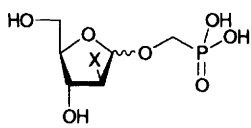
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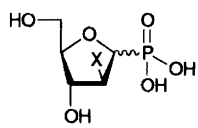
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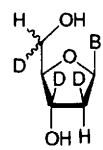
4 X = H/F



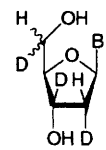
5 X = H/F



6 X = H/F



7

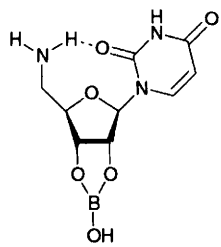


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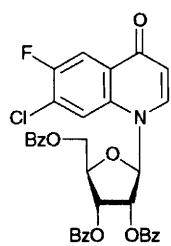
Calculations using the MM2 force field have been used to determine the conformational energies of 2′,3′-dideoxy-2′,3′-didehydrothymidine and the corresponding adenosine derivative.[20] NMR studies have been used to evaluate the relative significance of the anomeric effect and a 3′-OH gauche effect on the conformation of various natural and non-natural nucleosides; the results of these studies are rationalized in relation to the choice of β-D-2-deoxy-nucleosides for exploitation in the genetic code analysis.[21] 2′,3′-*O*-Borate ester

formation has been shown to force generation of the *syn*-conformation of 5′-amino-5′-deoxyuridine borate ester **9**; the effect is greater than on uridine itself, and it is also observed on formation of the corresponding 2′,3′-*O*-isopropylidene derivative.[22] Conformational changes induced by hard and soft metal binding to 2′-deoxyguanosine have been investigated.[23] Steric and stereoelectronic effects of 7- and 8-substituents of 7-deaza-2′-deoxy-adenosine and guanosine have been shown to influence dynamic puckering and rotation about the C4′–C5′ bond.[24] Comparative studies have been made using the DG-OMEGA, DG11 and GAT methods for the structural elucidation of a methylene acetal-linked thymine dinucleotide.[25]

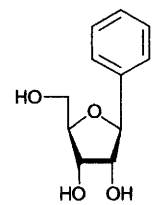
NMR studies have been used to investigate the conformation of 6,7-dihaloquinolone nucleoside derivatives, such as **10**.[26] A wide variety of heterocycles related to **11** have been studied using the PSEUROT program; the electronic nature of the aglycon was shown to dictate the pseudorotational equilibrium of the pentofuranose ring.[27] The structures of β-D-aristeromycin **12** and its 2′,3′-dideoxy derivative have been investigated in aqueous solution by NMR spectroscopy.[28]



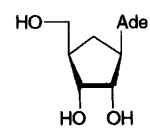
9



10



11

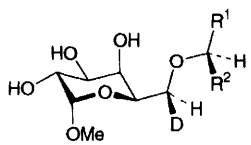


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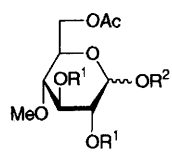
4 Pyranose and Related Systems

The dominating contribution of the *exo*-anomeric effect in determining the conformation of alkyl α- and β-galactopyranosides has been noted.[29] *Ab initio* calculations on 2-hydroxytetrahydropyran have been used to investigate the stereoelectronic factors influencing the conformation of the hemiacetal group in aldopyranoses; good agreement with experimental data was reported.[30] Factors controlling the relative stability of anomers and hydroxmethyl conformers of glucopyranose have been studied by quantum mechanical methods.[31] Conformational analysis of 6-*O*-[(*R*)- and (*S*)-1-carboxyethyl]-α-D-galactopyranosides **13** show them to be highly flexible molecules.[32] Experimental and theoretical studies have been conducted to determine the importance of stereoelectronic and hydrogen bonding factors on the reactivity of methyl α- and β-D-glucopyranosides towards ozonolysis.[33] Theoretical studies of alternative ring forms of α-L-fucopyranose have been reported.[34] The structure of ethyl β-L-arabinopyranoside, isolated from the roots of *Hibiscus rosa-sinensis*, has been extensively studied by NMR spectroscopy with the aid of molecular mechanics calculations.[35]

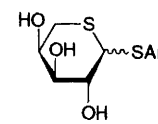
^{1}H NMR and CD data, together with empirical calculations, have been used to examine the effect of various aglycons on the chair conformation of protected glucosides **14**.[36] NMR studies have been used to investigate the formation, stability and cleavage of hydrazones, thiosemicarbazones and azines derived from glucose and *N*-acetylglucosamine, with a view to using such derivatives in the immobilization of saccharides.[37] α-Methoxy-α-trifluoromethylphenyl acetate (MTPA) esters of a series of mono-unprotected sugar derivatives have been used to show that such derivatives can be used for assignment of the absolute configuration of the sugar.[38] The mechanism of TMS-OTf-promoted anomerization of permethylated methyl D-glucopyranosides has been examined by NMR spectrosocpy and GLC; it appears that cyclic oxonium ions are the key intermediates for anomerization of α-glucosides, whereas acyclic oxonium ions are central to anomerization of the corresonding β-anomers.[39] The synthesis and conformational properties of potential antithrombotic 4-cyanophenyl and 4-nitrophenyl 1,5-dithio-L-arabinopyranosides **15**, and their enantiomers, have been reported.[40] The conformation of anhydrohexitol-derived nucleoside analogue **16**, and related compounds, have been analysed in an attempt to rationalize their activity against HSV-1 thymidine kinase.[41] The effect of intramolecular hydrogen bonding in 1,6-anhydrohexoses on the co-operative assembly of various derivatives has been studied by NMR spectroscopy.[42]



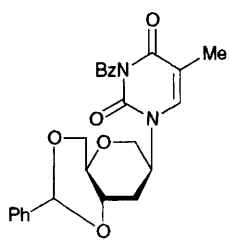
13 R^1 = COOH, Me
R^2 = Me, COOH



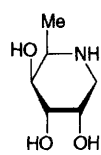
14 R^1 = 4-bromobenzoyl
R^2 = methyl, isopropyl, cyclohexyl, bornyl, menthyl



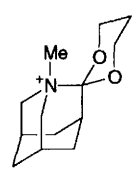
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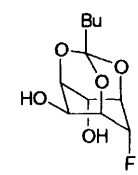
16



17



18



19

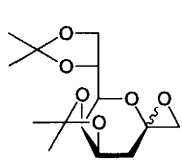
The conformation and distortion of flexible pyranoid rings in 1-(2-hydroxyiminopyranosyl)pyrazole carbohydrates has been analysed with the aid of X-ray crystallography.[43] NMR-derived conformations for four configurational isomers of 5-amino-5-deoxy-D-pentonolactam have been reported.[44] Molecular modelling studies provide a rationale for the surprisingly potent biological activity of 1-deoxy-D-gulonojirimycin **17**.[45]

Conformational preferences and the geometry at the anomeric centre of 1,3-dioxane **18** are consistent with a small, normal anomeric effect; no conclusive

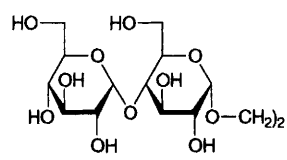
evidence for a reverse anomeric effect was found in this test system.[46] IR and NMR spectroscopy have been used to study intramolecular weak F···HO bonding in orthoester **19**.[47] As a contribution to understanding the various factors that determine the conformation of glycosyl radicals, 3-acyloxytetrahydropyran-2-yl radicals have been studied by EPR spectroscopy.[48] In such systems, anomeric and *quasi*-homo-anomeric effects, respectively, cause highly diastereoselective addition of hydrogen radical to give 1,2-*trans*-products.[49]

5 Disaccharides

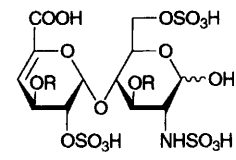
The stereochemical outcome of glycosylation reactions involving epoxide **20** (see Vol. 26, Chapter 3, ref. 148) plus sugar alcohols has been rationalized on the basis of semi-empirical quantum mechanics calculations of the transition states concerned.[50] Dimaltosides of varying anomeric configuration, such as **21**, have been synthesized from alkane diols and have been investigated by ^{1}H NMR methods for their ability to bind cinnamyl alcohol.[51] The conformation of sixteen differently protected benzyl Δ^4-uronate monosaccharides (synthesized by conventional chemical methods) and of seven Δ^4-uronate disaccharides **22** (obtained by treatment of heparin with heparin lyase) have been determined by ^{1}H NMR spectroscopy.[52] An MM3 force field parametrized for sulfate ester groups has been used on eight sulfated derivatives of the repeating units (**23**) of carragenans.[53]



20



21



22 R = H, Ac, Piv and others

–(α-D-Gal*p*-(1→3)-β-D-Gal*p*)–
23

α-L-Fuc*p*-(1→2)-β-D-Gal*p*-OMe
24

β-D-GlcNAc*p*-(1→4)-D-GlcNAc*p*
25

α-D-Man*p*-(1→2)-β-D-Glc*p*-OMe
26

The effects of conformational averaging, anisotropic tumbling and internal motion have been taken into account in calculating the rates of build-up of n.O.e. signals for disaccharide **24**.[54] The conformation of *N,N'*-diacetyl chitobiose (**25**) has been analysed by the application of simulated annealing.[55] The conformational flexibility and dynamics of disaccharide **26** have been analysed by Metropolis Monte Carlo and Langevin dynamics simulation.[56] Classical dynamics calculations have been carried out on a 2-degrees of freedom model Hamiltonian representing the symmetric glycosidic linkage of β,β-trehalose.[57]

Conformational analysis of disaccharide **27** has been carried out using a combination of NMR spectroscopy and molecular dynamics simulations.[58] Similar analysis of *O*- and *S*-linked disaccharides **28** and **29**, respectively, show that the *O*-disaccharide adopts one low energy conformation, whereas the *S*-analogue has two conformational families.[59]

β-D-GlcA*p*-(1→4)-L-Rha
27

α-L-Fuc*p*-X-(1→3)-D-GlcNAc
28 X = O
29 X = S

α-KDO-(2→8)-α-KDO-2-*O*-allyl
30

A refined 3-D structure, obtained using NMR spectroscopy, of the complex between the lectin hevein and methyl β-chitobioside has been published,[60] as has the structure of the complex between KDO-based disaccharide **30** and monoclonal antibody S25-2.[61]

6 Oligosaccharides

A sensitive and non-destructive ^{1}H NMR method has been developed for determining the glycosyl linkage position in oligosaccharides.[62] The ^{1}D^{1}H HADAMARD TOCSY pulse sequence has been applied to oligosaccharides.[63] The use of COSY cross peaks that represent pairs of protons that are spatially proximate but are not normally scalar couples has been used as a new diagnostic tool in the analysis of trisaccharide **31**.[64] All of the OH resonances of methyl 3,4-di-*O*-substituted α-D-galactopyranosides **32** have been assigned and used in conformational analysis.[65] 3-D ROESY-HSQC experiments on trisaccharide **33** provide through-space distance restraints which cannot be observed with conventional homonuclear ^{1}H techniques due to resonance overlap.[66] Multiple field ^{13}C NMR relaxation measurements have been performed on trisaccharide **34**.[67]

α-D-Man*p*
1
↓
6
α-D-Man*p*-(1→3)-α-D-Man*p*-OMe
31

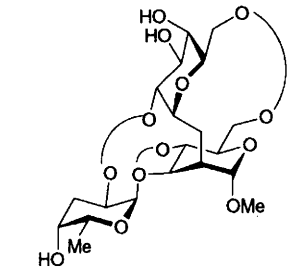
α-D-Glc*p*/α-L-Fuc*p*
1
↓
4
α-D-Glc*p*/α-L-Fuc*p*-(1→3)-α-D-Gal*p*-OMe
32

α-NeuAc-(2→3)-β-D-Gal-(1→4)-D-Glc
33

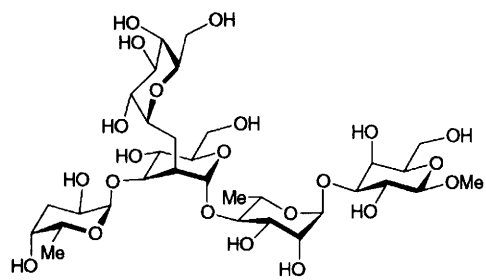
β-D-Glc*p*-(1→2)-[β-D-Glc*p*-(1→3)]-α-D-Glc*p*-OMe
34

The interactions of various trisaccharides related to **35** which contain an intramolecular tether,[68] and of pentasaccharide **36**[69] with specific monoclonal antibodies have been studied by NMR spectroscopy and titration microcalorimetry. Molecular dynamics simulations indicate that distortion of the cleaved pyranoid ring to a boat conformation at subsite-1 is critical in the mechanism of family 18 chitinases.[70] NMR and molecular dynamics simulations have been

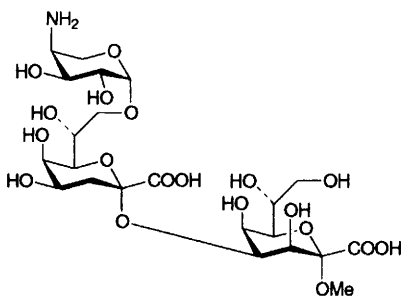
used to analyse two hyaluronan (HA) tetrasaccharides; the rapid exchange of intramolecular hydrogen bonds was noted, which might explain why NMR often fails to provide evidence for them in HA and other aqueous carbohydrate structures.[71] Molecular modelling studies have been used to investigate the interaction of interleukin 2 (IL-2) with sulfated polysaccharides, such as heparin; two putative binding sites on IL-2 were identified.[72] CP-MAS ^{13}C NMR spectroscopy provides evidence for the spatial location of para-crystalline regions in cellulose I.[73] Molecular modelling and molecular dynamics simulations have been used to delineate the epitope recognized by an antibody on *N*-glycolylneuraminic acid-containing gangliosides.[74]



35



36



37

α-D-Galp-(1→3)-α-D-GlcNAcp-(1→3)]-α-L-Rhap-OMe

38

A fragment, **37**, of the core oligosaccharide from *Burkholderia cepacia* lipopolysaccharide has been isolated and characterized by NMR spectroscopy.[75] With the aid of selectively 1-^{13}C-labelled sugars it has been possible to show that the conformation of the Gal-GlcNAc linkage in trisaccharide **38** is different to those in higher oligosaccharides.[76]

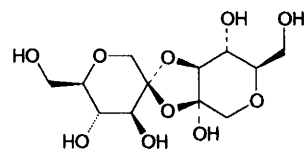
NMR and/or molecular modelling analysis of several oligosaccharides has been reported, including: the exopolysaccharide from *Altromonas macleodii* (originating from a deep sea thermal vent);[77] the O-specific polysaccharide from *Pseudoalteromonas elyakovii*;[78] the lipopolysaccharide from *Klebsiella oxytoca* rough mutant R29;[79] a new O-specific polysaccharide from *Proteus penneri*;[80] the pentasaccharide repeat unit of *Lactobacillus rhamnosus* extracellular polysaccharide;[81] a partial structure of the extracellular β-glucan from *Phytophera parasitica*;[82] various oligosaccharides from the brown alga *Ulva*

rigida, which might be useful for taxonomic purposes;[83] the lipopolysaccharide O-antigen from *Helicobacter pylori* strain UA861;[84] mono- and di-saccharide and oligomeric fragments of rhamnogalacturonan II from the primary cell wall of higher plants;[85] in waxy-type maize starches the effect of moisture content on helix formation;[86] α-dextrins which differ in the location of the branch point.[87]

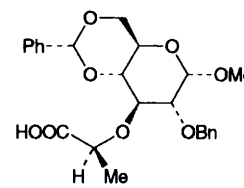
Annealed molecular dynamics calculations have been used to analyse the conformation of heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and its complexes with various dihydrofuranones.[88] Similar studies, backed up by NMR spectroscopy, have been performed on mono-(3-amino-3-deoxy)-α-cyclodextrin in aqueous solution.[89] A variety of spectroscopic techniques have been used in studies on 3-*O*-(2-methylnaphthyl)-β-cyclodextrin, which show it is a dimer at 10^{-4} M.[90] High resolution NMR studies and molecular mechanics calculations have been performed on cyclic oligosaccharide **39**.[91] Monte Carlo simulations have been used to analyse the structure and and assess the potential for inclusion complexing of cyclofructans – β-1,2-linked fructofuranose systems with 6–10 sugar units.[92]

{-(1→6)-[α-D-Glcf-(1→4)]-β-D-Glcf}$_3$

39



40



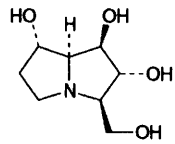
41

7 Other Compounds

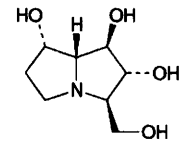
1,5-Anhydro-D-fructose has been shown by ^{1}H and ^{13}C NMR spectroscopy in non-aqueous solvents to exist in the dimeric form **40**.[93] The presence of 4-*O*-(1-carboxyethyl)mannose in the capsular polysaccharide of *Rhodococcus equi* serotype 3 has been confirmed by synthesis and NMR analysis of the authentic material.[94] Related mannosides and glucosides, such as **41**, have been synthesized and analysed in order to develop NMR methods for determining the absolute configuration of the 1-carboxyethyl group in natural products.[95]

The NMR spectra of naturally occurring alexine (**42**) have been analyzed and the consequences of configurational changes on the conformation of the molecule have been considered. Full ^{1}H NMR assignments are given, correcting some errors in the original published data for australine (**43**).[96] The conformation of carbopeptoid **44** has been examined by ^{1}H NMR spectroscopy and confirms a β-turn type of secondary structure.[97]

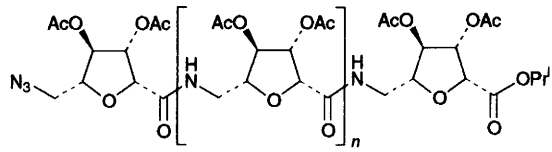
Highly resolved ^{1}H NMR spectra of the moenomycin antibiotics, at sub-critical micelle concentration, have been obtained in D_2O.[98] The conformation of lividomycin bound to an aminoglycoside antibiotic 3′-phosphotransferase



42



43



44 $n = 0, 2, 4$

has been reported.[99] The properties of aminoglycoside antibiotic neomycin B have been investigated by NMR spectroscopy.[100] ^{1}H and ^{13}C NMR assignments of 8-*O*-acetyl-shanzhiside methyl ester have been made using 2-D experiments.[101] Complete ^{1}H and ^{13}C assignments of the *Digitalis lanata* cardenolides, glucodigifucoside and glucogitoroside have been made.[102] Structural characterization of 4″-O-methyl erythromycin has been carried out by heteronculear 2-D NMR experiments.[103] ^{13}C CP-MAS has been used to characterize three glycosyl α-tocopherol derivatives.[104] Molecular modelling of clindamycins suggests a similarity to L-Pro-Met and the D-ribosyl ring of adenosine.[105]

8 NMR of Nuclei Other than ^{1}H and ^{13}C

The application of ΔJ values ($^{3}J_{CP}$) for the configurational assignment of diastereomeric phosphate-modified dideoxynucleotides has been reported.[106] In additon to ^{1}H and ^{13}C measurements, the use of ^{33}S NMR in the characterization of adducts formed by reaction of sodium bisulfite and malvidine 3-*O*-glucoside has been reported.[107] The microscopic acid–base properties of analogues of D-*myo*-inositol 1,2,6-triphosphate have been analysed by ^{31}P NMR titration experiments.[108]

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22
Other Physical Methods

1 IR Spectroscopy

A study of intramolecular F···HO bonds in orthoesters by IR and NMR spectroscopy has been reported.[1] The structural properties of trehalose–water complexes have been studied by IR spectroscopy; the structure of bound water changes from that of ice-like water to liquid-like water at 70 °C.[2] The vibrational spectra of 9-β-D-arabinofuranosyladenine and a hexadeuterated derivative have been recorded; theoretical stretching frequencies have been calculated.[3] Calculation and analysis of vibrational stretching frequencies of nitrate esters of methyl β-D-glucopyranoside have been published.[4,5] The relationships of configurations of different pyranoid carbohydrates to their FT-IR and Raman spectra have been examined.[6] Polarized Raman spectra and Raman scattering measurements have been reported for a single crystal of uridylyl(3′-5′)adenosine[7] and α-pseudouridine,[8] respectively. A fibre-optic Raman probe has been used to obtain on-line spectra of ribonucleotides separated by capillary isotachophoresis.[9]

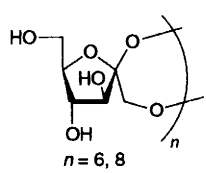
2 Mass Spectrometry

Reviews have appeared on the use of HPLC-MS and capillary electrophoresis-MS for the analysis of nucleosides, nucleotides and modified nucleotides.[10,11] Seventeen oligosaccharides derived from *N*-linked glycoproteins have been characterized by high energy collision induced dissociation (CID) with a double-focusing mass spectrometer fitted with a tandem orthogonal time-of-flight (TOF) analyser.[12] Collisionally activated dissociation (CAD) results in cleavage of internal monosaccharides from anthracycline aminodisaccharides.[13] Several oligosaccharides and *N*-linked glycan samples have been used to evaluate structural detail obtained by ion trap mass spectrometry (ITMS).[14] Difficulties have been reported in glycosidic linkage position determination, detection of the reducing end and sequence of the sugars in disaccharides using liquid secondary ion mass spectrometry (LSIMS) coupled with mass-analysed ion kinetic energy/collision activated dissociation (MIKE/CAD).[15] The use of various MS/MS techniques to investigate dissociation mechanisms of Ni(II) *N*-glycoside complexes has been reported.[16] MS analysis of the thermolysis of

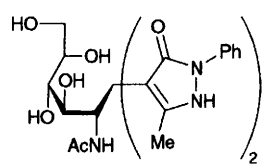
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several sugar derivatives indicates that the furanoid rings decompose at lower temperatures than do pyranoid rings.[17] MS techniques have been used to characterize derivatives of the antibiotics amipurimycin,[18] kanamycin[19] and gentamicin.[19] EI-MS fragmentation patterns of anhydro-sugars have been reported,[20] as have CI-MS data for sulfonic acid esters of sugars.[21] Reverse phase HPLC-MS-MS has been used to analyse glucuronides of a set of catechol-like drugs in urine.[22] In relation to work on xenotransplantation, rapid and sensitive GC-MS techniques have been developed for the characterization of α-Gal-(1→3)-Gal-containing saccharides from glycolipids of pig organs.[23]

Fast atom bombardment (FAB) spectra of carbohydrates contaminated with inorganic salts can be significantly improved by the inclusion of crown ether (*e.g.* 18-crown-6)[24] or of ammonium chloride, which gives rise to $[M + NH_4]^+$ adducts.[25,26] Linkage isomers of branched oligosaccharides (*e.g.* Le^a and Le^x)[27] and isomeric sulfated fucose-containing trisaccharides can be differentiated by FAB CID-MS/MS.[28] The determination of linkage position in oligosaccharides may be achieved by FAB CAD-MS/MS; acetylation of samples to be analysed gives more useful product ion patterns[29] and the fragmentation of anomeric linkages is assisted by the neighbouring carbonyl group.[30] The structural heterogeneity of sialic acid-containing oligosaccharides from *Hafnia alvei* lipopolysaccharide has been analysed by FAB MS.[31] The ability of permethylated cyclofructans **1** to discriminate enantiomers of amino acid ester hydrochloride salts has been assessed by FAB MS, and the mode of binding has been rationalized by analysis of the crystal structure of the cyclic hexamer with Ba^{2+}.[32] The characterization of mono- to medium-sized oligosaccharides by both PMP (1-phenyl-3-methyl-5-pyrazolone) and PA (pyridylamination) derivatization, followed by RP-HPLC separation and MS has been investigated. PMP derivatization, giving *e.g.* **2**, was preferred for simplicity of reaction conditions, good HPLC separation and better ionization. Electrospray (ESI) or matrix-assisted laser desorption (MALDI) ionization MS were more sensitive than FAB MS.[33]



1



2

The RP-HPLC MS-MS analysis of various saccharides using a multipurpose atmospheric pressure spray ionisation (APSI) interface was shown to be an order of magnitude more sensitive than electrospray or sonic spray ionisation techniques.[34] Diastereomeric diethylenetriamine *N*-glycoside zinc(II) complexes (formed variously with the sugar C2 and C4 groups) can be differentiated by ESI MS in a quadrupole ion trap.[35] ESI ion trap MS has been demonstrated to be an effective method for the structural characterization of

permethylated *N*-linked complex glycoprotein oligosaccharides.[36] The application of microbore-HPLC with ESI-ion-mobility spectrometry detection has been shown to give fmol–pmol level detection of glucose and glucitol in a demonstration separation.[37] Ion-spray MS with an atmospheric pressure ion source, coupled with CAD MS/MS, has been used for identification of the non-reducing terminal sugar of glycosaminoglycans.[38] ESI CID-MS/MS has been used to analyse a range of anti-retroviral nucleoside drugs, such as AZT, ddC, ddI and 3TC.[39] ESI and MALDI FT ion cyclotron resonance (FT-ICR) MS of permethylated oligosaccharides provides extensive structural characterization.[40]

MALDI MS has been used as a tool for characterizing β-cyclodextrin and five modified cyclodextrins (heterogeneous, methylated, 2-hydroxypropylated or carboxymethylated);[41] the stereochemistry of individual glycosidic linkages influences their ease of cleavage.[42] MALDI, in conjunction with ionization Fourier transform mass spectrometry (FTMS) has been used for sequencing alkaline degradation products derived from oligosaccharides.[43] MALDI of saccharides in three common matrices were investigated; the most suitable matrix proved to be 2,5-dihydroxybenzoic acid (DHB).[44] The formation of $[M + Na]^+$ and $[M + K]^+$ adducts proved to be dominant features of the spectra obtained.[44,45] High resolution MALDI-TOF spectra have been obtained of oligosaccharides derivatized with 4-amino-2-diethylaminobenzoate.[46] MALDI CID spectra reflect the preferential cleavage of saccharides with branches up to the branch points in oligosaccharides, so facilitating their sequencing; this point was demonstrated for ribonuclease B and human α_1-acid glycoprotein.[47] Studies on xyloglucan-derived hepta- and octa-saccharides conclude that MALDI-TOF is a powerful tool for structural analysis of highly branched oligosaccharides.[48,49] The high through-put, microscale release of *N*-linked glycans for MALDI-TOF analysis permits analysis of the glycosylation of recombinant tissue-type plasminogen activator on a 0.1–50 μg scale.[50]

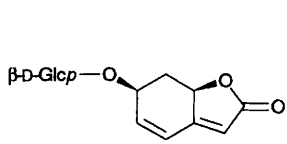
3 X-Ray and Neutron Diffraction Crystallography

Specific X-ray crystal structures have been reported as follows (solvent molecules of crystallisation are frequently not reported).

