SPECIALIST PERIODICAL REPORTS

Carbohydrate Chemistry

VOLUME 27

Monosaccharides, Disaccharides, and Specific Oligosaccharides

A Review of the Literature
Published in 1993

THE ROYAL SOCIETY OF CHEMISTRY

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A