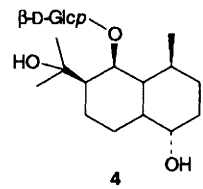
3.1 Free Sugars and Simple Derivatives Thereof. – 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6-dideoxy-α-D-*ribo*-hex-5-yno-furanose.[51] (See also structures **17** and **18** in Section 3.3 for related analogues).

3.2 Glycosides, Disaccharides and Derivatives Thereof. – X-ray analyses of alkyl (C7–C10) α- and β-D-glucopyranosides have been reported, along with an investigation of their thermotropic properties.[52] The crystal structure of balhimycin, a relative of vancomycin, has been reported.[53] The structures of a number of naturally occurring glycosides have been reported, including: phyllanthurinolactone **3** (a plant bioregulator),[54] dictamnoside **4** (isolated

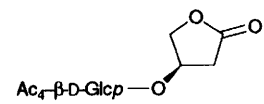
from root bark of *Dictamnus dasycarpus*),[55] the (3*R*)-hydroxybutanolide peracetate **5** (isolated from the plant *Anoectochilus formosanus*),[56] brasilicardin A **6** (a potent immunosuppressive from *Nocardia brasiliensis*)[57] and diacetyldihydrocotylenin A **7** (which possesses an interesting acetal structure derived from a 4-keto-glucose derivative).[58] Structures of muramic acid lactam **8**[59] and xylose-based disaccharide derivative **9**[60] have also been reported.



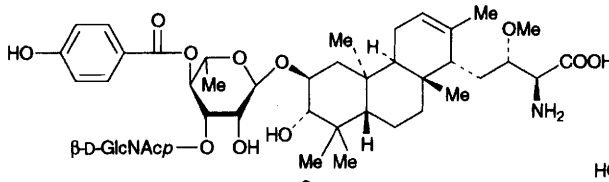
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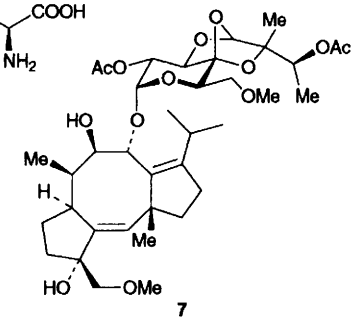
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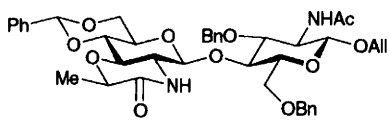
5



6



7



8

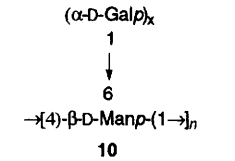
2,3,4-Tri-*O*-acetyl-β-D-Xyl*p*-(1→3)]-2,4-di-*O*-acetyl-β-D-Xyl*p*-SEt

9

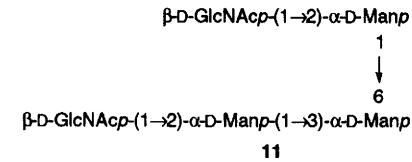
3.3 Higher Oligosaccharides and *C*-Glycosides. – The crystal structures of cyclodextrins and their inclusion complexes have been reviewed.[61] Several amphiphilic cyclodextrins have been studied by X-ray scattering and freeze-fracture electron microscopy.[62] The crystal structure of hexakis(2,3,6-tri-*O*-acetyl)-α-cyclodextrin displays a cavity the shape of a rectangular box, with both ends closed and a water molecule included in the molecular cage.[63] Crystal structures of two forms of a 2:1 inclusion complex of α-cyclodextrin and 4,4′-biphenyldicarboxylic acid (BPDC) show that the BPDC (guest) interacts with another BPDC molecule by guest–water–guest hydrogen bonding.[64]

The 3-D structure of the plant polysaccharide guaran **10** has been studied by X-ray diffraction.[65] It has been demonstrated that the complex of the lectin concanavalin A with the *N*-linked glycan core pentasaccharide **11** shows a substantial distortion of the psi-torsion angle (>50°) of the GlcNAc-β-1,2-Man linkage on the 1,6-arm of the pentasaccharide.[66]

Crystal structures of various *C*-glycosides have been published, including:

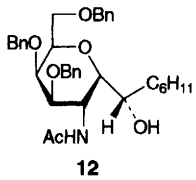


10

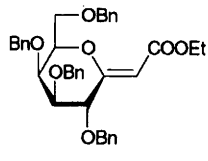


11

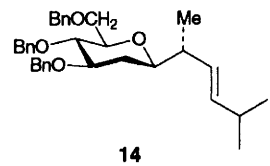
α-GalNAc derivative **12**,[67] glycosylidene derivative **13**,[68] 2-deoxy-β-*C*-glucoside **14**,[69] *C*-linked lactose **15** bound to peanut lectin,[70] and alkyne derivatives **16**, **17** and **18**.[71]



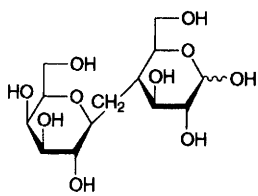
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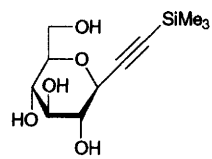
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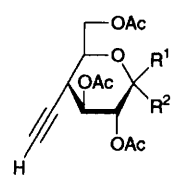
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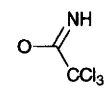
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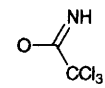
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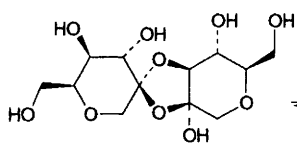
17 R^1 = H, R^2 =



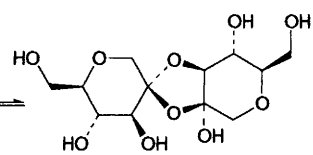
18 R^2 = H, R^1 =



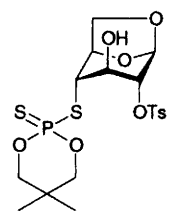
3.4 Anhydro-sugars. – The structure of 1,5-anhydro-D-fructose in non-aqueous solvents (DMSO, pyridine) has been investigated; under different acetylation conditions, the crystalline dimer peracetates of **19** or **20** were obtained, as shown by X-ray analysis.[72] The crystal structure of 1,6-anhydro-D-glucose derivative **21** has been reported,[73] as has the structure of methyl 2,6-anhydro-3-deoxy-D-*lyxo* - and D-*arabino*-hept-2-enoates.[74]



19

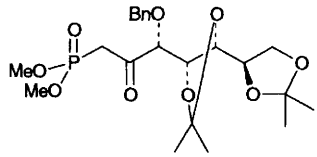


20

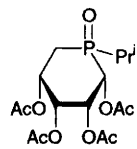


21

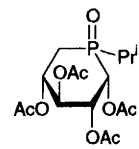
3.5 Phosphorus, Sulfur and Nitrogen-containing Compounds. – Structures of acyclic phosphonate **22**[75] and cyclic phosphine oxides **23–25**[76] have been reported. X-ray crystallography has been used to confirm the structures of novel 3′,6′- and 2′,6′-epithionucleosides **26** and **27**.[77] The structures of sulfinate ester **28** and sulfonate esters **29** have been investigated,[78] as have the structures of sulfoxide **30** and sulfone **31**,[79] and sulfonamides **32** and **33**.[80] The latter paper relates to extensive SAR studies on the anticonvulsant properties of topiramate **32**.[80]



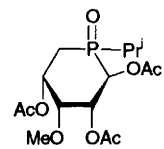
22



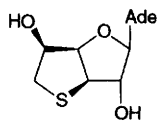
23



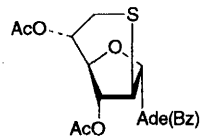
24



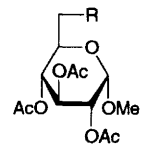
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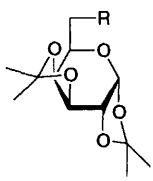
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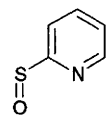
27



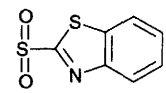
28 R = SO.Ph
29 R = SO_2.Ph

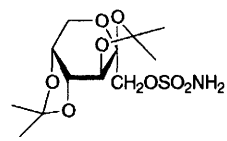


30 R =

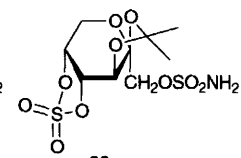


31 R =





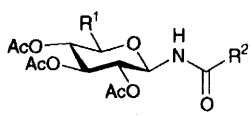
32



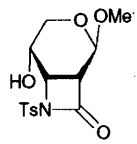
33

The structure and conformational preferences of glycosyl amides **34–37** have been reported,[81] as have structures for *N*-β-D-glucopyranosylbenzamide[82] and *N*-β-D-glucopyranosylurea.[83] Structures for β-lactams **38** and **39**,[84] and triazolopyridazine **40** have also appeared.[85]

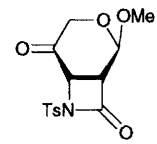
X-ray structures of several azasugars have been reported. The structure of naturally occurring α-homonojirimycin **41** has been published.[86] Kinetic



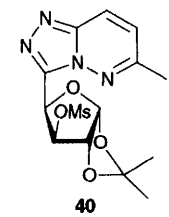
34 $R^1 = CH_2OAc$, $R^2 = H$
35 $R^1 = CH_2OAc$, $R^2 = CH_3$
36 $R^1 = H$, $R^2 = H$
37 $R^1 = H$, $R^2 = CH_3$



38

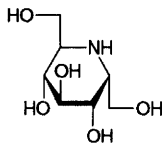


39

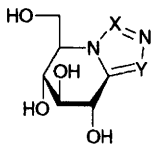


40

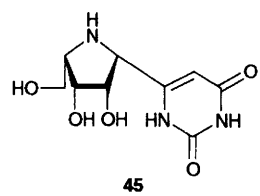
studies and X-ray structural studies have been used to explain why **42** and **43**, but not **44**, are strong β-glycosidase inhibitors.[87] The X-ray structure of **45** confirms its L-*lyxo* configuration, so contradicting the earlier proposed D-*ribo*-configured structure (*J. Org. Chem.*, 1996, **61**, 6079).[88] The structure of **46**, an intermediate in the synthesis of 1-deoxymannojirimycin, has been reported.[89] Structures have also been reported for bicyclic 'diazasugars' **47** and **48**, derived from L-arabinose and D-ribose, respectively.[90]



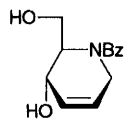
41



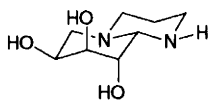
42 X = Y = N
43 X = CH, Y = N
44 X = N, Y = CH



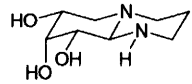
45



46



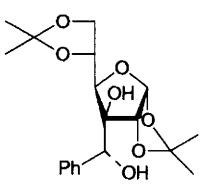
47



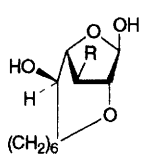
48

3.6 Branched-chain Sugars. – Structures have been determined for branched sugars **49**[91] and **50**,[92] as well as for spiro-compound **51**.[93]

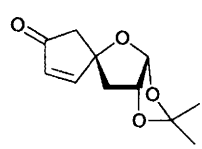
3.7 Sugar Acids and Their Derivatives. – The X-ray structure of methyl β-D-glucofuranosidurono-6,3-lactone has been recorded.[94] Compound **52**, produced by aldolase-catalyzed condensation of glycine with *O*-isopropylidene glyceraldehyde, proved to be crystalline, whereas its C-3 epimer acts at a gelator in organic solvents.[95] (See also orthoester derivative **64** in section 3.9).



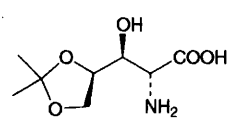
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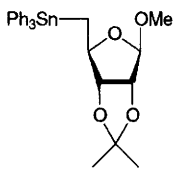
50 R = COOMe



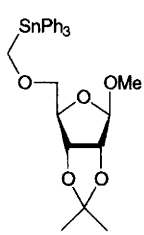
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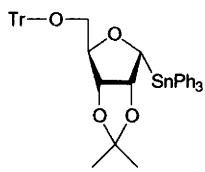
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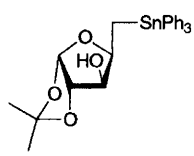
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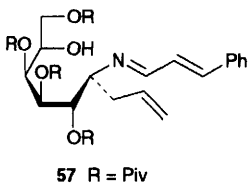
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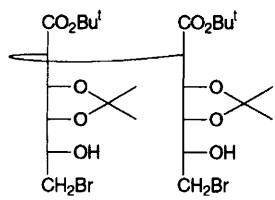
56

3.8 Inorganic Derivatives. – X-ray crystal structures of organotin derivatives **53–56** have been determined.[96,97,98] The structure of a methyl α-D-mannopyranoside–bismuth(III) complex has been reported.[99]

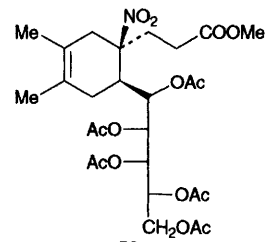
3.9 Alditols and Cyclitols and Derivatives Thereof. – The conformational polymorphism of D-glucitol in the solid state has been investigated[100] and a structure for 1,2:4,5-di-*O*-isopropylidenegalactitol has been reported.[101] The structure of D-*glycero*-L-*manno*-configured aminoalditol **57** has been determined,[102] as has the structure of **58**, a by-product arising from samarium diiodide promoted hydrodimerization of α,β-unsaturated esters derived from bromodeoxyalditols.[103] The X-ray structure of nitroalditol derivative **59** has been determined.[104]



57 R = Piv



58



59

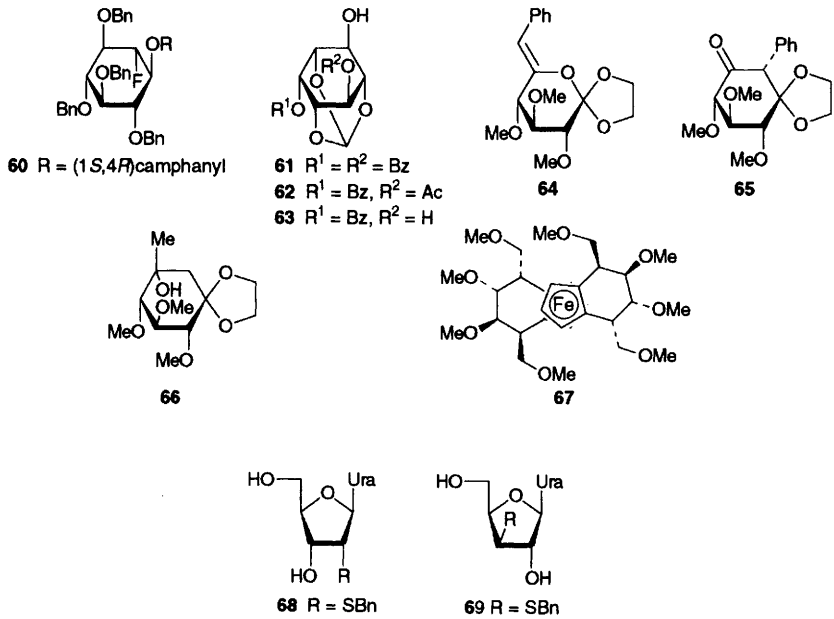
The structure of a copper(II) complex of 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol has been reported,[105] as has the structure of fluorodeoxy-*scyllo*-inositol **60**.[106] Structures of *myo*-inositol orthoformates **61–63** have been reported,[107,108] as has the structure of *myo*-inositol 1,3,5-bicyclic phosphate.[109]

Lewis acid-catalyzed rearrangement of enol-ether **64** gave branched chain cyclitol **65**; structures of both compounds have been reported, as has the structure of **66**, derived from a related enol-ether on treatment with methylmagnesium iodide.[110] Ferrocene derivative **67** has also be characterized by X-ray crystallography.[111]

3.10 Nucleosides and Their Analogues and Derivatives Thereof. – Structures have been reported for a number of nucleoside analogues where the sugar ring is not the standard unmodified L-ribose or 2-deoxy-L-ribose: 6-propylcytidine,[112] β-D-xylofuranosyluracil,[113] adenosine 5′-carboxylic acid,[114] 2′-*S*-benzyl-2′-thiouridine **68** and 3-*S*-benzyl-3-thio-β-D-xylofuranosyl uracil **69**,[115] 2,2′-anhydro-β-D-lyxofuranosyl thymine,[116] halogenated nucleosides 5′-bromo-5′-deoxythymidine[117] and 2′-chloro-2′-deoxyadenosine.[118]

A number of structures have been reported for nucleoside analogues where a modified base is incorporated: 3-hydroxy-2-methyl-1-(β-D-ribopyranosyl)-4-pyridone **70**,[119] pyrazolopurine **71**,[120] N^4,5-dimethyl-2′-deoxycytidine **72**,[121] deoxyadenosine isostere **73**,[122] 1,2,4-triazolo[4,3-c]pyrimidinone **74**,[123] 6-aza-5-substituted-2′-deoxyuridines **75–78**,[124] 1-deaza-3′-*O*-methyladenosine **79**,[125] and 4-thiouracil-2′-trifluoroacetamide-3′,5′-diacetyl-β-D-ribofuranoside **80**.[126]

The structure of α-L-talose-based nucleoside **81** has been determined,[127] as

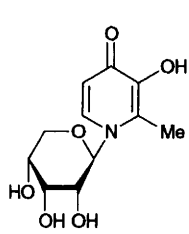


have the structures of *C*-branched nucleoside **82**,[128] and carbanucleoside analogues **83**,[129] **84** and **85**.[130]

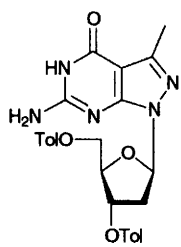
4 Ultraviolet and Other Spectroscopies and Physical Methods

Helix theory has been used to predict optical rotations for common monosaccharides and their methyl glycosides,[131,132] optically active inositols and their methyl derivatives.[133] Empirical relationships between structure and optical rotation for a series of inositols have also been noted.[134] The sign and size of the optical rotations of a series of THP derivatives have been correlated with their structure, conformation and absolute configuration.[135]

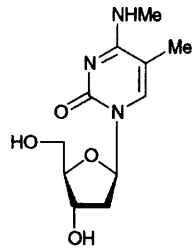
Spectroscopic studies on the calcium ion-dependent interaction of pradimicin **86** and mannose derivatives have been reported; these studies aim to explain the anti-fungal properties of these mannan-binding natural products.[136] Copper(II) complexes of the aminoglycoside antibiotic tobramycin have been studied by potentiometric and spectroscopic (UV-Vis, CD, EPR) methods.[137] NMR, UV-Vis, fluorescence and CD spectroscopy have been used to demonstrate that 3-*O*-(2-methylnaphthyl)-β-cyclodextrin is a dimer a 10^{-4} M concentration.[138] The optical properties of chondroitin sulfate A–acridine orange complex have been reported.[139] A theoretical basis for using CD spectroscopy to predict the conformation of Δ^4-uronate has been reported; ^{1}H NMR data are in agreement with predictions from CD.[140] CD spectral differences between anomers of alkyl glucopyranosides have been shown to correlate with differences in chair conformation, which agree with NMR data



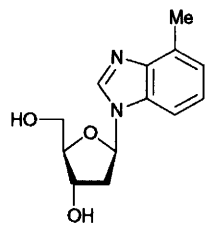
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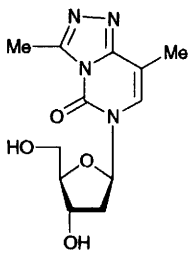
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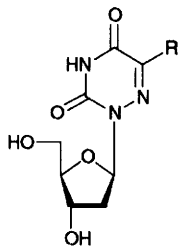
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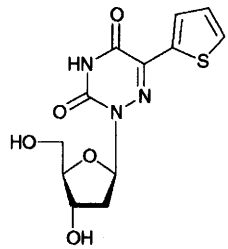
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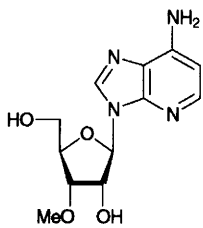
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76 —Bu^t

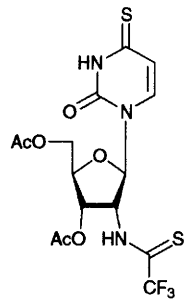
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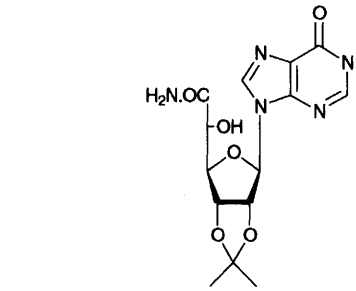
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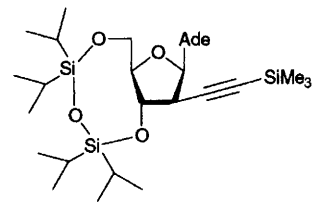
80

and empirical calculations[141] Complexes of aminosugars with cobalt(III) bis(phenanthroline) have been isolated and studied by NMR, absorption and CD spectroscopy, backed up by molecular modelling.[142] Conformational preferences of synthetic fragments of *O*-specific polysaccharides of *Vibrio cholera* have been revealed by CD spectroscopy.[143]

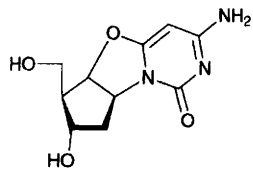
The nature of the interaction between calcofluor and carbohydrates of α_1-acid glycoprotein has been studied by fluorescence spectroscopy.[144] EPR studies have provided evidence for the formation of an allylic radical from (*E*)-2′-fluoro-methylene-2′-deoxycytidine 5′-diphosphate by *E. coli* ribonucleotide reductase.[145] Laser flash photolysis of **87** gives rise to an anomeric radical, as shown by EPR spectroscopy.[146] This technique has also been used to study the addition of carbohydrate radicals to methacrylic acid.[147] Photon correlation spectroscopy and viscosity measurements have been performed on α,α-treha-



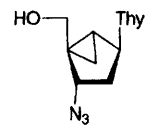
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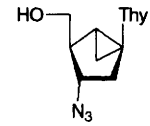
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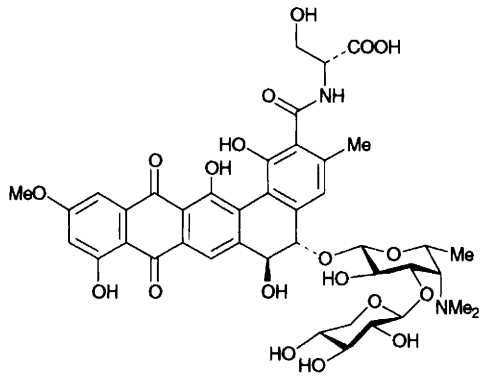
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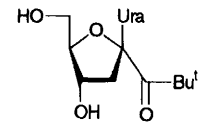
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lose.[148] The dynamic properties of aqueous sucrose solutions have been studied by acoustic spectroscopy.[149]

DSC studies have been used to investigate the self-assembly properties of glycolipids related to membrane components of archaebacteria.[150] Preferential solvent interactions and the dissolution of the B-type crystalline polymorph of starch in aqueous solution have been studied by DSC and comparison made with predictions derived using Flory-Huggins theory.[151] Surface plasmon resonance has been used to investigate the interaction of immobilized macrocyclic sugar clusters with lectins and water soluble polymers.[152] This technique has also been used to analyse specific interactions between synthetic glycopeptides carrying *N*-acetyllactosamine and related compounds with lectins.[153] Immobilization of gangliosides on carboxymethyldextran-coated gold has been used to develop optical biosensor for analysing protein–carbohydrate interactions.[154]

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23
Separatory and Analytical Methods

The use of micro-bore HPLC-MS and capillary electrophoresis-MS for analysis of the nucleosides and nucleotides present in covalent adducts of DNA with chemical carcinogens has been reviewed.[1] Reviews on the analysis of macrolide and aminoglycoside antibiotics in biological fluids using a range of techniques have also been published.[2,3]

1 Chromatographic Methods

1.1 Gas–Liquid Chromatography. – The BF_3:OEt_2-induced formation and anomerization of glucopyranosides from the β-pentaacetate have been investigated by GC.[4] The position of sugar acylation in modified ceramides was analysed by peracetalation, replacement of the acyl group by an *O*-methyl group, followed by methanolysis, per-trimethylsilylation and GC-MS analysis.[5] Analysis of the positions of substitution of acetate/butyrate and acetate/propionate in cellulose esters have been achieved by reductive cleavage and GLC-MS.[6,7] GLC has been used to separate and quantify enantiomeric 3,6-anhydrogalactoses following conversion to the corresponding 3,6-anhydrogalactonic acids and esterification with sec-butanol.[8] 2-Hydroxypropyl-γ-cyclodextrin and a mixture of homologues and isomers in monkey plasma were analysed by GC-MS following per-deuteromethylation, hydrolysis and per-trimethylsilylation.[9]

1.2 Thin-layer Chromatography. – Bile acids, their glycones and a range of sugar conjugates have been analysed by reverse phase 2D-TLC using a methylated β-cyclodextrin-containing eluant in the second dimension.[10] The separation of aldoses and alditols by TLC and their detection (500 ng to 1 μg range) using alkaline silver nitrate–sodium thiosulfate have been reported.[11] The use of an iodine-azide ion reagent for detection of sugar phosphorothioates on TLC plates, following *in situ* ester hydrolysis, has also been described.[12]

1.3 High-pressure Liquid Chromatography. – Recent reviews describe the use of HPLC and HPLC-MS for analysis of nucleosides and nucleotides,[13] aminoglycoside and macrolide antibiotics in pharmacokinetic applications[14]

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and in meat and milk.[15,16] A review covering the period 1990–1997 (78 references) on the use of reverse phase HPLC (RP-HPLC) in the analysis of glucuronide conjugates of drug metabolites in body fluids has also been published.[17]

The practical limits for detection of minor nucleoside reaction products by HPLC with UV detection have been investigated.[18] Site localization of Sia Le^x on α_1-acid glycoprotein has made use of HPLC coupled to electrospray mass spectrometry.[19] Mapping techniques (2-D) for fluorescently-labelled (amino-naphthalene trisulfonate) neutral and sialyloligosaccharides have been reported.[20] HPLC on aminopropyl silica (APS) columns has been used to monitor the product distribution in iodine-catalysed methyl glycosidation reactions.[21] Highly fluorescent anthranilic acid derivatives have proved effective for high resolution, high sensitivity oligosaccharide mapping by normal phase HPLC.[22] Ascorbate and related compounds have been analysed by HPLC with fluorescence detection following post-column derivatization with alkaline benzamidine.[23] Ten different components were identified in commercial samples of the aminoglycoside antibiotic amikacin using HPLC with pulsed electrochemical detection (PAD).[24] Guanine, its nucleosides and nucleotides, have been analysed by HPLC-gel filtration using an eluant based on phenylglyoxal, which forms fluorescent derivatives in a post-column reaction.[25]

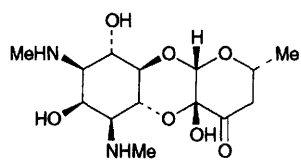
Separations of glucose, sucrose and a fructo-oligosaccharide have been carried out on a micro-pellicular aminopropyl-bonded silica column.[26] The separation and analysis of various pentose and hexose phosphates by HPLC-MS was achieved with the aid of a β-cyclodextrin-bonded column.[27] Normal phase HPLC has been used to analyse impurities in α-cyclodextrin, namely malto-oligosaccharides, β- and γ-CD and several unidentified components.[28] A combination of normal and RP-HPLC has been used to separate alditols derived from toad oviducal mucin on the basis of molecular size and stereochemistry, respectively.[29] The composition of flavanol glycosides in berry extracts has been analysed by HPLC-MS.[30] HPLC-PAD has been used to identify and isolate hamamelose (2-hydroxymethyl-D-ribose) in plant leaves. This technique is notably less sensitive when assessing 2-carboxy-D-arabinitol and its phosphate esters.[31] Microbore HPLC with electrospray ionisation–ion-mobility spectrometry (ESI-IMS) has been used to detect a variety of carbohydrates (aldoses, alditols, oligosaccharides, aminosugars) at the fmol to pmol level.[32]

Analysis of carbohydrates by a semi-microcolumn anion exchange resin has been reported.[33] Alditols, mono- and di-saccharides have been separated by isocratic elution (13 mM KOH) on an anion-exchange HPLC column made by absorption of cryptand *n*-decyl-[2.2.2] onto a polystyrene-type resin, which forms anion-exchange sites by complexing potassium ions from the mobile phase.[34] HPAEC-PAD can be used for the routine simultaneous evaluation of picomole quantities of *N*-acetyl- (Neu5Ac) and *N*-glycolyl- (Neu5Gc) neuraminic acid,[35] and for the determination of glucosamine and glucosamine 4-phosphate in Lipid A preparations.[36] Preparative HPAEC purification of high

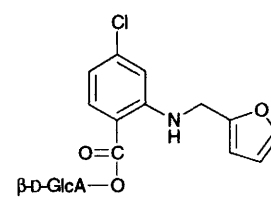
milligram quantities of gangliosides G_{M3}(Neu5Ac) and G_{M3}(Neu5Gc) from hybridoma cells has also been reported.[37] An Au/Cu bimetallic electrode has shown promise for amperometric detection of various carbohydrates in alkaline HPLC eluates; applications in analysis of coffee and red wine are envisaged.[38] HPAEC-PAD of various saccharides show decreased retention times with increased temperature; even small changes (± 5 °C) resulted in considerable changes in retention time and in elution order.[39] Spectinomycin **1** residues in bovine tissues have been analysed by ion-exchange HPLC following appropriate derivatization, coupled with RP-HPLC-MS.[40]

Various membranes have been assessed for use in microdialysis of oligosaccharides, prior to HPAEC-PAD analysis, for monitoring bioprocesses.[41] Carbamylated dehydroascorbic acid levels in urine and plasma have been analysed by HPAEC,[42] as have ascorbic acid and its' 4-phosphate in aquaculture feeds.[43] The PAD detector response in the analysis of malto-oligosaccharides has been shown to decrease from DP 3-7, but to level out at DP larger than 15.[44] Cation exchange HPLC has been used in connection with determination of glucose levels in human urine.[45] Glucose, glucose-3-phosphate, glucose-6-phosphate and reversion products formed on hydrolysis of starch have been analysed by HPAEC-PAD.[46] Similar compounds in wine have been analysed by cation exchange HPLC with FTIR detection.[47] Dinucleotide (5,5′)polyphosphates have been prepared and analysed by a combination of reverse phase and amino-exchange HPLC.[48] Various positional isomers arising from α-mannosidase-catalysed mannosylation of cyclodextrin have been analysed by HPLC.[49]

Positional isomers of partially methylated and acetylated or benzoylated 1,5-anhydro-L-arabinitol have been analysed by RP-HPLC.[50] RP-HPLC analysis of fluorescent derivatives of vitamin C in natural products has been reported,[51] as has the analysis of *N*-acetyl- and *N*-glycolyl-neuraminic acid in healthy and cancerous mouse lung tissues.[52] The photodegradation and acyl migration products of furosemide 1-*O*-acyl glucuronide **2**, the major metabolite of furosemide has been isolated by RP-HPLC.[53]



1

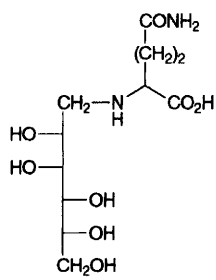


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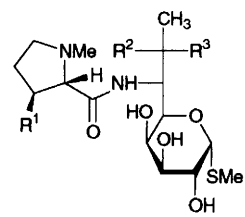
Macrolide antibiotics in human serum have been analysed by RP-HPLC using pre-column derivatization with 9-fluorenylmethoxycarbonyl chloride and fluorescence detection.[54] RP-HPLC-MS has been used to analyse the macrolide josamycin in human plasma[55] and to analyse the antibiotic spectinomycin in bovine milk.[56] It has also been used to determine adenosine and deoxyadenosine in urine,[57] 8-oxo-,8-dihydro-2′-deoxyguanosine in biological

fluids,[58] and the AIDS drug 2′-β-fluoro-2′,3′-dideoxyadenosine in human plasma.[59] The RP-HPLC separation of deoxyribonucleosides has been optimized with respect to eluant composition for gradient elution.[60] A new doxorubicin glucuronide prodrug and its metabolites in human lung tissue have been analysed.[61] Anti-nutritional inositol phosphates in under-utilized Nigerian legumes were analysed by on-pair RP-HPLC.[62] Opines **3** in the leaves of transgenic tobacco expressing *Agrobacterium* opine synthesis genes have been analysed by RP-HPLC following derivatization with 4-fluoro-7-nitrobenzoxadiazole.[63]

The RP-HPLC analysis of *o*-phthalaldehyde-derivatized aminoglycoside antibiotics has been reviewed.[64] Related compounds have been analysed by ion pair RP-HPLC.[65] Macrolides from biological matrices have been analysed by RP-HPLC on cyanopropyl silica.[66] Simultaneous RP-HPLC determination of various macrolides in commercial samples[67] and in meat have been reported.[68] A simplified analysis of ascorbic acid in food using RP-HPLC has been reported.[69] The pyrenacyl ester derivatives of seven bile acids and their monoglycosides were separated by RP-HPLC with or without methylated β-cyclodextrin as a mobile phase additive.[70] Elution times for 93 pyridinylaminated *N*-linked oligosaccharides have been reported.[71] 1-Phenyl-3-methyl-5-pyrazolone (PMP) and pyridylamine (PA) derivatives of mono- to medium-sized oligosaccharides have been analysed; the former proved easier and more effective to use.[72] Ion-pair RP-HPLC has been used to separate lincomycin **4**, 7-epi-lincomycin **5** and lincomycin B **6**.[73]



3



4 R^1 = Pr, R^2 = OH, R^3 = H
5 R^1 = Pr, R^2 = H, R^3 = OH
6 R^1 = Et, R^2 = OH, R^3 = H

The retention behaviour on RP-HPLC of positional isomers of 6,6′-di-*O*-trityl- and di-*O*-*tert*-butyldimethylsilyl-α-, β- and γ-cyclodextrins has been reported.[74] RP-HPLC-MS-MS has been used to analyse glucuronides of catechol-type drugs in urine.[75] Atmospheric pressure spray ionization (APSI), in conjunction with RP-HPLC-MS, of various saccharides has been described.[76] Intracellular levels of cyclic ADP-ribose have been analysed by a combination of HPAEC and ion pair RP-HPLC.[77]

1.4 Column Chromatography. – Immobilized *p*-aminophenyl β-cellobioside has been used as an affinity ligand for exo-cellulases (more specifically cellobiohydrolases).[78] A specific binding site for raw starch on *Bacillus* α-amylase

has been exploited in the one-step purification of the enzyme on α-cyclodextrin-sepharose.[79] Highly selective analysis of D-glucitol and D-mannitol in foodstuffs has been achieved by anion exchange using a molybdate-based eluant.[80] Column separation of nucleosides on a polymer comprised of β-cyclodextrin, cross-linked with epichlorohydrin, with or without copper ions has been reported.[81]

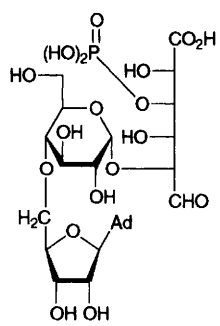
2 Electrophoresis

Derivatization of carbohydrate compounds subjected to capillary electrophoresis (CE) has been reviewed,[82] as has the analysis of nucleotides using this technique.[83] Using data from CE separation of 12 normal and modified nucleosides in urine samples, artificial neural networks have been trained to distinguish samples from cancer patients from healthy individuals.[84] CE separation of 15 urinary and modified nucleosides from cancer patients has also been reported.[85] The detection, analysis and separation of mono- and oligo-saccharides, glycolipids and glycopeptides has been reviewed.[86] Di- and oligo-saccharides have been used for enantioselective separation of atropisomeric binaphthyl derivatives by CE[87] which has been used to map *N*-linked oligosaccharides in glycoproteins.[88] High performance CE of a series on 1-aminophenyl-1-deoxy sugars has been reported,[89] as has quantitative analysis of sugar constituents of glycoproteins by CE with laser-induced fluorescence detection.[90] Chemically-modified celluloses have been characterized by CE[91] which has been used to analyse unsaturated disaccharides produced by enzymatic depolymerization of heparin.[92] It has also bee used to analyse phosphate and sulfate esters of ascorbic acid in fish feed, plasma and tissue.[93] The four common deoxynucleoside monophosphates have been separated by CE using a pluronic copolymer liquid crystal gel-like phase.[94] Various sugars present in a single plant cell vacuole were determined by CE with UV detection of Cu(II) chelates.[95] The analytical separation of aldose phosphates and related compounds was achieved by CE with indirect UV detection using potassium phosphate.[96] CE separation of α-, β-, γ- and δ-cyclodextrin was achieved using 4-*tert*-butylbenzoate and methyl orange in the electrolyte.[97]

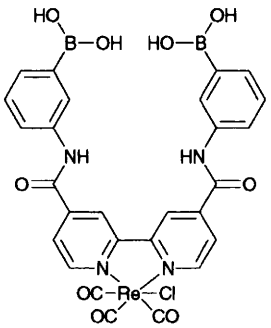
A detailed discussion has been presented of the impact of borate complex formation on CE separation of 18 acid monosaccharides and related lactones.[98] Addition of 'polybrene', a polycationic water soluble polymer, can give enhanced resolution in such separations.[99] The use of organic polymer capillaries, made from poly(methylmethacrylate), for the separation of 2-aminoanthracene-labelled oligosaccharides has been reported.[100] CE analysis of cyclodextrins using 8-anilinonaphthalene-1-sulfonic acid in the buffer gives dynamic fluorescent labelling of the saccharides.[101] Neutral sugars can be separated and detected as their Cu(II) chelates by CE with UV detection.[102] The migration behaviour of flavonoid glycosides on CE can be predicted by means of topological indices.[103] CE has been used to determine the ascorbic

acid content of a single plant cell.[104] Fibre-optic Raman probes have been used as in-line detectors for CE analysis of ribonucleotides.[105]

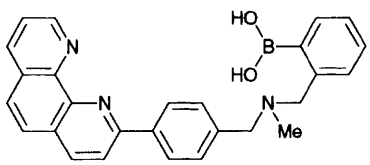
It is claimed that CE using magnesium chloride and β-cyclodextrin gives better separation of such compounds than does MEKC.[106] Quantitative analysis of the insecticidal β-exotoxin thuringiensin **7** was achieved by micellar electrokinetic capillary chromatography (MEKC) using sodium dodecyl sulfate (SDS) in a borate buffer.[107] MEKC has been shown to give improved separation of adenosine and its various phosphate esters.[108]



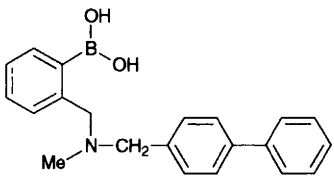
7



8



9



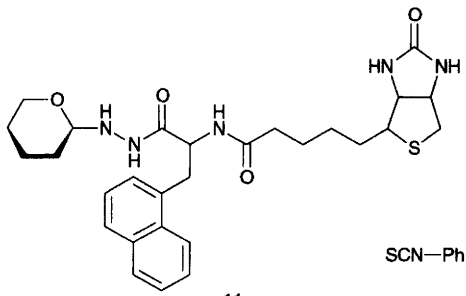
10

3 Other Analytical Methods

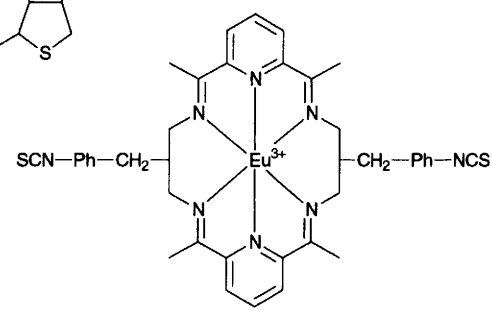
A number of recent papers report the use of arylboronic acid systems, such as **8**,[109] **9**[110] and **10**,[111] as sugar selective sensors.

Exploitation of the aminoglycoside antibiotic neomycin as an anion selective chelator has been reported.[112] NMR relaxation times have been used to analyse paramagnetic contributions to the formation of cupric ion complexes of aminoglycoside antibiotics.[113] UV absorption spectrophotometry has been used to quantify cytidine 3′,5′-cyclic phosphate in aqueous solutions.[114] Changes in lipophilicity of glucuronidation have been shown to be more effective for phenols and carboxylic acids than for alcohols.[115] The lactosylceramide binding specificity of *Helicobacter pylori*, the cause of gastric ulcers, has been determined.[116] α-Amylase digestion, together with selective precipitation (DP>8), has been used to analyse the distribution of methyl substituents over branched and linear regions in methylated starches.[117] Antigenic epitopes in anti-ulcer pectic polysaccharides have been determined by enzymatic diges-

tion.[118] Monoclonal antibodies have been used to map wild-type and mutant β-1,4-galactosyltransferases.[119] Fluorescent biotinyl-L-3-(2-naphthyl)alanine hydrazide (BNA) has been used for labelling reducing saccharides, to give structures such as **11**, for use in probing protein–carbohydrate interactions.[120]



11



12

Macrocyclic europium chelates **12**, referred to as quantum dyes, have been investigated as alternatives to radioactive tracers for protein–carbohydrate interaction studies. Such compounds have the potential to replace ^{125}I-labelling, since they do not decay, have a long shelf-life and give more consistent results in repeated experiments.[121] Dendritic hydrogen bonding receptors have been used to generate 'dendroclefts' for stereoselective complexation of saccharides.[122] Sub-nanomolar quantities of sugars have been analysed by oxidation with periodate followed by analysis of remaining oxidant.[123]

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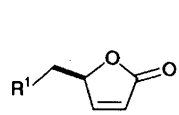
24

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

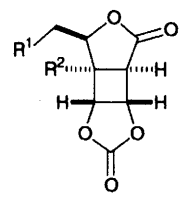
1 Carbocyclic Compounds

A review has appeared which detailed the synthesis of a wide variety of natural products from carbohydrates, including a number of carbocyclic systems.[1]

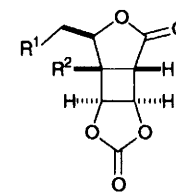
1.1 Cyclopropane and Cyclobutane Derivatives. – Two cyclopropanone syntheses have been described. The first reports synthesis of cyclopropanone (1*S*,2*S*,3*S*,4*S*,6*R*)-3-benzyl-7,9-dioxatricyclo[4.2.1.$0^{2,4}$]nonan-5-one following reaction of levoglucosenone with the sulfonium ylide derived from $Me_2S^+CH_2$-COPh bromide salt,[2] and the second the isolation of the individual diastereomeric 1-α-[2,2-dibromo-1-(methylcyclopropyl)methyl) 2,3,4,6-tetra-*O*-methyl-D-glucopyranosides.[3] The latter are applied to synthesis of enantiomeric 2,2-dibromo-1-hydroxymethyl-1-methylcyclopropanes. The tricyclic cyclobutane-containing compounds **2** and **3** have been obtained, in up to 92% d.e., through [2+2] cycloaddition of the homochiral 5-alkyl-2(5*H*)-furanones **1** and vinylene carbonate.[4]



1 R^1 = H
R^1 = O-acyl group
R^1 = OTbdps

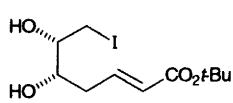


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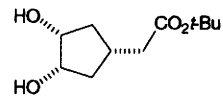


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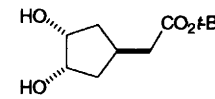
1.2 Cyclopentane Derivatives. – Samarium diiodide mediated reductive carbocyclization of ω-iodo-α,β-unsaturated ester **4**, derived from 2-deoxy-D-ribose, afforded a high yield of **5** and **6** in approximately 7:1 ratio.[5]



4



5

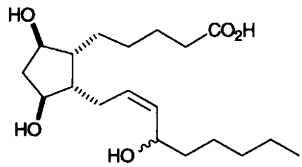


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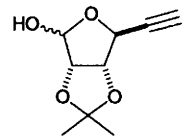
The first synthesis of 15(*R,S*)-2,3-dinor-5,6-dihydroxy-8-epi-$PGF_{2\alpha}$ **7** (a mixture of C15 diastereomers therefore) has been achieved from diacetone-D-

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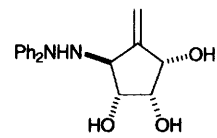
glucose as starting material.[6] Tributyltinhydride-mediated radical cyclization of δ-functionalized tethered acetylene derivatives (*via* 5-*exo*-*trig* pathway) provided a route to polyfunctionalized cyclopentanes. For example, synthesis of **9** from **8**, wherein the phenylhydrazone derived from **8** undergoes cyclization (tributyltin hydride/triethylborane) to the vinyl stannane, followed by acidic ethanol and methyloxirane to yield **9**.[7]



7

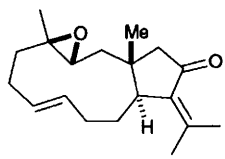


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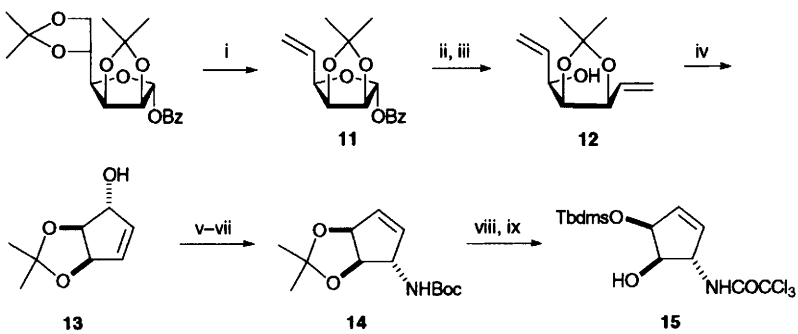
9

The marine dolabellane diterpenoid claenone **10** has been synthesized from D-mannitol, *via* a bicyclo[2.2.1]heptane intermediate, through Michael reaction, with formation of a cyclopentane intermediate by retro-aldol reaction and cyclization of a sulfone.[8]



10

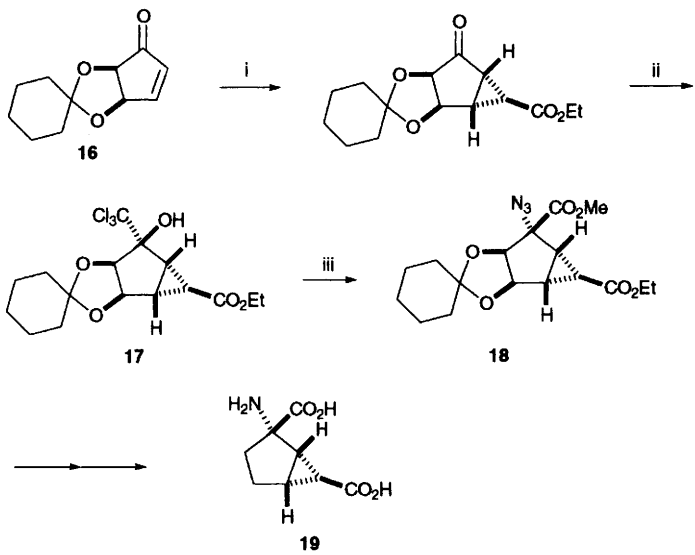
D-Mannose has been elaborated into the cyclopentenamine **14** and derivative **15**, key steps being the Wittig homologation of **11** to give diene **12**, and the metathesis reaction of this diene [using Grubbs ClRu(PCy)=CHPh catalyst] to provide carbocycle **13**. This was then subjected to Overman rearrangement, and the nitrogen protecting group exchanged to afford **14**. Removal of the isopropylidene group and selective mono-silylation then provided **15** which contains all the key functionality and stereochemistry of the cyclopentene unit of nucleoside Q (Scheme 1).[9]



Reagents: i, HOAc, then $HC(OEt)_3$, HOAc, then Ph_3CCO_2H, Δ; ii, KO*t*-Bu, MeOH; iii, $CH_2{=}PPh_3$; iv, $Cl_2Ru(PCy_3)_2{=}CHPh$; v, CCl_3CN, DBU; vi, Δ, xylene; ii, NaOH, then Boc_2O; viii, HOAc, H_2O; ix, TbdmsCl, Pyr

Scheme 1

The cyclopropane-fused cyclopentane **19** (an agonist for G-protein-coupled glutamate receptors) has been prepared from D-ribonolactone, *via* the known cyclopentenone **16**. Cyclopropanation was effected using a sulfur ylide, while the interesting quaternary α-amino acid function was introduced by trichloromethylation of the ketone (to give **17**), and modified Corey-Rink reaction led to azide **18** *via* the dichloroepoxide as intermediate. Several steps involving key deoxygenation then converted intermediate **18** into **19** (Scheme 2).[10]



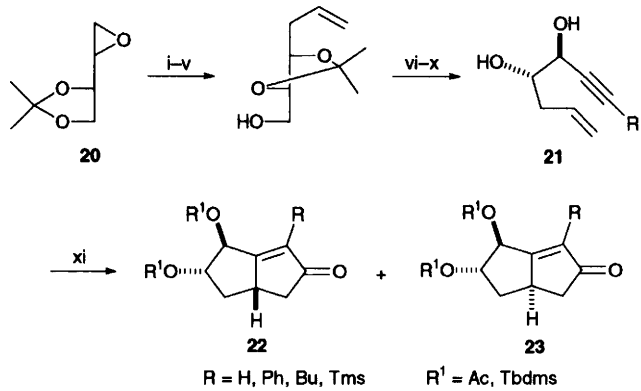
Reagents: i, $Me_2S^+CH_2CO_2Et\ Br^-$, DBU; ii, $HCCl_3$, LHMDS; iii, DBU, 18-crown-6, NaN_3, MeOH

Scheme 2

L-Ascorbic acid was the starting material for a synthesis of chiral bicyclo-[3.3.0]octenones **22** and **23** by the Pauson-Khand reaction. The synthesis proceeds *via* the known epoxide **20** (E. Abushanab *et al.*, *J. Org. Chem.*, 1988, **53**, 2598). A series of standard reactions leads to the eneyne **21**, the substrate (after diol protection) for the Pauson-Khand process, which generates a mixture of the diastereomeric products **22** and **23** (Scheme 3).[11]

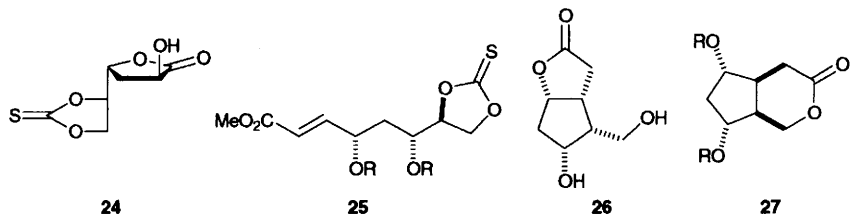
A review on the synthesis and biosynthesis of the isoprostanes includes some examples which use carbohydrate-based synthesis. For example, L-glucose-derived **24** generates **25** (R = H) on reduction and Wittig homologation, which then undergoes radical cyclization (under deoxygenation conditions) through conjugate addition, giving **26** when the free diol (**25**, R = H) is used and **27** when the diacetate or bis-Tbdms derivatives are employed. The change in pathway was rationalized on the basis of intramolecular H-bonding conformational effects in the case of the free diol form of **25**.[12]

The spirocyclopentenone **29** was derived from D-glucose derivative **28** (Scheme 4).[13] The bicyclic system **32** has been prepared from tri-*O*-acetyl-D-galactal, key steps for introducing new chiral centres being conjugate addition

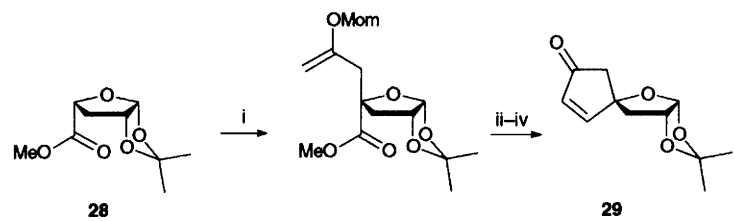


Reagents: i, H_2C=CHMgBr, CuI; ii, c. HCl; iii, TbdmsCl, Et_3N; iv, $Me_2C(OMe)_2$, PPTS; v, TBAF; vi, Swern; vii, Ph_3P, CBr_4; viii, BuLi; ix, H^+; x, alkylation; xi, $Co_2(CO)_8$

Scheme 3



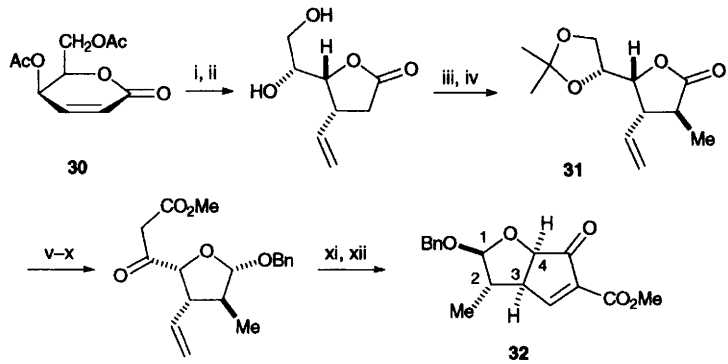
to **30**, and stereoselective enloate methylation to give **31** (Scheme 5). The racemic version of cyclopentanone **32** has previously been converted into the macrocyclic triene, terpestacin (an inhibitor of HIV synctium formation), and this current work therefore provides an enantioselective route to the (+)-isomer.[14]



Reagents: i, $ICH_2C(=CH_2)OMom$, KHMDS; ii, DIBAL; iii, NBS, $NaHCO_3$; iv, Ph_3P, CH_2Cl_2

Scheme 4

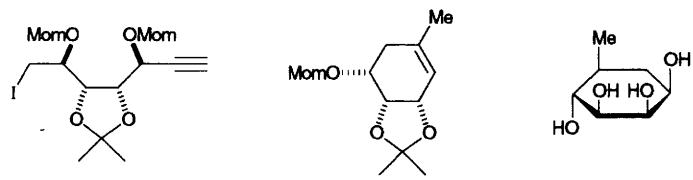
1.3 Cyclohexane Derivatives. – Cyclohexene **34** has been prepared starting from 5-*O*-Tbdps-2,3-*O*-isopropylidine D-ribose *via* the intermediate **33** which undergoes 6-*exo* radical cyclization, with the intermediate vinyl radical effecting radical fragmentation loss of the adjacent OMom group. Other examples using similar methodology were also described.[15] Cyclohexene **34**



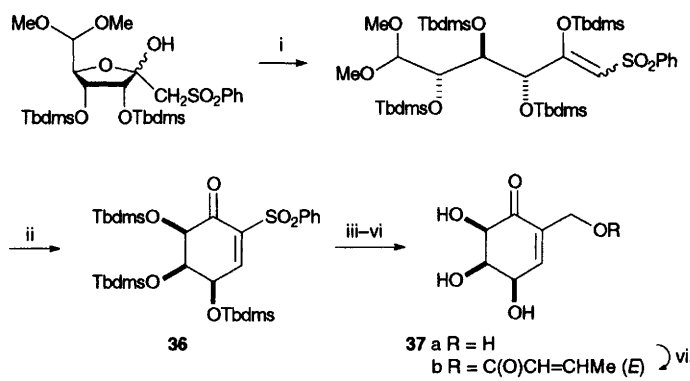
Reagents: i, $BrMgCH{=}CH_2$, CuI, Ph_3P; ii, HCl, MeOH; iii, $Me_2C(OMe)_2$, PPTS; iv, LHMDS, MeI; v, DIBAL; vi, BnBr, NaH; vii, HOAc, H_2O; viii, $NaIO_4$; ix, CH_3CO_2Me, LHMDS; x, DMSO, PCC; xi, O_3, Ph_3P; xii, NaOMe

Scheme 5

was also further elaborated *via* hydroboration and then deprotection to give carba-β-D-rhamnose (**35**).



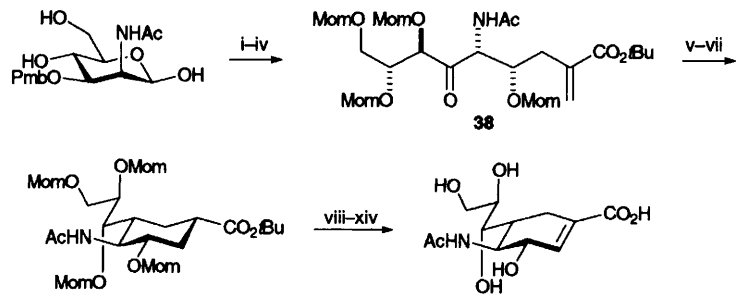
The related cyclohexenone derivative **37** has also been prepared from carbohydrate starting materials. The key hydroxymethyl side-chain was introduced by lithiation of the vinyl sulfone **36** followed by reaction with formaldehyde (Scheme 6).[16]



Reagents: i, TbdmsOTf, lutidine; ii, $SnCl_4$; iii, Bu_3SnLi; iv, HCHO; v, SiO_2, PhH; vi, CF_3CO_2H; vii, (*E*)-$MeCH{=}CHCO_2H$, $BF_3.Et_2O$, MeCN

Scheme 6

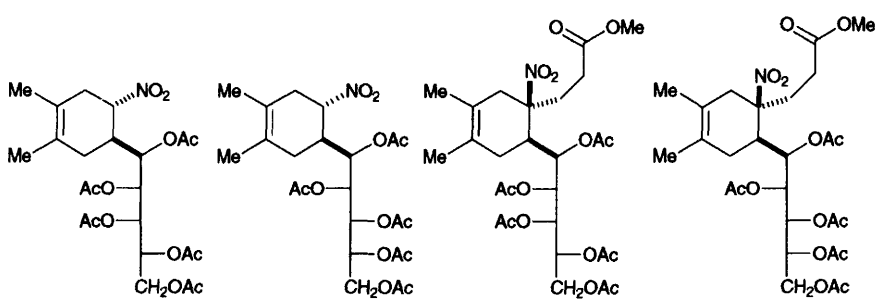
Carbocyclic analogue (**39**) of DANA has been prepared from *N*-acetylmannosamine. Key steps involve the indium-mediated allylation to introduce the extra carbon atoms, and carbocyclization of **38** (Scheme 7).[17]



Reagents: i, In, MeCN, $BrCH_2C(=CH_2)CO_2tBu$; ii, MomCl, iPr_2NEt; iii, DDQ; iv, Dess-Martin periodinane; v, SmI_2, HMPA; vi, Martins sulfurane; vii, H_2, Pd-C; viii, LICA, Ph_2Se_2; ix, H_2O_2, CH_2Cl_2; x, Pyr; xi, HCl, MeOH; xii, CH_2N_2, MeOH; xiii, Ac_2O, MeOH; xiv, Et_3N, H_2O then DOWEX H^+

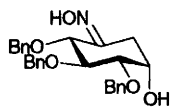
Scheme 7

Sugar-derived nitrocyclohexenes **40** (D-*talo*) and **41** (D-*manno*) (from Diels–Alder reactions of sugar-derived nitroalkenes) undergo stereoselective Michael additions (*trans* to the sugar side-chain), for example to methyl acrylate, to afford systems with new quaternary chiral centres (*e.g.* **42** and **43**, respectively).[18]

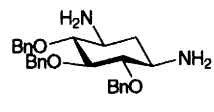


D-Glucose-derived oxime **44** (through carbohydrate-inosose Ferrier rearrangement) was converted into the protected 2-deoxystreptamine derivative **45** by LAH reduction, mesylation and azide displacement and then reduction (some analogues were also described).[19] D-Glucose was also the starting material for a synthesis of FR65814 (**46**), a novel immunosuppressant, which allowed proof of the absolute stereostructure of this natural product.[20]

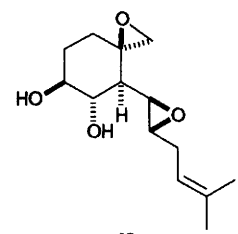
(+)-Cyclophellitol (**50**) and the epoxide diastereoisomer have been prepared from D-xylose-derived **47**, by the metathesis cyclization and the introduction of the epoxide through an iodolactonization, lactone reduction, Hunsdiecker-



44

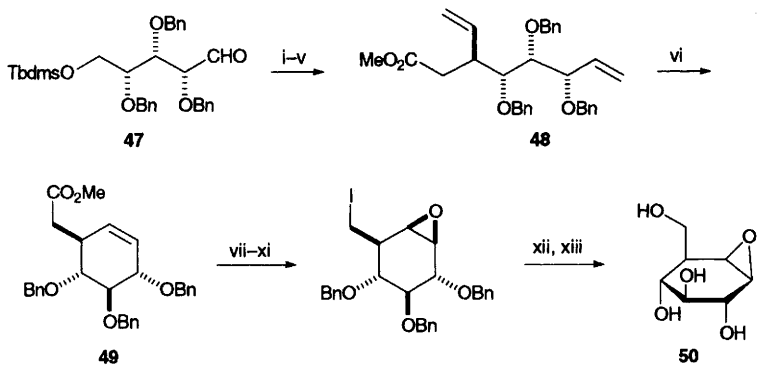


45



46

type reaction and a base-mediated cyclization of intermediate hydroxy iodide. The target **50** was then obtained through oxidation of the methylene radical and global debenzylation (Scheme 8).[21]



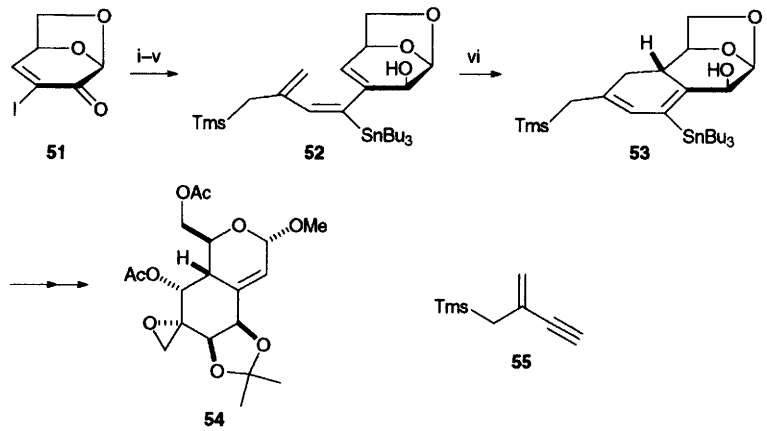
Reagents: i, $Cp_2TiCH_2ClAlMe_2$; ii, TBAF; iii, DMSO, $(COCl)_2$, Et_3N; iv, $Ph_3P{=}CHCO_2Me$; v, $(H_2C{=}CH)_2CuMgBr$, TMSCl; vi, $(Cy_3P)Ru(CHPh)Cl_2$; vii, LiOH; viii, I_2, I^-, $KHCO_3$; ix, DIBAL; x, $PhI(OAc)_2$, I_2; xi, KOH; xii, Bu_3SnH, O_2; xiii, $Pd(OH)_2/C$, H_2

Scheme 8

As part of a synthesis directed towards tetrodotoxin, levoglucosenone has been converted to the intermediate **54** *via* the vinyl iodide **51**, which, after reduction of the ketone, was coupled with eneyne **55**. The product was protected and stannylated under Ni-catalysis to give **52**. Cope rearrangement then provided entry to the tricyclic skeleton of **53**, which was further elaborated into **54** (Scheme 9).[22]

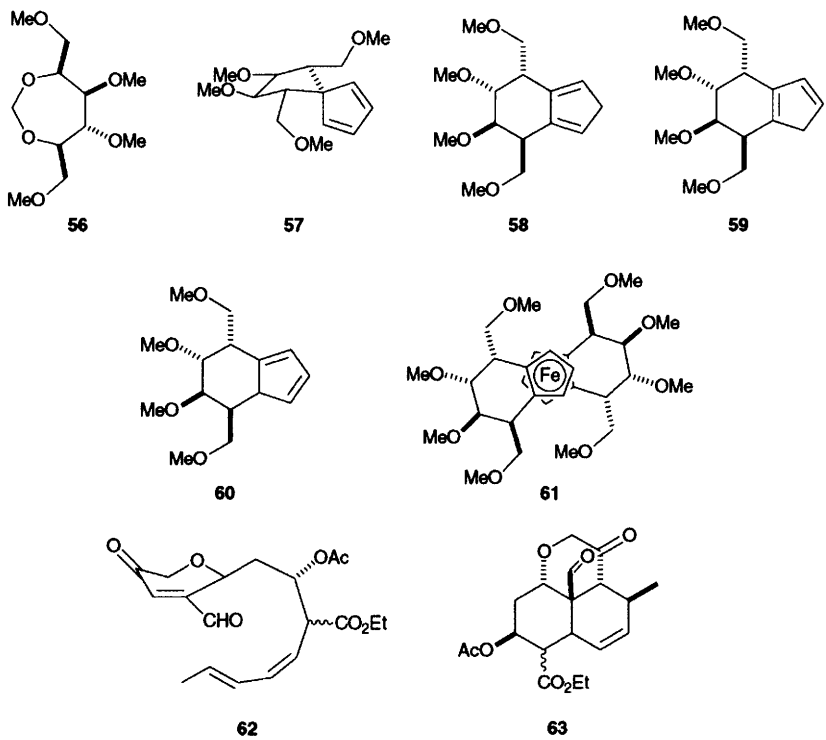
D-Mannitol-derived acetal **56** has been converted (HCl and then mesylation) into the *spiro*-cyclopentadiene **57** along with **58** and **59** (8:1:1). Thermolysis of **57** or the mixture of **57–59**, gave **58** and **59**, plus smaller amounts of the isomer **60**. On treatment of this mixture with ethylmagnesium bromide and iron(II) chloride the dimeric ferrocenyl product **61** was obtained.[23]

L-Rhamnal has been elaborated into the intramolecular Diels–Alder substrate **62**, which undergoes cycloaddition to give **63**, a precursor to the *trans*-decalin component of azadirachtin.[24]



Reagents: i, $NaBH_4$, $CeCl_3$; ii, **55**, $Pd(OAc)_2$, Ph_3P, CuI, *n*$BuNH_2$; iii, Ac_2O, Pyr; iv, Bu_3SnH, $NiCl_2(PPh_3)_2$; v, K_2CO_3, MeOH; vi, Δ, PhMe

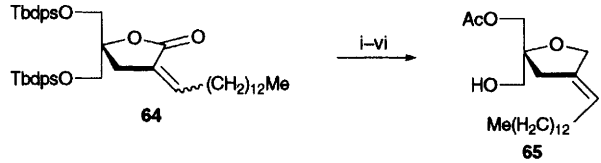
Scheme 9



2 Lactones

2.1 γ-Lactones. – The exocyclic alkene functionalized tetrahydrofuran **65** was made (as a conformationally restricted analogue of diacylglycerol) in six steps

from the known precursor lactone **64** (R. Sharma *et al.*, *J. Med. Chem.*, 1996, **39**, 29) (Scheme 10).[25]

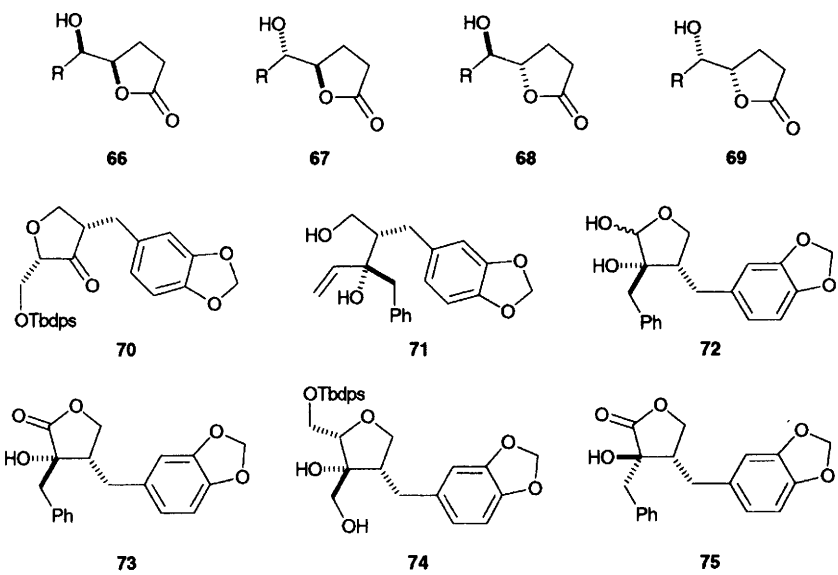


64 **65**

Reagents: i, DIBAL; ii, $HC(OMe)_3$, BF_3; iii, Et_3SiH, BF_3; iv, $HF.Et_3N$; v, Bu_2SnO; vi, CH_3COCl

Scheme 10

All four stereoisomers **66–69** of muricatacin have been prepared from D-glucose.[26] The lignan (2*S*,3*S*)-2-benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (**73**) has been prepared from L-arabinose-derived **70** *via* diol **71** and then, through its alkene cleavage, **72**.[27] In related work, the same group elaborated from L-arabinose-derived **74** into (2*R*,3*S*)-2-benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone **75** (in this case the phenyl group was introduced by $Ph_2CuCNLi_2$ ring opening of the intermediate *spiro*-epoxide precursor of **75**).[28]



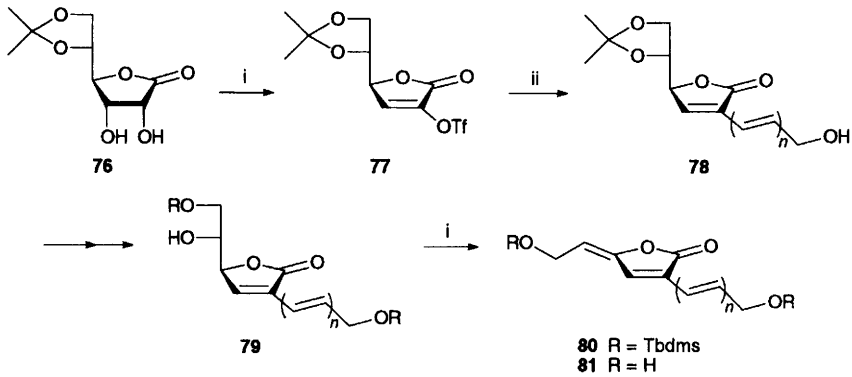
66 **67** **68** **69**

70 **71** **72**

73 **74** **75**

Lactone (**76**) has been converted into the chiral butenolides **79**. Key steps involve the conversion of the diol to vinyl triflate **77**, which then undergoes Stille coupling to introduce the critical new C–C bond of **78** [n = 1 or 2], then elaborated to **79** (Scheme 11).[29] (This chiral compound was also further elaborated – by elimination of a triflate derivative – to *achiral* **80** and **81**).

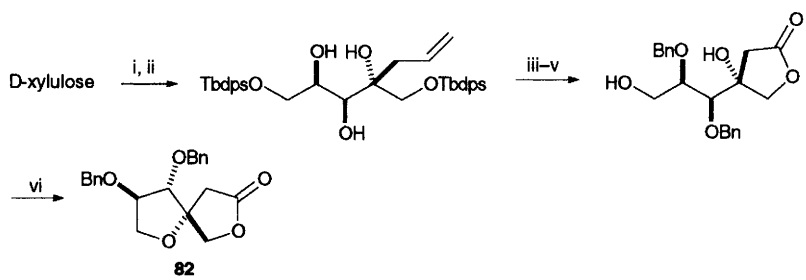
The known spirolactone **82** has been prepared from D-xylulose, by a sequence in which stereoselective indium-mediated carbonyl addition reaction plays a key role (Scheme 12). This group have used **82** to prepare syributins



Reagents: i, Tf_2O, Pyr; ii, $Bu_3Sn(CH{=}CH)_nCH_2OH$, $Pd_2dba_3.CHCl_3$, $AsPh_3$, LiCl

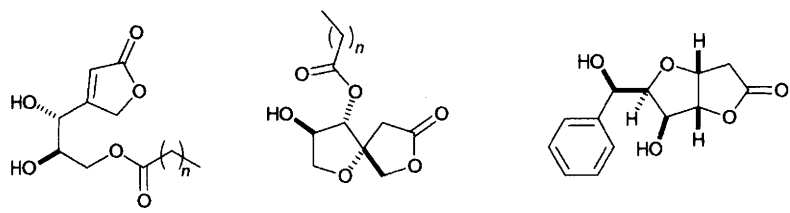
Scheme 11

and secosyrins **83** and **84**.[30] (+)-Goniofufurone (**85**) has been synthesized from D-glucurono-6,3-lactone by use of an indium-mediated regio- and diastereoselective allenylation.[31]



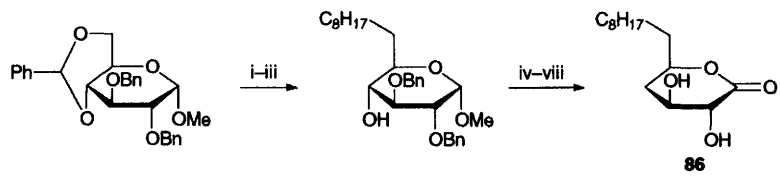
Reagents: i, TbdpsCl; ii, AllBr, In, aq. THF; iii, BnBr, NaH; iv, O_3, NaOH, MeOH; v, TBAF; vi, TsCl, Et_3, DMAP

Scheme 12



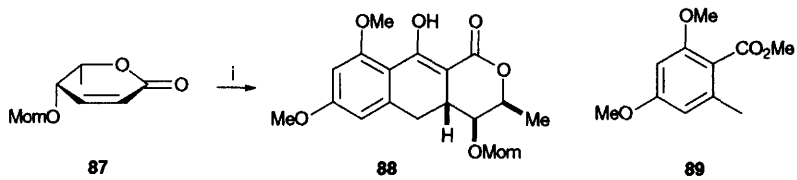
2.2 δ-Lactones. – The enantiomer **86** of a biologically active δ-lactone from *Seiridium unicome* has been prepared from D-glucose (Scheme 13).[32]

The lactone **88** has been prepared by a Michael-Dieckman sequence from the carbohydrate precursor **87** (Scheme 14). A biaryl dimer of **88** is bioxanthacene (–) ES-242-4, an antagonist of *N*-methyl-D-aspartate receptor.[33]



Reagents: i, TsOH, MeOH; ii, TsCl, Pyr; iii, nC$_8$H$_{17}$MgBr, CuI; iv, Ph$_3$P, CCl$_4$; v, Bu$_3$SnH, AIBN; vi, H$_2$SO$_4$, dioxane; vii, PDC; viii, H$_2$, Pd(OH)$_2$-C

Scheme 13



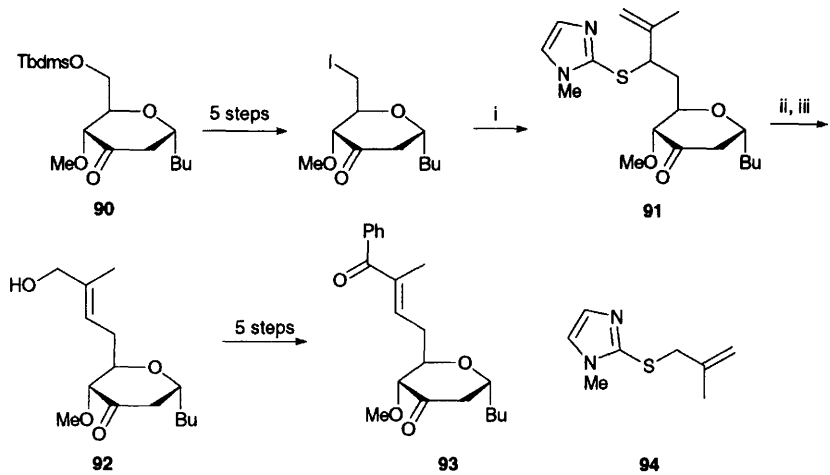
Reagents: i, LDA, **89**

Scheme 14

3 Macrolides, Macrocyclic Lactams and Their Constituent Segments

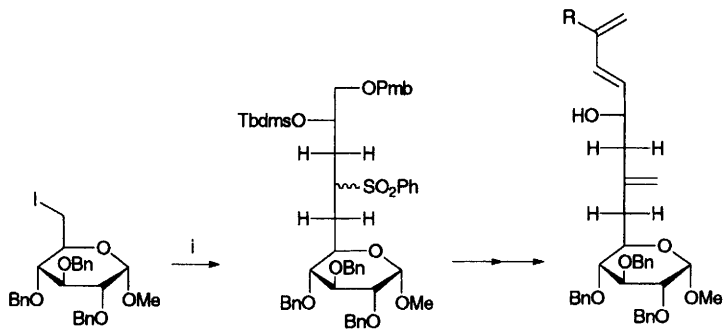
A review has appeared on use of main group organometallics in synthesis (reviewing July 1996–June 1997), in which a number of carbohydrate examples are described. Amongst these examples is a synthesis of an FK-506 intermediate, but also syntheses of *C*-glycosides, carbohydrate catalysts of diethyl zinc additions and allylindium additions to carbohydrates. The chemistry described is all covered in Volume 30 and this current volume.[34]

The homologated enone **93** (a component of maytansine) has been prepared from **90**, a known starting material derived from D-glucal. The key step in this synthesis involves the 2,3-sigmatropic rearrangement of the sulfoxide intermediate generated from **91**, and the resulting sulfenate ester being trapped by diethylamine, affording allylic alcohol **92** (Scheme 15).[35]



Reagents: i, nBuLi, **94**; ii, MCPBA; iii, Et$_2$NH

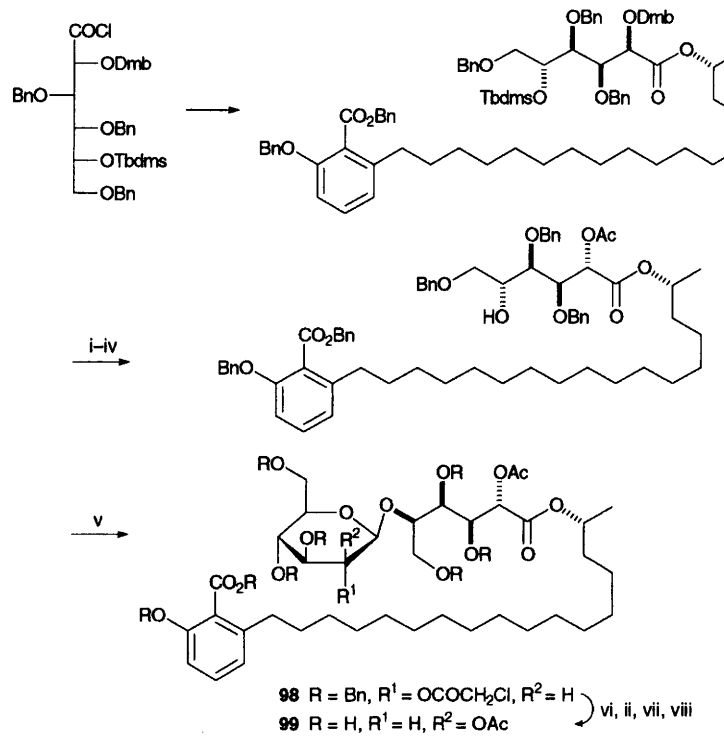
Scheme 15



95 **96** **97** (R = H or Cl)

Reagents: i, *n*BuLi, HMPA, $PhSO_2CH_2CH_2CH(OTbdms)CH_2OPmb$

Scheme 16



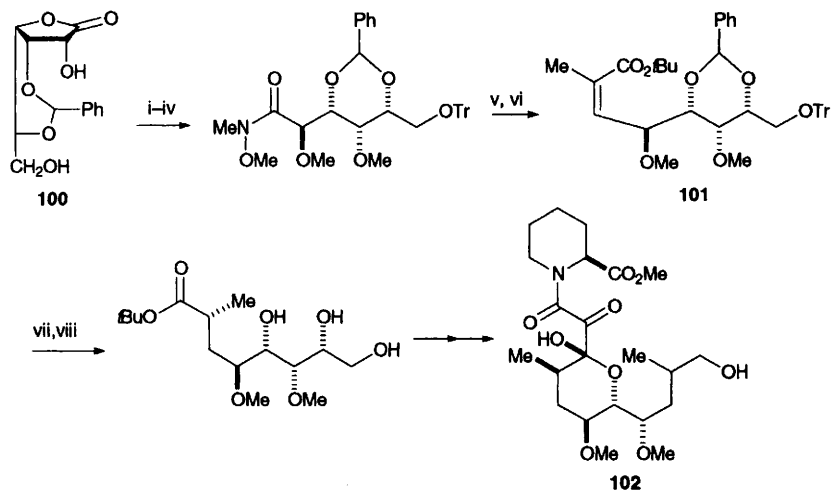
Reagents: i, DDQ; ii, Tf_2O, Pyr; iii, KOAc, DMF; iv, $BF_3.OEt_2$; v, Ag^+ on silica/alumina, 2-*O*-chloroacetyl-3,4,6-tri-*O*-benzyl-a-D-glucosyl bromide; vi, NH_2CSNH_2; vii, *t*-Bu_4NOAc; viii, H_2, Pd-C, MeOH, HOAc

Scheme 17

The chain extended system **97** is a model of the spongistatins (marine antitumour agents) showing *in vitro* anticancer activity, and has been prepared from the D-glucose derivative **95** *via* sulfonate **96** (Scheme 16).[36]

A total synthesis of the fungal metabolite caloporoside **99** (an inhibitor of phospholipase C), which contains a carbohydrate ring and an adjoining acyclic section that is also carbohydrate-derived in this synthesis has been reported (Scheme 17). A key step involves initial attachment of a 2-chloroacetyl glucoside (giving **98**) which undergoes subsequent inversion (after selective deprotection of O-2) at C-2 by OAc displacement of triflate, to construct the requisite 2-*O*-acetylmannoside **99**.[37]

The C-10–C-17 segment of FK-506 (**102**) has been prepared starting from 3,5-*O*-benzylidene-D-gulonolactone (**100**), by a method involving a key diastereoselective hydrogenation of deprotected **101** (Scheme 18).[38]



Reagents: i, TrCl, Et_3N; ii, $AlMe_3$; iii, MeONHMe; iv, MeI, Ag_2O; v, $LiHAl(OEt)_3$; vi, $Ph_3P{=}C(Me)CO_2t\text{-}Bu$; vii, TFA, viii, H_2, $Pd(OH)_2$

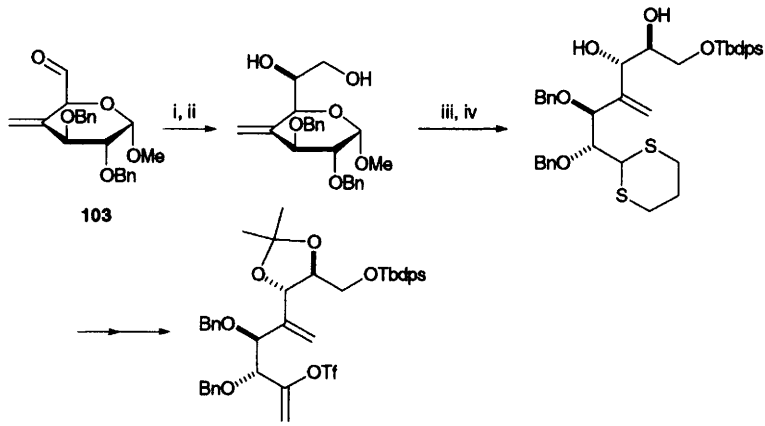
Scheme 18

The vinyl triflate **104**, a component required for preparation of the marine metabolite amphidinolide A1, has been prepared from **103** (Scheme 19).[39]

A component **105** of the macrocyclic lactone scytophycin C (from a terrestrial blue-green algae) has been prepared from tri-*O*-acetyl-D-glucal in a number of steps.[40]

4 Other Oxygen Heterocycles, Including Polyether Ionophores

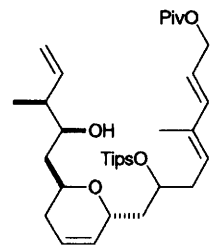
4.1 Three-membered *O*-Heterocycles. – A review has appeared describing the synthesis of thromboxane compounds from carbohydrate starting materials (52 refs).[41]



103 **104**

Reagents: i, $PhSCH_2SiMe_2CH_2MgCl$; ii, H_2O_2, SeO_2, K_2CO_3; iii, TbdpsCl, Et_3N; iv, $HS(CH_2)_3SH$, $BF_2.OEt_2$

Scheme 19



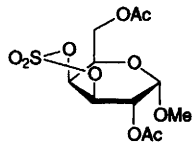
105

The epoxide **107** was prepared from the precursor sulfate **106** (see Chapter 11 for synthesis of this material) by treatment with lithium or sodium cyanide in DMF or acetone. The epoxides **108** and **109** (prepared from precursor diols *via* naphthyl sulfonate derivatives conversion to chloride and cyclization by treatment with sodium methoxide) were converted into the four-membered heterocycles **110** and **111** by reaction with Me_3SOI and potassium butoxide in *tert*-butanol (the diastereoisomeric epoxide was also similarly elaborated).[42] See also Chapter 5 on anhydrosugars.

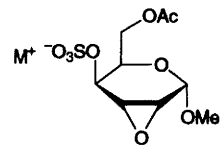
The diastereoisomeric epoxides **114** and **113** (1:3) were obtained from *m*-CPBA oxidation of **112**. Epoxide **114** was then further elaborated by standard means to **115**, an intermediate for acetogenin synthesis (**113** was similarly elaborated to the diastereomer of **115**) (Scheme 20).[43]

4.2 Four-membered *O*-Heterocycles. – The four-membered system **119** was prepared through Paterno-Büchi reaction of L-ascorbic acid derivatives **116**, which gave the lactone regioisomers **117** and **118**.[44] Reduction of **117** gave **119** and treatment of **119** with sulfuric acid afforded the acyclic ketone **120**.

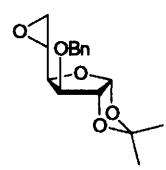
Paquette's group prepared **125** (to probe charge accelerated oxy-Cope rearrangements), converted to **126** by rearrangement of the intermediate **126a**.



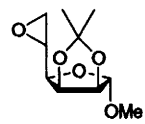
106



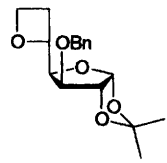
107 M = Na, Li



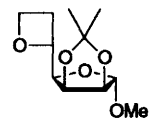
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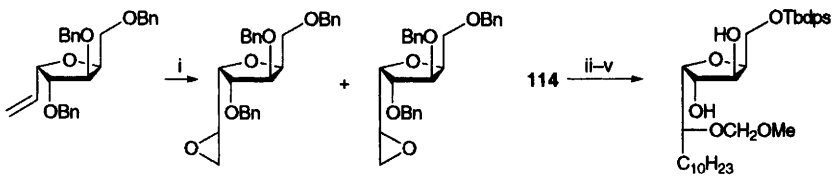
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110



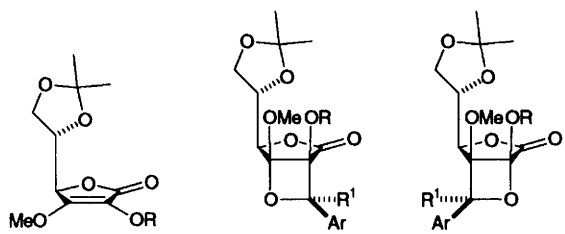
111



112 **113** **114** **115**

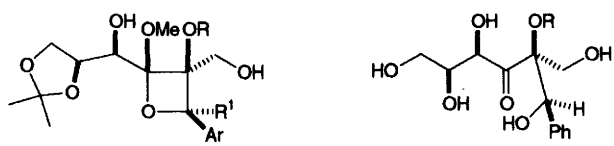
Reagents: i, MCPBA; ii, $LiCCC_7H_{15}$; iii, $MeOCH_2Cl$, $i\text{-}Pr_2NEt$; iv, H_2, Pd/C; v, TbdpsCl, Im, DMF

Scheme 20



116 **117** **118**

R = Me, Bn; R^1 = Ph, H;
Ar = Ph, 4-Cl-C_6H_4, 4-MeO-C_6H_4

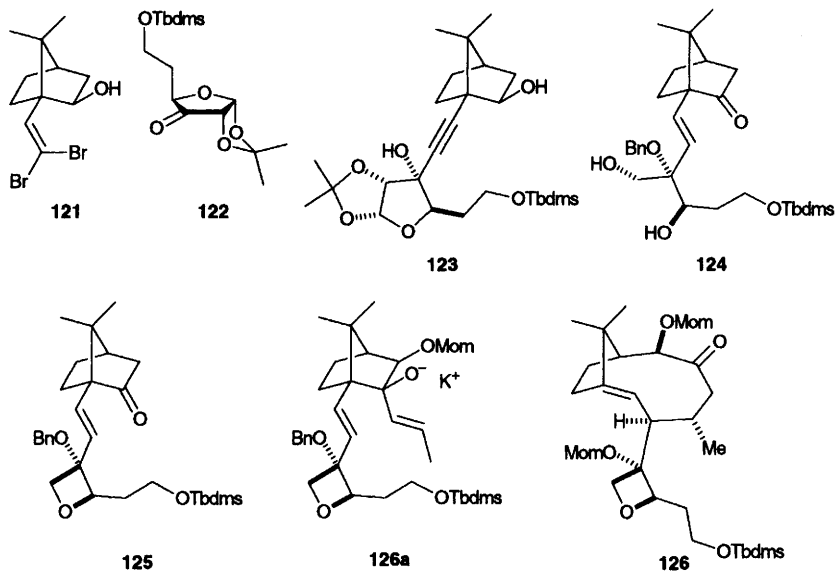


119 **120**

R = Me, Bn, Ar = Ph, R^1 = H

The intermediate lithium acetylide from **121** adds to D-glucose derivative **122** to give **123**, which was elaborated to **124** (*via* LAH reduction of the propargylic alcohol, silylation of the primary alcohol, Dess-Martin oxidation, benzylation, removal of the acetal with titanium tetrachloride, a further Dess-Martin oxidation and then a selective sodium borohydride reduction). Treatment of

124 with KHMDS and *N*-(5-chloro-2-pyridyl)triflimide generated the heterocycle **125**. The ketone function was α-hydroxylated by treatment of the silyl enol ether derivative with Oxone® (and TBAF work-up), the hydroxyl was protected as its Mom ether, and the ketone reacted with (*E*)-crotyl bromide and *t*-BuLi. Finally, treatment with KH generated intermediate potassium alkoxide **126a**, which rearranged to **126**.[45]



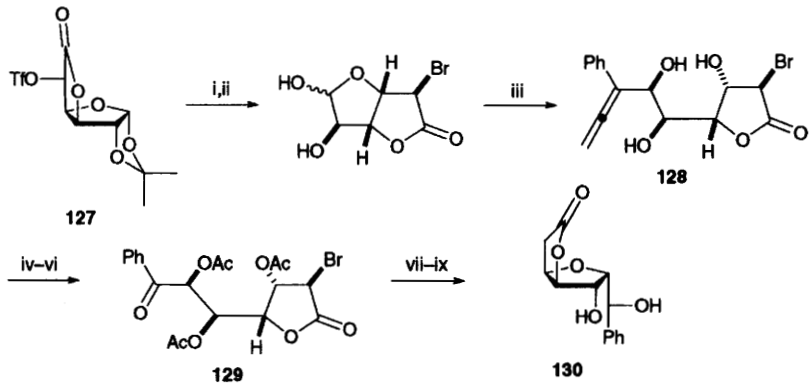
4.3 Five-membered O-Heterocycles. – A stereospecific synthesis of (+)-*epi*-muscarine from D-glucose employs the stereospecific cyclization of the 3,5-di-*O*-tosylate and selective hydrogenation of an unsaturated 2,5-anhydro-L-idose intermediate as key steps.[46]

A total synthesis of (+)-goniofurfurone **130** from glucoronolactone derivative **127**. Key steps involve the formation of allene intermediate **128** and the diastereoselective reduction of the resultant ketone from allene ozonolysis leading to **129** (Scheme 21).[47]

4.4 Six-membered O-heterocycles. – *4.4.1 Monocyclics.* The branched 6-amino-4,6-deoxyheptopyranuronic acid **132**, a component of amiparimycin, has been synthesized starting from the serine-derived oxazolidine aldehyde **131** (both enantiomers prepared) and a carbohydrate precursor.[48]

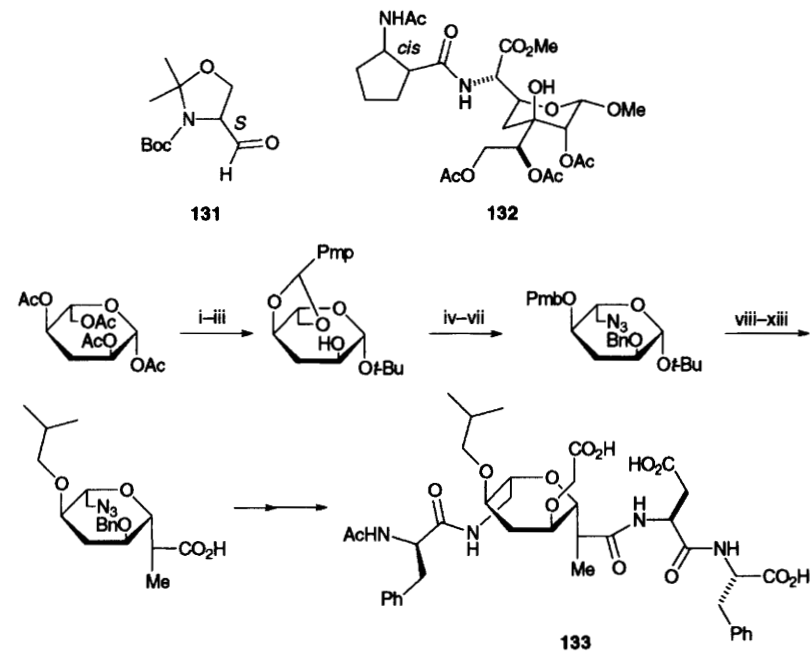
The peptidic system **133** has been prepared (as an inhibitor of mammalian ribonucleotide reductase) in a multi-step synthesis. Key steps include a Wittig homologation of the anomeric carbon to provide the acid functionalilty for a dipeptide attachment, and elaboration of C-6 to an amino-containing function for attachment of the other amino acid unit (Scheme 22).[49]

Intramolecular nitrone cycloaddition chemistry has been applied to the synthesis of bridged oxepanes or fused tetrahydropyrans. 3-*O*-Allyl-D-glucose



Reagents: i, LiBr, Me_2CO; ii, CF_3CO_2H, H_2O; iii, $PhCCCH_2Br$, HCl; iv, O_3, MeOH, Me_2S; v, $NaBH_4$; vi, H_2SO_4, Ac_2O; vii, $NaHSO_3$, $Na_2S_2O_3$; viii, HCl, MeOH

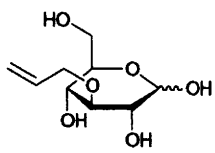
Scheme 21



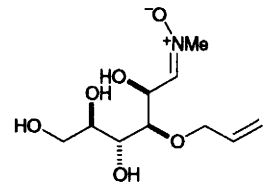
Reagents: i, HBr, Ag_2O, *t*-BuOH; ii, NaOMe; iii, *p*-methoxybenzaldehyde dimethylacetal, H^+; iv, BnBr, NaH; v, DIBAL; vi, MsCl; vii, NaN_3; viii, DDQ; ix, NaH, Me_2CHCH_2Br; x, AcOH, H_2O; xi, $Ph_3P{=}C(Me)CO_2Et$; xii, NaOMe; xiii, LiOH

Scheme 22

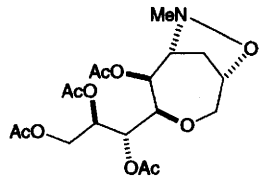
(**134**) is converted into oxepane **136** in 53% yield *via* intermediate **135** (MeNHOH.HCl then acetic anhydride and pyridine), whilst the analogous D-allose allyl ether provides tetrahydropyran **137** (plus the epimer at the starred position). Other sugars evaluated were altrose (2,3-*threo*) which affords oxepane product, and mannose (2,3-*erythro*), providing tetrahydropyran.[50]



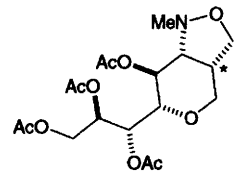
134



135

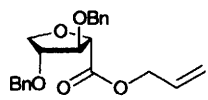


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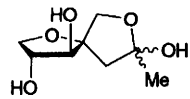


137

4.4.2 Spiro- and Bridged Systems. Spirocyclic ether **139** has been synthesized from 2,5-anhydro-D-lyxonic acid ester-derivative (**138**) by orthoester Claisen rearrangement (giving *S* configuration at new quaternary centre), ester reduction, silylation, exchange of benzyl for acyl protecting groups, then Wacker type oxidation and methoxide-mediated cyclization.[51]



138

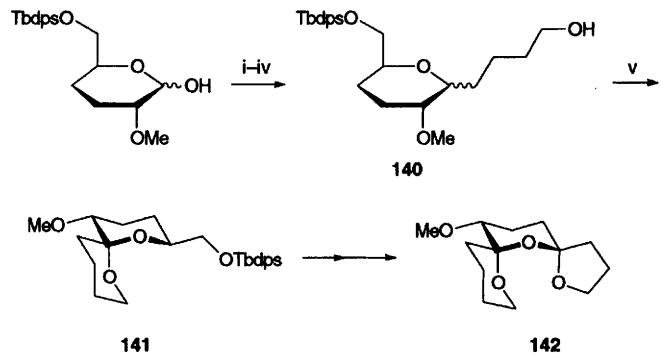


139

D-Galactose is the starting material for a synthesis of the chiral dispiroacetal **142** (other related compounds also prepared) *via* the key hypervalent iodine oxidant-mediated (under photolytic conditions) conversion of *C*-glycoside **140** into spirocyclic **141** and enantiomer [1.4:1] (Scheme 23).[52] The C-1–C-14 spiroacetal segment of spongistatins **146** has been prepared from tri-*O*-acetyl-D-glucal, which was converted into the known (*Tetrahedron Lett.*, 1988, **29**, 1255) epoxide **143** in six steps, then elaborated into both **144** and **145**. All the chiral centres are carbohydrate-derived (Scheme 24).[53]

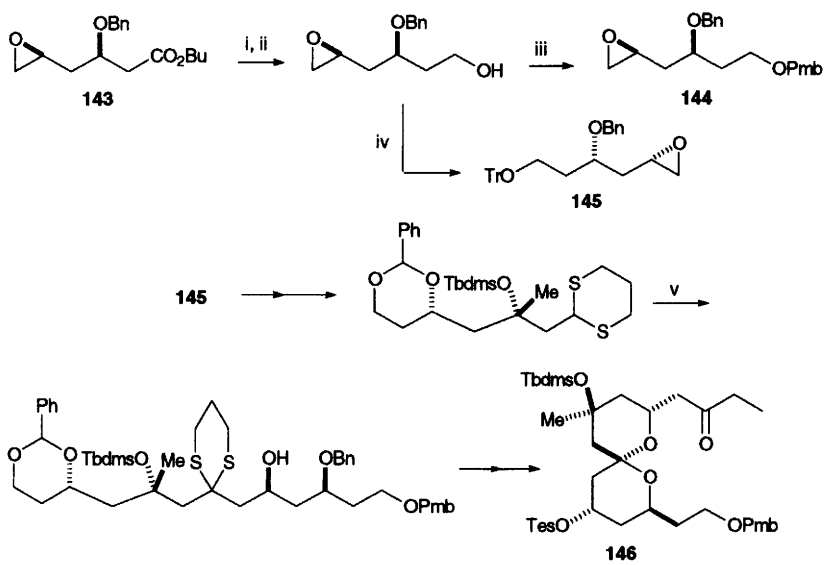
Once again, the squalestatin/zaragozic acid ring system has attracted synthetic attention this year with two syntheses being reported of the core bicyclic system from carbohydrate starting materials. The first of these commences with the known (*Tetrahedron Lett.*, 1994, **35**, 2241; *Aust. J. Chem.*, 1994, **47**, 1537) furanoside **147**, which undergoes Ireland-Claisen rearrangement, esterification and reduction to afford **148**. The second key quaternary centre is introduced through addition of an organometallic reagent to lactone **149**, acid-catalyzed isopropylidene acetal cleavage concomintantly affords the bridged acetal core ring system, final steps being oxidation and esterification to afford **150** (Scheme 25).[54]

The second approach provides a synthesis of core analogue **154** from another known (*J. Org. Chem.*, 1989, **54**, 4100) furanosyl compound **151**. The



Reagents: i, Ph_3P, CCl_4; ii, $H_2C{=}CH(CH_2)_3MgBr$; iii, O_3; iv, $NaBH_4$; v, $PhI(OAc)_2$, I_2, *hν*

Scheme 23

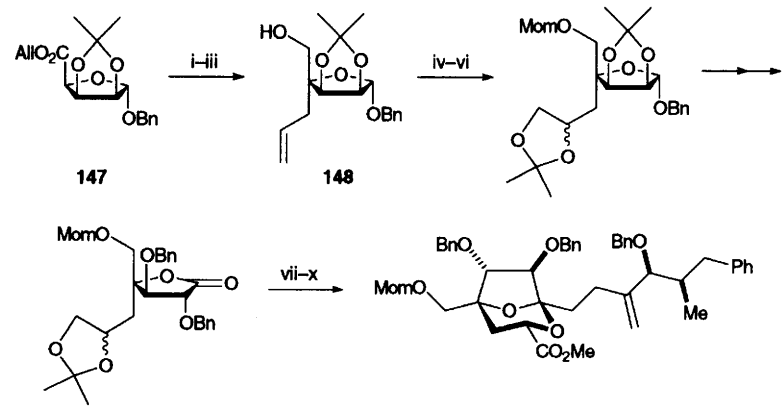


Reagents: i, DIBAL; ii, $NaBH_4$; iii, PmbOH, DIAD, Bu_3P; iv, TrCl, Et_3N; v, BuLi, HMPA then **144**

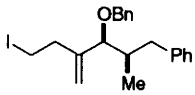
Scheme 24

(first) quaternary centre (the second one is actually not present in this core analogue) is introduced through a stereocontrolled (4:1) ester enolate aldol reaction to give **152**. The epimeric mixture was separated two steps later (**153**) after ester reduction and alcohol benzylation (Scheme 26).[55]

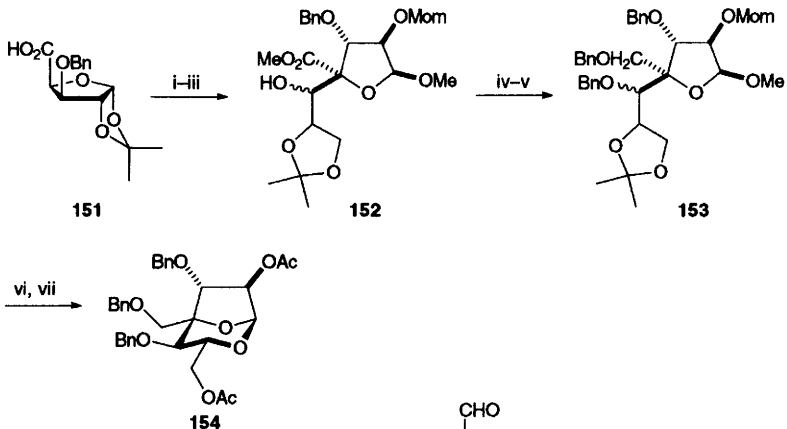
*4.4.3 Fused Polycyclics.*A considerable number of carbohydrate-based syntheses of polyether fragments have been reported this year. The C-15–C-38 fragment of okadaic acid has been prepared from methyl 3-*O*-benzyl-4,6-benzylidene-D-glucoside, *via* *C*-allyl glucoside **155** which was elaborated in 4 steps into aldehyde **156** (R = Tbdms) (4,6-protection, *O*-2 silylation with

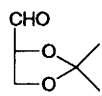


Reagents: i, LDA, TmsCl; ii, NaOH, CH_2N_2; iii, $LiAlH_4$; iv, MomCl, *i*-Pr_2NEt;
v, OsO_4, $K_3Fe(CN)_6$; vi, $(MeO)_2CMe_2$, PPTS; vii, 2 eq. BuLi;
viii, HCl, MeOH; ix, Dess-Martin periodinane;
x, $NaClO_2$, CH_2N_2



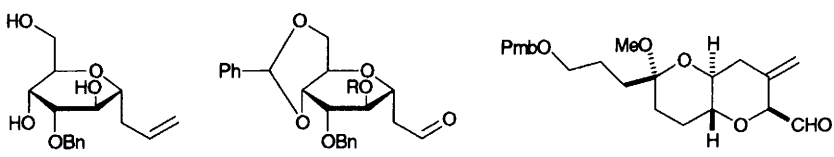
Scheme 25



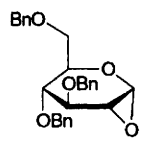
Reagents: i, MeOH, H^+; ii, MomCl; iii, KHMDS, $CeCl_3$  ; iv, $LiAlH_4$; v, NaH, BnBr;
vi, Dowex 50W, MeCN; vii, Ac_2O, Py

Scheme 26

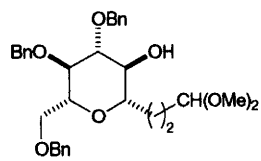
TbdmsOTf, then hydroboration and Swern oxidation) and thence to the C-16–C-27 fragment **157** and ultimately the larger C-15–C-38 fragment.[56]



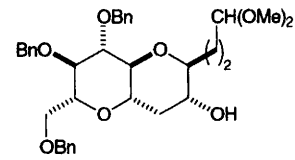
The glucal epoxide **158** (from dioxirane oxidation of the glycal; with 6:1 selectivity) undergoes ring opening with $BrMg(CH_2)_2CH(OMe)_2$ to the *C*-glucoside **159**. PPTS-catalysed reaction gives a new bicyclic enol ether, which is then used as a substrate for a further round of dioxirane epoxidation and ring opening with Wittig reagent, to give **160** and **161** in a 1:2 ratio. The stereochemistry of **160** is appropriate for polyether antibiotics and was itself then further elaborated through a further cyclization to a tricyclic system **162**. The same chemistry was used to make the 6,7-ring system **163**.[57] An analogous ring opening of the same epoxide (**158**) using allyl magnesium bromide was effected, and after acylation and ester olefination (CH_2Br_2, Zn, $TiCl_4$, $PbCl_2$), olefin metathesis chemistry of intermediate **164** (R = H, Me) was used to generate **165**, and thence on to ring system **166** (note that for R = H, **166** is the same as **162**).[58]



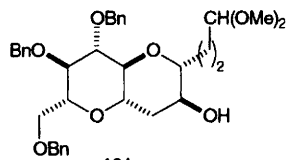
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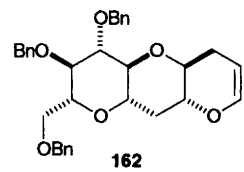
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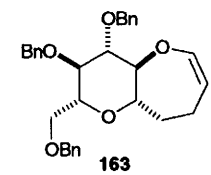
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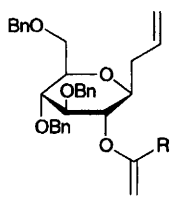
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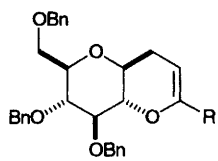
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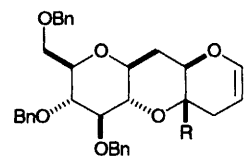
163



164

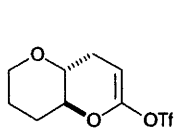


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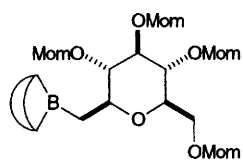


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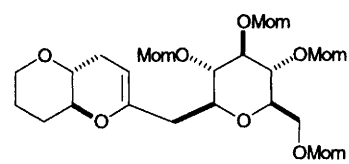
Suzuki coupling (using Pd(0), aq. Cs_2CO_3, Ph_3As) of enol ether vinyl triflate **167** and carbohydrate-derived borane **168** (from olefination of a sugar-lactone precursor with Cp_2TiMe_2 then hydroboration with 9-BBN) has been developed for polyether synthesis, providing the intermediate **169** (set up for closure of a fourth ring).[59]



167

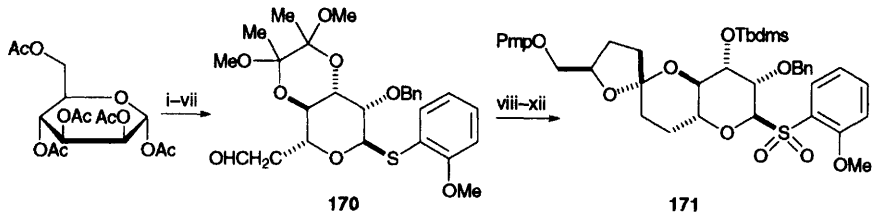


168



169

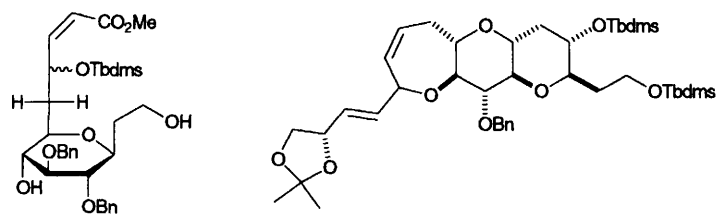
The intermediate **171**, one of three components for total synthesis of protein phosphatase inhibitor okadaic acid, has been prepared in twelve steps from pentaacetyl-α-D-mannose. The synthesis employs the *trans*-3,4-diol protection system, along with a series of standard elaborations to generate **170**. This undergoes a Horner-Emmons type reaction, and the intermediate olefin undergoes acid-catalyzed cyclization with the sugar-derived 4-OH to give (after silylation and sulfur oxidation) **171** (Scheme 27).[60]



Reagents: i, 2-methoxythiophenol, BF_3; ii, K_2CO_3, MeOH; iii, MeC(O)C(O)Me, $(MeO)_3CH$, CSA; iv, BnBr, NaH; v, Tf_2O, Et_3N; vi, NaCN, DMF; vii, DIBAL; viii, LDA, PmpO–⟨O⟩–$P(O)Ph_2$; ix, KO*t*-Bu; x, TFA; xi, TbdpsCl, Imid; xii, MCPBA

Scheme 27

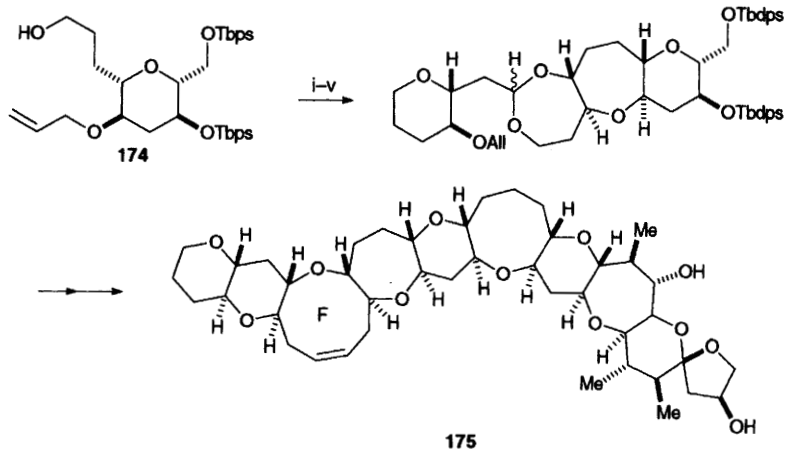
A full report of the synthesis of the ABC ring system of ciguatoxin has appeared, which involves 17 steps to convert D-glucose into **172** and then by further elaborations into the ABC ring system **173**.[61]



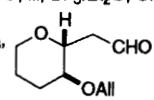
An approach to the F–M ring fragment (**175**) of ciguatoxin has been reported from the glucose-derived intermediate **174** (Scheme 28). The synthesis involves a 20-step elaboration of **174** followed by convergency with a J–M ring fragment and a further 10 subsequent steps to yield **175**.[62]

D-Mannose is the starting carbohydrate material in a 56-step synthesis of hemibrevetoxin B. The sugar derivative **176** was elaborated through intermediates **177**, **178** and **179**.[63] Another synthesis of hemibrevetoxin proceeded from **180** to give intermediate **181** in 25 steps (Scheme 29).[64]

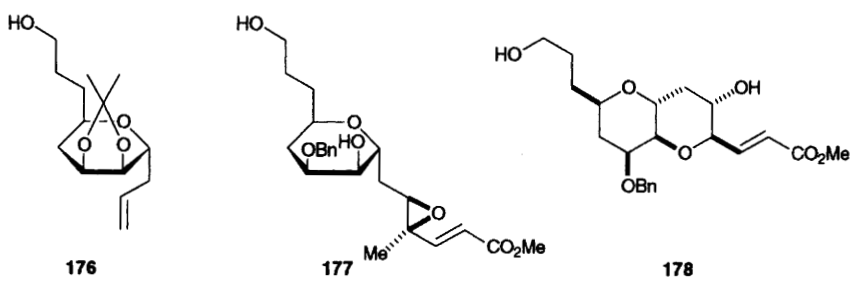
Diastereomers of the biaryl system ES-242-4 (**183**) have been prepared (as a mixture of both atropisomers) from **182**, using copper chloride mediated Ullman type coupling (Scheme 30).[65]

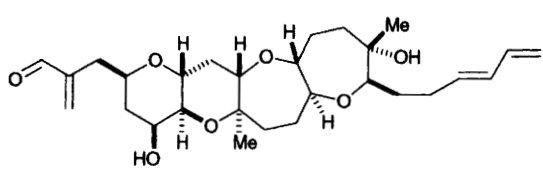


Reagents: i, *s*-BuLi, *n*-Bu_3SnCl; ii, SO_3.Py, Et_3N, DMSO; iii, $BF_3.Et_2O$, CH_2Cl_2; iv, 9-BBN then H_2O_2, $NaHCO_3$; v, $Sc(OTf)_3$,



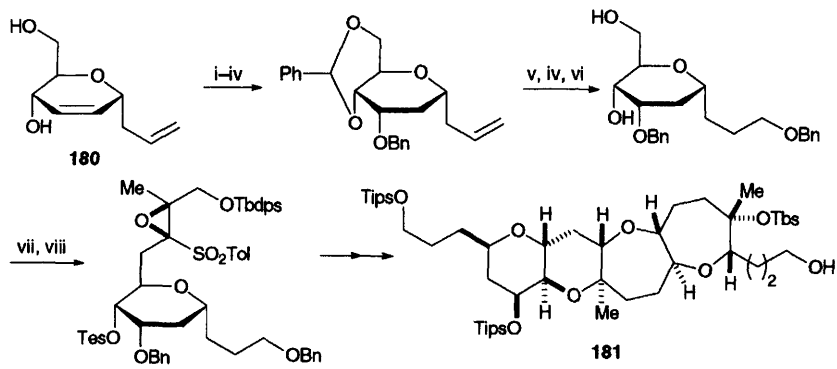
Scheme 28

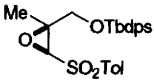




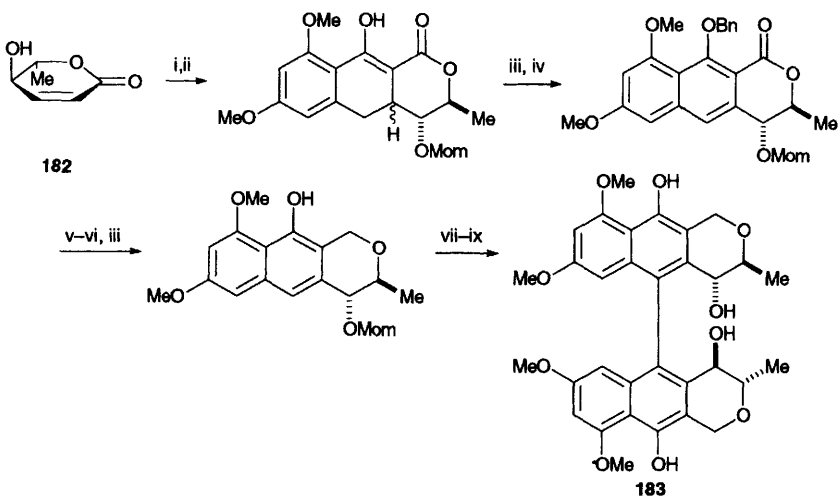
4.5 Seven-membered and Larger O-Heterocycles. – Chiral oxazepine **184** has been synthesized from D-xylose *via* Wittig homologation, *O*-allylation and a final metathesis reaction to construct the ring (Scheme 31).[66] Full details have appeared (Vol. 28, Chapter 24, p. 362, ref. 62) of the synthesis of medium sized (7–10 membered) oxygen heterocycles **185** from C-1-alkynylated-D-glucals *via* dicobalthexacarbonyl complexes, cyclization and decomplexation.[67]

Macrocyclic ethers **186** have been prepared from methyl 6-*O*-benzyl-2,3-diprotected-α-D-glucosides (Scheme 32).[68]



Reagents: i, MCPBA; ii, $PhCH(OMe)_2$, H^+; iii, $LiAlH_4$; iv, BnBr, NaH; v, 9-BBN then H_2O_2, NaOH; vi, HCl, H_2O; vii, TesOTf, Tf_2O; viii, BuLi, HMPA, 

Scheme 29



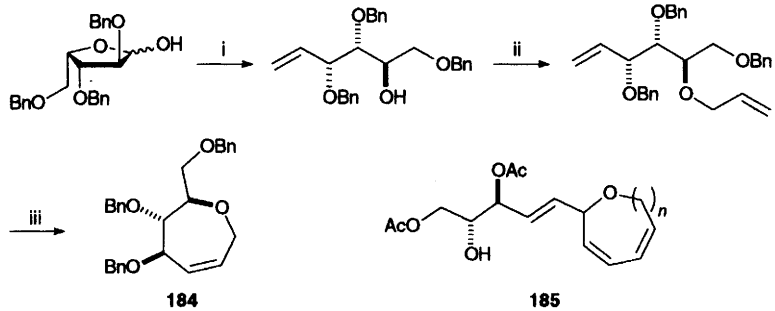
Reagents: i, $(MeO)_2CH_2$, P_2O_5; ii, methyl 2,4-dimethoxy-6-methyl benzoate; iii, Pd/C,cyclohexene; iv, BnBr, K_2CO_3; v, DIBAL; vi, Et_3SiH, TFA; vii, $CuCl_2$, O_2; viii, NaOH; ix, HCl

Scheme 30

5 N- and S-Heterocycles

A review has appeared covering syntheses of saturated nitrogen heterocycles published during 1997, which includes a number of examples of syntheses of systems from carbohydrate starting materials.[69]

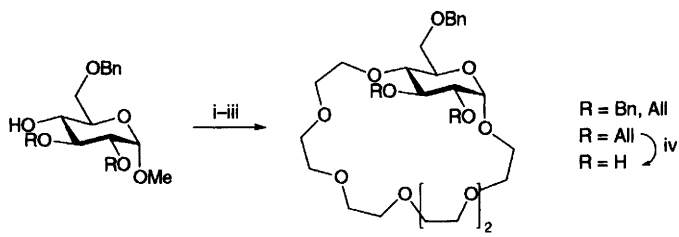
D-Glucono-1,5-lactone or D-manno-1,4-lactone have been converted into the aziridine **187** (2,2-dimethoxypropane/acetone/MsOH; MsCl/Py; then conc. aq. ammonia). The same reaction sequence applied to **189** leads to azidine **190**.



184 **185**

Reagents: i, $Ph_3P^+MeBr^-$, *n*-BuLi; ii, $CH_2{=}CHCH_2Br$, NaH; iii, $Cl_2[P(C_6H_{11})_3]Ru{=}CHPh$, catalyst

Scheme 31



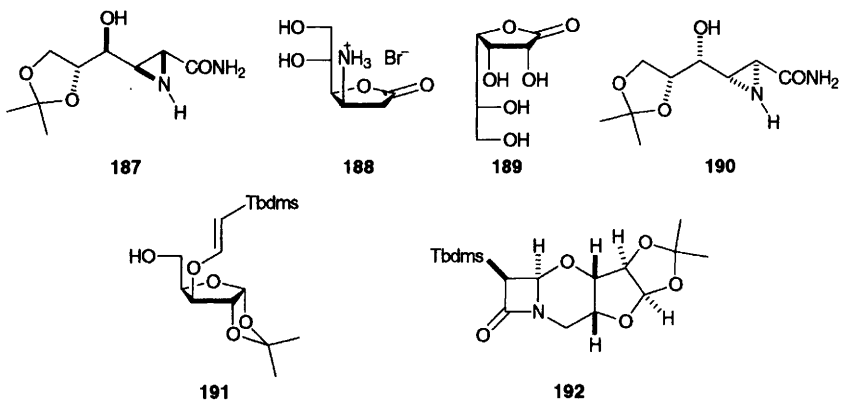
186

Reagents: i, $[Cl(CH_2)_2]_2O$, KOH, H_2O, TBAHS; ii, $O(CH_2CH_2OCH_2CH_2OH)_2$, KOH; iii, TMSOTf, MeCN, KBF_4; iv, Pd/C, TsOH, MeOH, H_2O, reflux

Scheme 32

Treatment of **187** with hydrazine, then aq. TFA and finally bromine converted it into **188**.[70] The azetidinone **192** has been prepared from 1,2-*O*-isopropylidine-3-*O*-(2′-silylvinyl)-5-*O*-trityl-α-xylofuranose (**191**) by [2+2] cycloaddition with chlorosulfonyl isocyanate, followed by bond formation between the azetidinone nitrogen and C-5 of the sugar.[71]

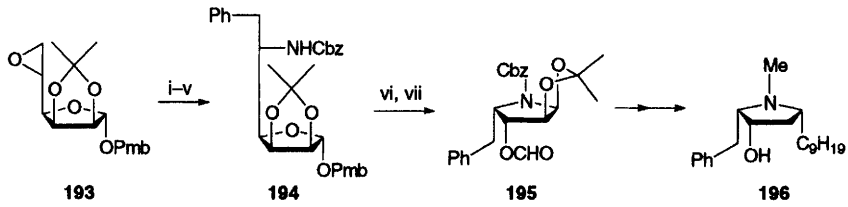
A synthesis of (+)-preussin (**196**) has been reported from carbohydrate-



187 **188** **189** **190**

191 **192**

derived **193**. The key heterocyclization step involves conversion of **194** into **195** (Scheme 33).[72]

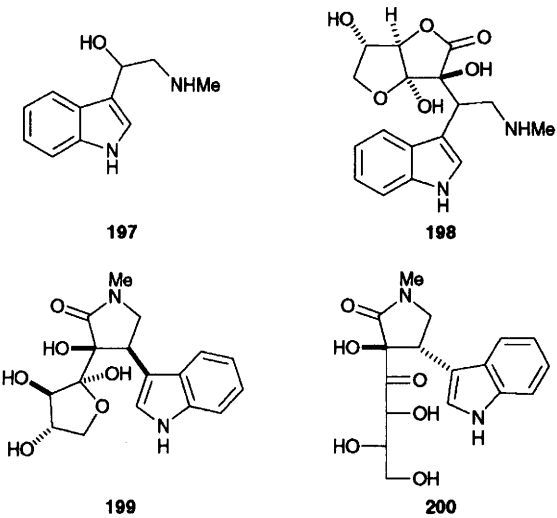


193 **194** **195** **196**

Reagents: i, PhMgCl, CuI; ii, Tf_2O, Py; iii, NaN_3, DMF; iv, $LiAlH_4$; v, $ClCO_2Bn$, Py; vi, DDQ; vii, PhIO, I_2

Scheme 33

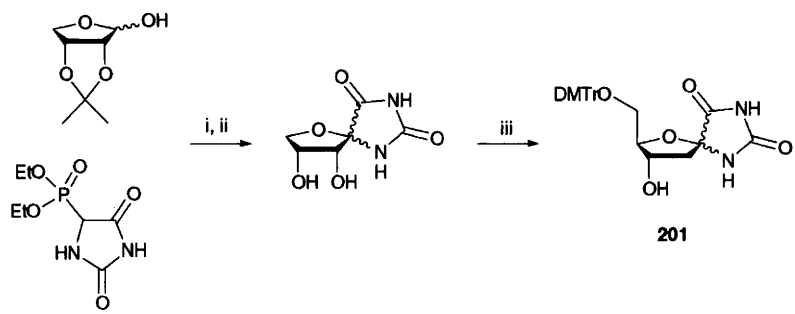
Reaction of ascorbic acid with **197** gives a mixture of **199** and **200**, *via* the intermediate **198**.[73]



197 **198**

199 **200**

A synthesis of deoxyhydantoin derivative **201** from 2,3-*O*-isopropylidine-D-erythrose is outlined in Scheme 34, the unusual rearrangement process followed by tritylation at the furanoid ring oxygen position.[74]

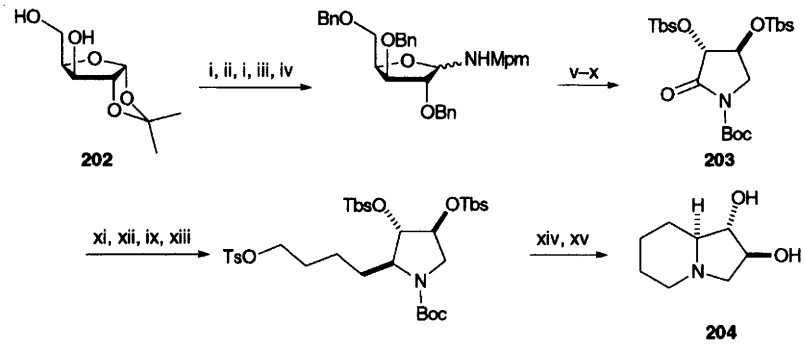


201

Reagents: i, EtONa; ii, TFA, H_2O then Et_3N; iii, DMTrCl, Py

Scheme 34

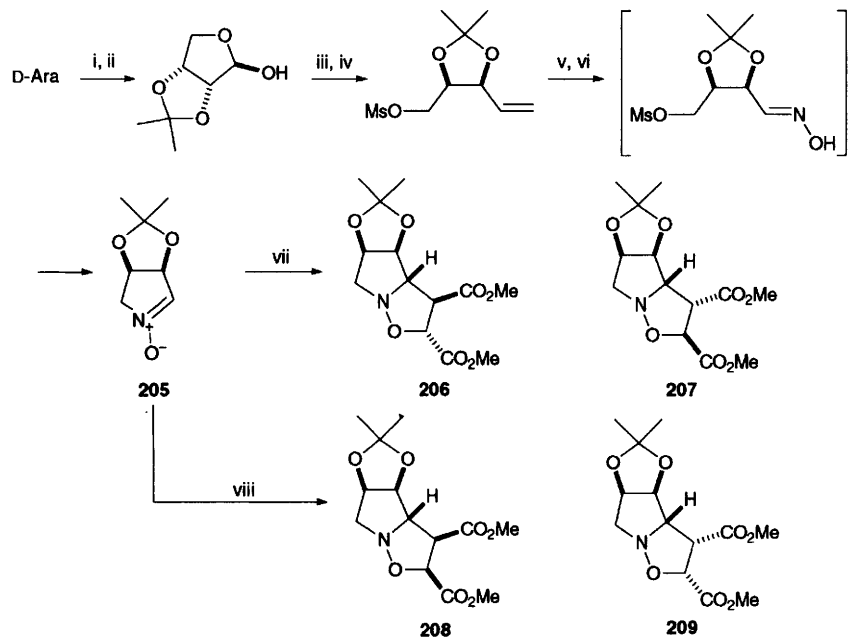
Lentiginosine (**204**) has been synthesized in 17 steps from **202**. Key steps include the Grignard alkylation of lactam intermediate **203** followed by dehydroxylation with triethylsilane, boron trifluoride, and the ultimate formation of the piperidine ring through *N*-alkylation using the side-chain tosylate (Scheme 35).[75]



Reagents: i, NaH, BnBr; ii, c. HCl, MeOH; iii, 80% AcOH; iv, $MpmNH_2$; v, LAH; vi, PCC; vii, CAN, MeCN, H_2O; viii, $(Boc)_2O$, DMAP; ix, Pd black, HCO_2H, MeOH; x, TbsCl. ImH; xi, $BnO(CH_2)_4MgBr$; xii, Et_3SiH, $BF_3.OEt_2$; xiii, TsCl, Py; xiv, $BF_3.OEt_2$; xv, KOH, MeOH

Scheme 35

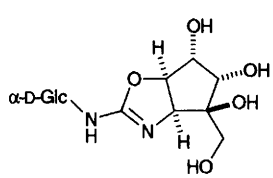
D-Arabinose was the starting material in the synthesis of four cycloadducts **206**–**209**, through key 1,3-dipolar additions to sugar-derived **205** (dimethyl maleate gives one pair of isomers and dimethyl fumarate the other pair) (Scheme 36).[76]



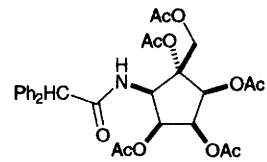
Reagents: i, TsOH, 2,2-dimethoxypropane, DMF; ii, $NaIO_4$ then $NaHCO_3$; iii, $Ph_3P{=}CH_2$; iv, MsCl; v, O_3 then DMS; vi, $NH_2OH.HCl$, $NaHCO_3$, MeOH, H_2O; vii, dimethyl fumarate; viii, dimethyl maleate

Scheme 36

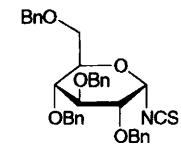
A total synthesis of (+)-trehazolin and (+)-6-epitrehazolin (**210**) has been developed by the use of the reaction of cyclopentane **211** (from 3-benzyloxymethylcyclopentadiene) and the carbohydrate isothiocyanate **212**.[77] The known *bis*-mesylates **213** (R = Pr, Bu and others) from D-mannitol have been converted into the sugar dipoles **214**, and used for the synthesis of systems such as **215**.[78]



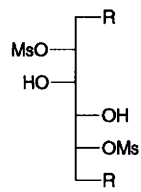
210



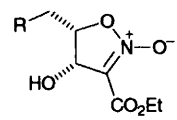
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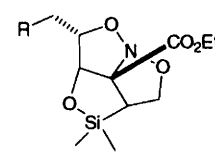
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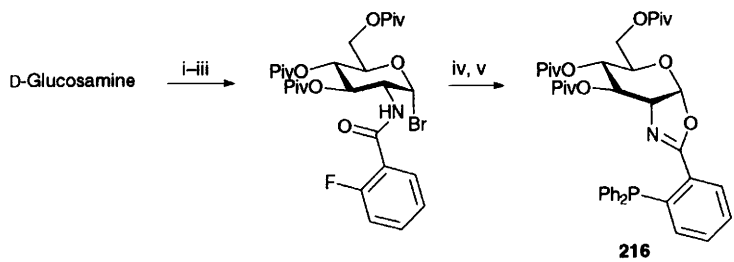


214



215

Glucosamine has been converted into the oxazole **216** (Scheme 37) which has been evaluated as a chiral ligand (see Section 7).[79]



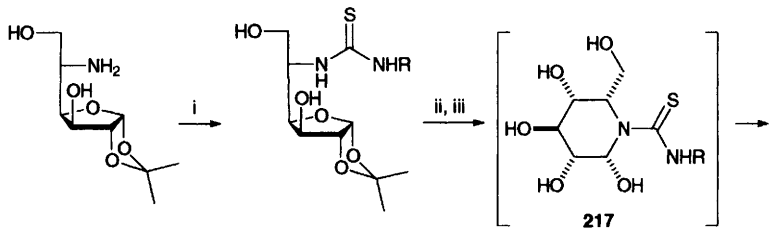
216

Reagents: i, o-F-BzCl, $NaHCO_3$; ii, PivCl, Py; iii, HBr, AcOH; iv, Et_4NBr, Na_2CO_3, MeCN; v, $KPPh_2$

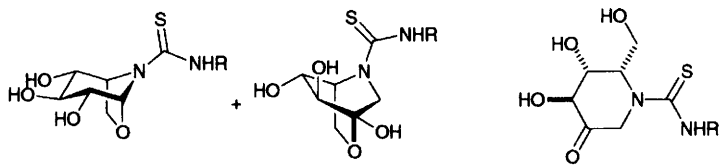
Scheme 37

The bicyclic system **218** has been prepared from carbohydrate materials, and is related to calystegine B_2 (a plant secondary metabolite). The bicyclization proceeds through monocyclic intermediate **217**, with alternate cyclization generating the major product **218**, or the minor product **219** followed by alternative ring close onto the ketone of intermediate **220** (Scheme 38).[80]

Ring closing metathesis has been applied to syntheses of pyrrolizidine and quinolizidine systems **223** and **225**. Sugar-derived **221** was converted to **222** which underwent ring closing metathesis to yield **223**, whilst analogous six-membered system **224** gave **225** (Scheme 39).[81]



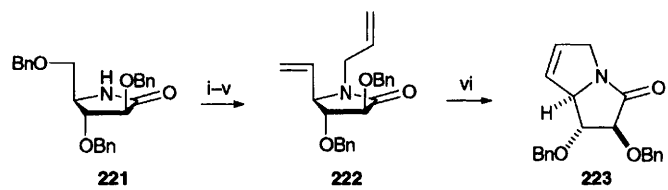
R = Me, Ph, β-D-Glc, 2,3,4,6-pentaacetyl-β-D-Glc



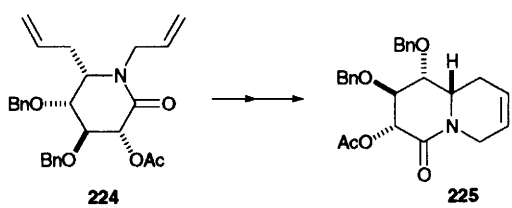
218 **219** **220**

Reagents: i, RNCS, Py, Et_3N; ii, 9:1 TFA/H_2O; iii, Amberlite IRA-68

Scheme 38



221 **222** **223**



224 **225**

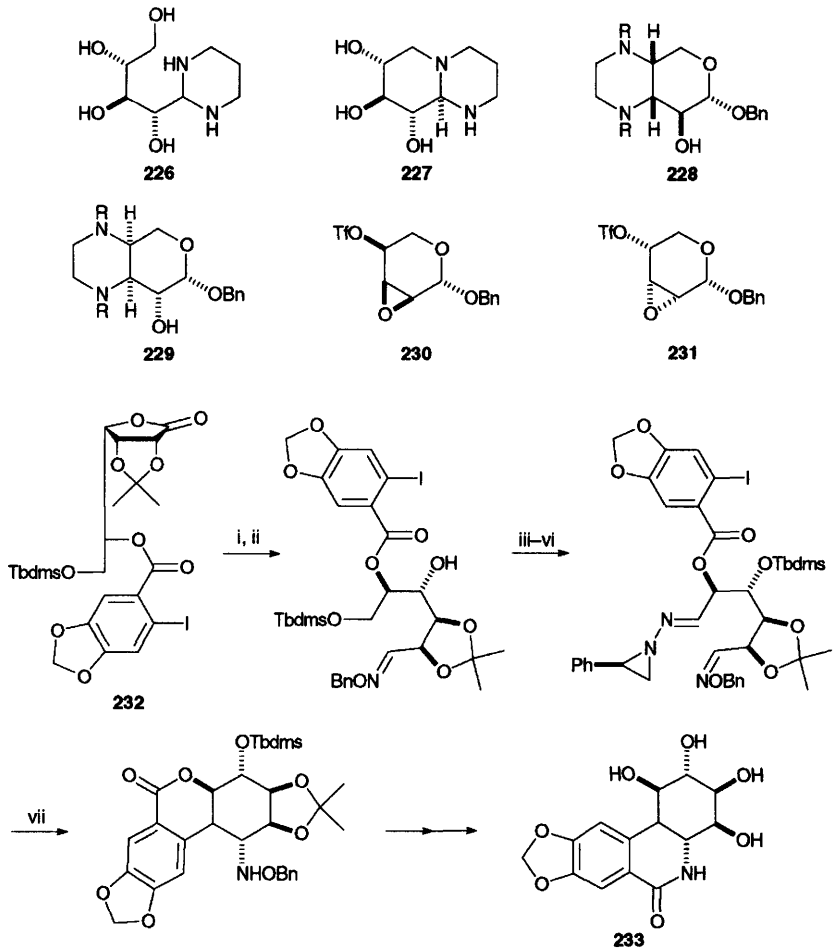
Reagents: i, allyl bromide, KOH; ii, $FeCl_3$, Ac_2O; iii, NH_3, MeOH; iv, periodinane; v, Ph_3PMeBr, KHMDS; vi, $Cl_2Ru(PCy_3)(=CH-CH=CPh_2)$, PhH, Δ

Scheme 39

D-Xylose-derived aminal **226** underwent Mitsunobu-type reaction (triphenylphosphine in carbon tetrachloride) to yield the bicyclic aza-sugar system **227**,[82] while chiral bicyclic piperazines **228** and **229** were obtained from reaction of sugar-derived epoxides **230** and **231**, respectively, with 1,2-diaminoethane or appropriate *N,N*-dialkylated derivatives (R = H, Me, Et, Bn, Ph).[83]

An improved synthesis of deoxypancratistatin (**233**) from the sugar-derived intermediate **232** has been reported. A radical tandem reaction sets up the ring system (Scheme 40).[84]

Ascorbic acid-derived **234** has been converted into ribosyl diazepinone **238**, the core ring system of the liposidomycins. The convergent synthesis utilizes



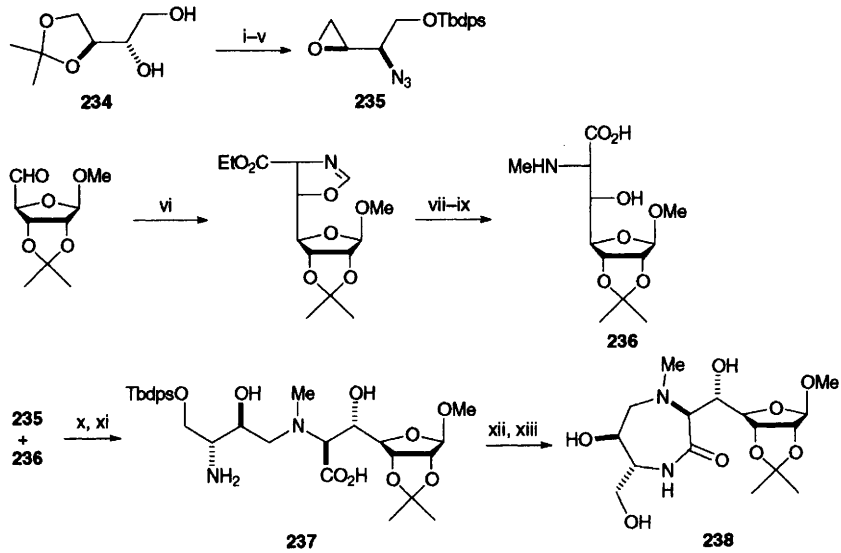
Scheme 40

ring opening of epoxide **235** with sugar-amine **236** and a penultimate step involving the DCC-mediated lactamization of **237** (Scheme 41).[85]

The cyclic sulfonate ester **239** was prepared as a conformationally constrained analogue of diacylglycerol (Scheme 42).[86]

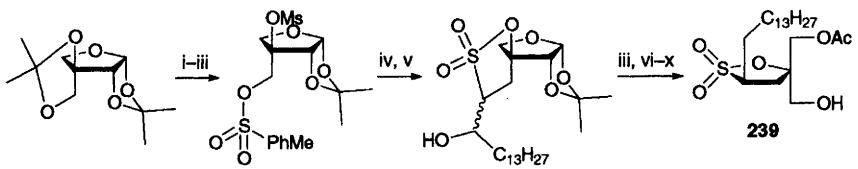
6 Acyclic Compounds

3,4-Isopropylidene-D-mannitol has been converted into (3*R*,4*R*)-hexane-3,4-diol by conversion into 1,2,5,6-tetratosyl mannitol (**240**) (TsCl, Py then $CuCl_2.2H_2O$, MeCN) and reduction of this with lithium aluminium hydride.[87] D-Mannitol was also the starting material for synthesis of the β-*N*,*N*-dialkyl-



Reagents: i, TbdpsCl. ImH; ii, Tf_2O, lutidine; iii, NaN_3; iv, TFA, H_2O; v, Ph_3P, DIAD; vi, $CNCH_2CO_2Et$, Et_3N; vii, Me_3OBF_4; viii, $NaHCO_3$, H_2O; ix, KOH, H_2O; x, NaH; xi, Pd/C; xii, DCC; xiii, Bu_4NF

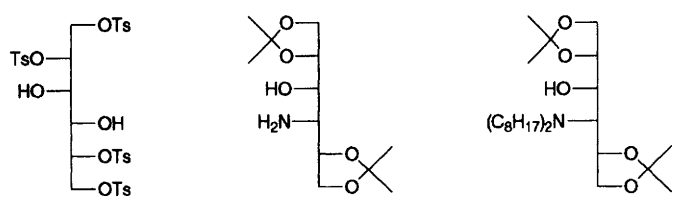
Scheme 41



Reagents: i, AcOH, H_2O; ii, $MePhSO_2Cl$, Py; iii, MsCl, base; iv, HCCLi, DMSO; v, BuLi,$Me(CH_2)_{12}CHO$; vi, DBU; vii, H^+; viii, $NaIO_4$; ix, $NaBH_4$; x, Ac_2O. DMAP, Py

Scheme 42

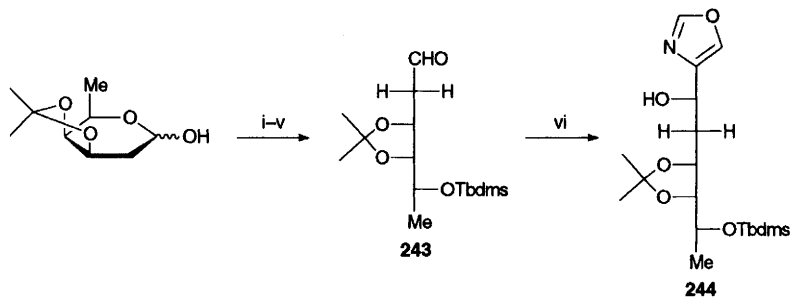
aminoalcohol **242** (used as a chiral catalyst – see Section 7) *via* **241** (B. Kim and K.B. Sharpless, *Tetrahedron Lett.*, 1989, **30**, 655).[88]



240 **241** **242**

Oxazole **244** (and diastereomer), an advanced intermediate towards synthesis of Bengazole A (a marine sponge antifungal), has been synthesized in six

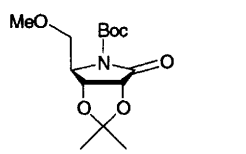
steps, with introduction of the heterocycle by addition of its 2-lithio derivative to aldehyde **243** (Scheme 43).[89]

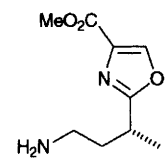


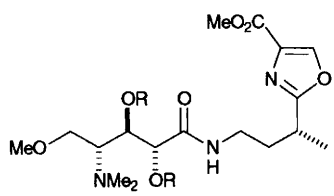
Reagents: i, Li, NH_3; ii, PivCl, DMAP; iii, TbdmsCl, ImH; iv, LiOH; v, DMSO, $(COCl)_2$, Et_3N; vi, 2-lithiooxazole

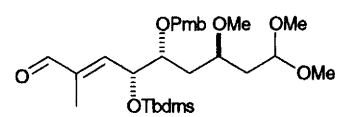
Scheme 43

A total synthesis of protein phosphatase inhibtiors (+)-calyculin A and B utlilizes the intermediate **247**, which is obtained from elaboration of the product of coupling **245** and **246**.[90] D-Xylose has been used as the starting material for a synthesis of the aldehyde **248**, which is an intermediate in the synthesis of the C-31–C-46 side-chain unit of the marine natural product phorboxazole A.[91]



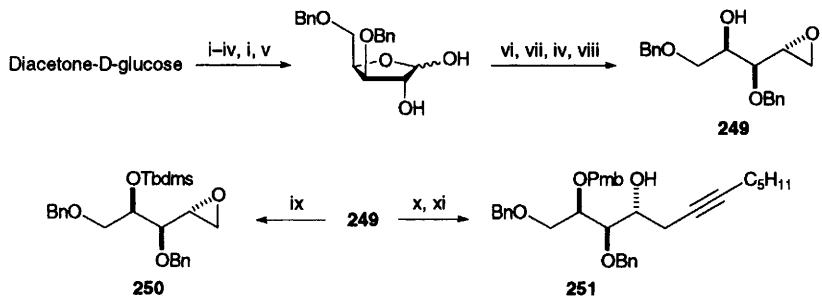






Sphingosines continue to be targets for carbohydrate-based synthesis. Diacetone-D-glucose has been elaborated into the sphingosine precursors/analogues **251** and **250** *via* the common epoxide intermediate **249** (Scheme 44).[92]

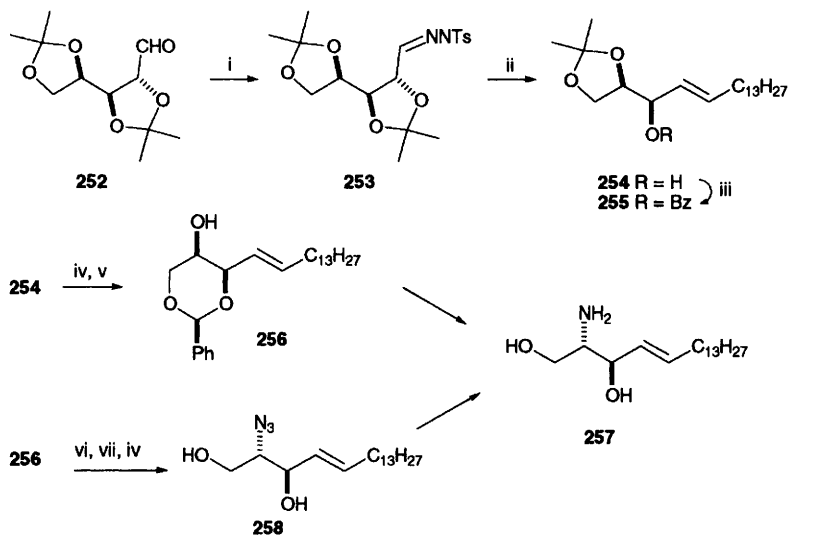
D-Xylose was the starting material for synthesis of D-(+)-*erythro*-sphingosine (**257**) *via* the known intermediate **252**. Two approaches diverge from intermediate **254** and **255**, one proceeding *via* known precursor **256** and the other *via* known precursor **258**. Conversion of both **256** and **258** into **257** has been described previously (R.R. Schmidt and P. Zimmermann, *Tetrahedron Lett.*,



Reagents: i, NaH, BnBr; ii, H_2SO_4, H_2O-MeOH; iii, $NaIO_4$, $NaHCO_3$, H_2O; iv, $NaBH_4$; v, Amberlyst 15, MeOH, r.t.; vi, TsCl, Py; vii, CF_3CO_2H, TFA-H_2O; viii, K_2CO_3, MeOH; ix, TbdmsCl, ImH; x, NaH, PmbCl; xi, *n*-BuLi, heptyne, $BF_3.OEt_2$

Scheme 44

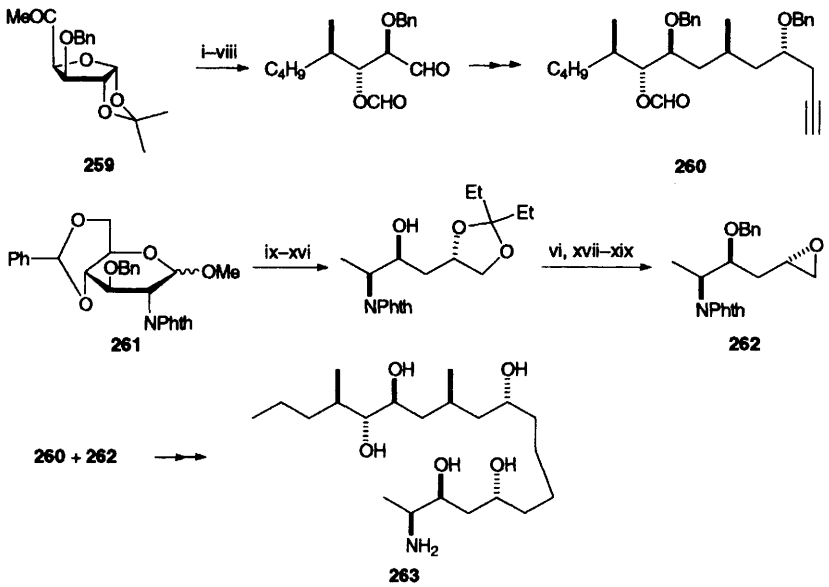
1986, **27**, 481). The addition–fragmentation reaction of hydrazone **253** is a key step (Scheme 45).[93]



Reagents: i, $TsNNH_2$, MeOH; ii, $C_{13}H_{27}MgBr$; iii, BzCN, Et_3N; iv, TsOH, MeOH; v, TsOH, $PhCH(OMe)_2$; vi, MsCl, Py; vii, NaN_3, DMF

Scheme 45

Fumonisin B_1-AP (**263**) (a cancer producing toxin from plant pathogens in corn), has been synthesized in a convergent synthesis from glucose and glucosamine. Thus, glucose-derived **259** was elaborated into section **260**, and galactosamine-derived **261** was converted into section **262**. Ring opening of the epoxide of **262** with acetylide of **260** and subsequent reduction thus afforded the target system (Scheme 46).[94]



Reagents: i, $BuPPh_3^+Br^-$, base; ii, H_2, Pd–C; iii, Ca, l. NH_3; iv, $(COCl)_2$, DMSO; v, $NaBH_4$; vi, NaH, BnBr; vii, H_2SO_4, AcOH, H_2O; viii, $NaIO_4$; ix, H^+; x, TbdmsCl, ImH; xi, NaH, CS_2, MeI; xii, Bu_3SnH, AIBN; xiii, MeOH, TsOH; xiv, $HSCH_2CH_2SH$, BF_3; xv, Ni (Ra); xvi, EtCOEt, H^+; xvii, MeOH, H^+; xviii, TsCl, Py; xix, NaH

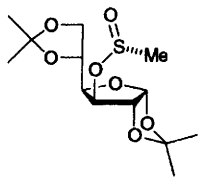
Scheme 46

Multiply labelled syringolide 2 (a microbial elicitor) has been synthesized from D-xylulose.[95]

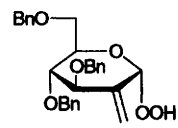
7 Carbohydrates as Chiral Auxiliaries, Reagents and Catalysts

7.1. Carbohydrate-derived Reagents and Auxiliaries. – The use of disposable tethers in organic chemistry, of which carbohydrate examples include sigmatropic rearrangements, radical cyclization (silicon-tethered units, either or both of which are sugars) and related glycosylation cyclizations utilizing a tether between donor and acceptor sugars has been reviewed.[96] Another review includes examples of sugar-based reagents (*e.g.* **264**) used as sources of chiral sulfoxide units, and carbohydrate peroxides (*e.g.* **265**) employed as chiral oxidants for Lewis acid-catalyzed oxidation of sulfides to sulfoxides.[97] A further review covering 1995–1996 literature discusses alkylations of the enolate of **266** the sugar unit of which was used as a chiral auxiliary.[98]

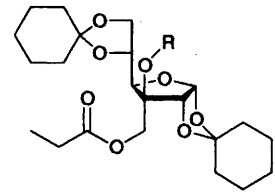
The individual diastereomeric 1-α-(2,2-dibromo-1-methylcyclopropylcarbinyl)-2,3,4,6-tetra-*O*-methyl-D-glucopyranosides have been prepared and applied to synthesis of enantiomeric 2,2-dibromo-1-hydroxymethyl-1-methylcyclopropane.[3]



264

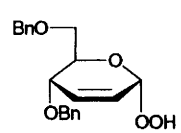


265

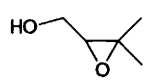


266 R = H, Tms

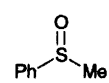
The carbohydrate-derived hydroperoxide **267** (from the precursor ethyl glycoside by reaction with hydrogen peroxide and molybdenum trioxide) effects asymmetric epoxidations and sulfoxidations, affording epoxide **268** with 55% e.e. and chiral sulfoxide **269** with 18% e.e [both (+) rotations].[99] The sugar-derived reagent **270** effects cyclopropanation with Lewis acid catalysis (Et_2AlCl) of simple *trans* alkenes such as *trans*-methylstyrene in 51% e.e.[100] The 1,3-oxazin-2-one **271** (obtained in four steps from D-fructose) has been used as an auxiliary in aldol, Diels-Alder and α-bromination reactions of groups attached to the nitrogen atom.[101] A study of the enantioselectivity of Grignard and allyltin additions to the aldehyde **272** has been undertaken.[102] The *O*-allyl glycoside **273** reacts with *s*-Buli then Et_3Al to give an organometallic reagent able to add to benzaldehyde with good diastereoselectivity affording 94% of **274** (where R* = the auxiliary component from **273**).[103]



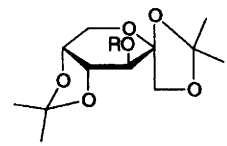
267



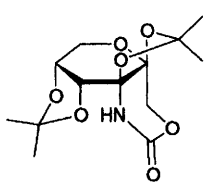
268



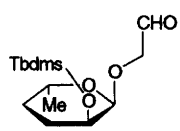
269



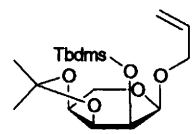
270 R = $ZnCH_2I$



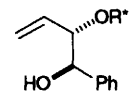
271



272



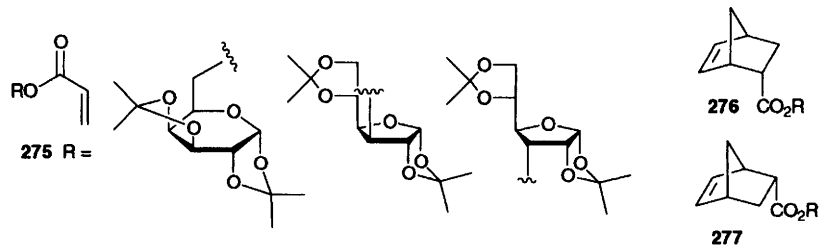
273



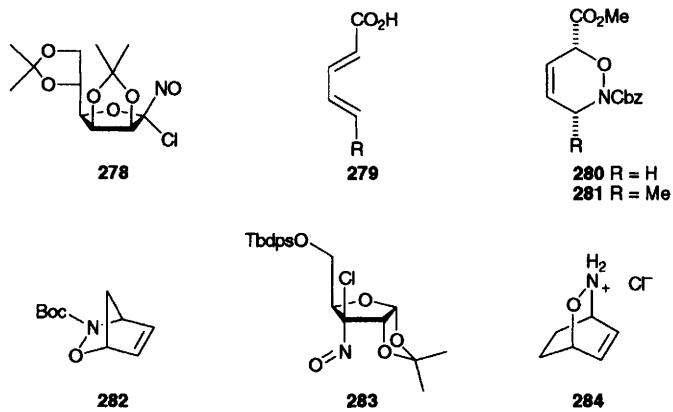
274

The use of carbohydrate auxiliaries targeted at the control of stereoselective cycloadditions has again provided some useful examples this year. Sugar acrylates **275** react with cyclopentadiene under Lewis acid catalysis (Et_2AlCl, $SnCl_4$, $MgBr_2$) to give good *endo*/*exo* ratios (98:2), but modest facial selectivity (*ca.* 60%) to afford mixtures of **276** and **277**.[104]

Several examples of the use of chloronitroso sugars in hetero-Diels-Alder reactions have been described this year. The carbohydrate dienophile **278** reacted with dienes **279** (R = H,Me) to give the adducts **280** or **281** (after esterification and *N*-protection) with good enantioselectivity (See Vol. 30, Chapter 24, ref. 104 for preliminary work). These were elaborated to chiral δ-lactams (see Chapter 16).[105] The chloronitroso sugar **278** undergoes diastereo-



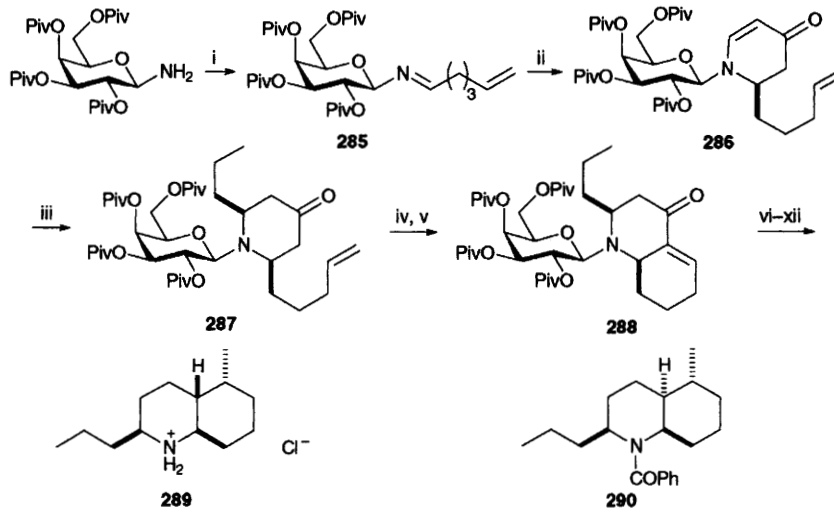
selective hetero-Diels-Alder reaction (Lewis acid-catalysed) with cyclopentadiene to give (after *N*-cleavage and protection) **282**, an intermediate, *via* reductive ring opening (sodium borohydride, molybdenum hexacarbonyl), for carbocyclic nucleoside precursors (See Chapter 18).[106] Chloronitroso sugar **283** undergoes cycloaddition with cyclohexadiene, to afford, after auxiliary cleavage, **284** in 96% e.e., plus recovered ketone precursor to **283**.[107]



Kunz's group have reported another application of imine derivatives of glycosyl amines. Thus, imine **285** reacted with Danishefsky's diene to yield the anticipated **286** (>40:1 d.e.). This then underwent copper conjugate addition to give **287** (>10:1 d.e.). Oxidative cleavage of the remaining alkene and intramolecular aldol condensation afforded **288**, which was then a substrate for a second conjugate addition which proceeded to give a 15:1:0:0 mixture of diastereomers. Removal of the auxiliary, *N*-protection, ketone removal and *N*-deprotection gave the *trans*-decahydroquinoline **289**. If the auxiliary was removed from **288** and the free heterocycle *N*-benzoylated, this substrate undergoes conjugate addition to give the *cis*-ring system **290** (Scheme 47).[108]

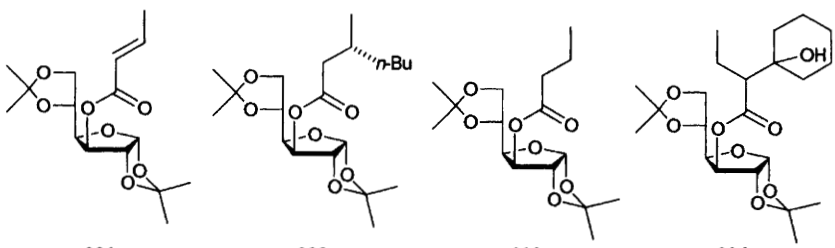
Glucose-derived system **291** undergoes conjugate addition (*n*-BuCu.BF_3) to give **292** (*R* configuration at new stereocentre with 60% d.e.), whilst **293** undergoes aldol reaction with cyclohexanone to give adduct **294**, but with only 10% d.e.[109]

7.2 Carbohydrate-derived Catalysts. – The chiral D-mannitol-derived β-dialkylaminoalcohol **242** (see Section 6 for structure and synthesis) acts as catalyst



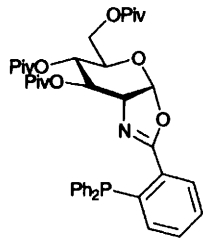
Reagents: i, hex-5-enal, pentane, 4Å sieves; ii, Danishefsky's diene, $ZnCl_2.OEt_2$; iii, *n*-PrMgCl. CuCl, $BF_3.OEt_2$; iv, $NaIO_4$, K_2OsO_4 (cat.); v, NaOH, dibenzo-18-C-6; vi, Me_2CuLi, TmsCl; vii, TBAF; viii, HCl. aq. MeOH; ix, Z-Cl, $NaHCO_3$; x, ethanedithiol, $BF_3.OEt_2$; xi, H_2, Raney Ni; xii, HCl

Scheme 47

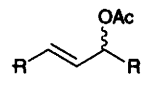


for enantioselective diethylzinc addition to a range of aldehydes (including benzaldehyde, butanal, hexanal, dodecanal) to give alcohols of *R*-configuration with 88–94% e.e.[88] The chiral phosphine **216** (see Section 5 for synthesis) is an effective catalyst (at 1.2 mol %) for π-allyl palladium $[Pd(C_3H_5)Cl)_2]$-mediated asymmetric alkylation of allyl acetates **295** (R = Me, Et, Ph, *n*-Pr) with dimethylmalonate to give **296**, giving the *R*-configured product in 69–98% e.e. It also acts as a catalyst for synthesis of non-symmetrical products such as **297** (88% e.e.) and **298** (92% e.e., but as a 56:44 mixture of regioisomers).[79]

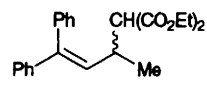
D-Mannitol has been converted into the chiral bis-phosphine **299**, Rh complexes of which catalyze alkene hydrogenation with >90% e.e.[110] The chiral bis-phosphine **302** [1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphosphino)-L-iditol] catalyzes asymmetric carbonylation (ligand, CO, MeOH, $CuCl_2$, $PdCl_2$) of **300** to give (*S*)-naproxen (**301**) in up to 81% e.e.[111] A range of new chiral bis-phosphites **303** have been prepared and some are useful for Rh(I) catalyzed processes.[112]



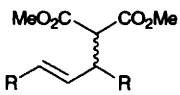
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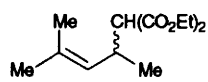
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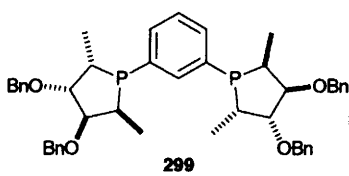
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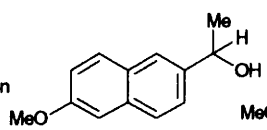
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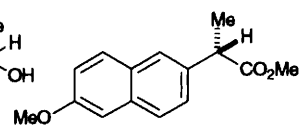
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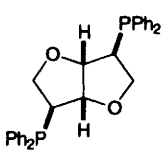
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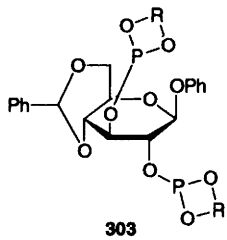
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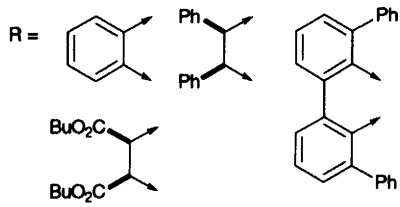
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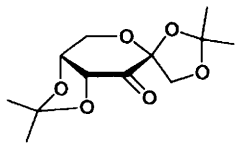
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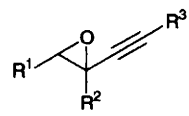
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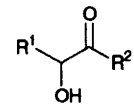
The utility of the fructose-derived ketone **304** (see Vol. 31, Chapter 24) as a chiral catalyst which mediates enantioselective epoxidations (with Oxone® as primary oxidant) has been further expanded this year. A range of eneynes were epoxidized to give acetylenic epoxides **305** in >90% e.e.[113] Silyl enol ethers were oxidized to give chiral α-hydroxy ketones with e.e. up to 82% (R^1 = Me, Et, Ph; R^2 = Me, *t*-Bu, Ph; R^3 = Me, *t*-Bu).[114] The same group also used the same catalytic oxidation system to convert *vic*-diols into chiral α-hydroxy ketones, for example **306** (R^1 = Ph; R^2 = Ph) obtained in 46% e.e. (*R* predominating).[115] Another report describes conversion of both silyl enol ethers and enol esters to the corresponding epoxides (*e.g.* **307** and **308**; 80% and 91% e.e. respectively) or α-hydroxy ketones (*e.g.* **309**; 90% e.e.).[116] Epoxyacetate **308** was converted into α-hydroxy ketones **309** (K_2CO_3, MeOH) or enantiomer **310** (heated at 195 °C then K_2CO_3, MeOH). The catalyst **304** mediates epoxidation of (*E*,*E*)-1,4-diphenyl-1,4-butadiene to give monoepoxide **311** and bis-epoxide **312** in a 22:1 ratio, both in 97% e.e.[117] This group have also reported an evaluation of modifications to the acetal substitutents of **304** showing that different alkenes react optimally with different catalyst variants.[118] In another variation, this group has shown that using ozone also provides a means to convert **304** into the intermediate chiral dioxirane and that this procedure can be used to (regiosepecifically) epoxidize dieneol **313** and other hydroxyalkenes, which are mostly epoxidized in >90% e.e.[119]



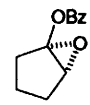
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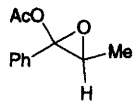
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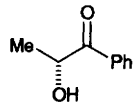
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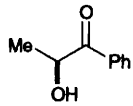
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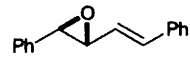
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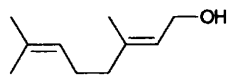
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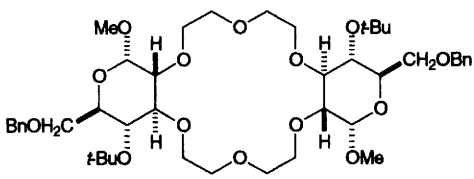


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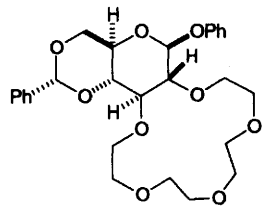


313

Two reports have appeared on the use of chiral carbohydrate-fused crown ethers as chiral phase-transfer catalysts for Michael additions. Use of catalyst **314** leads to Michael addition of methyl phenylacetate to methyl acrylate (potassium *t*-butoxide, catalyst) giving adduct in 84% e.e.[120] The crown ether **315** catalyzes Michael addition of 2-nitropropane to chalcone with 82% e.e., as well as the Darzens condensation of phenacyl chloride with benzaldehyde in 74% e.e.[121]



314



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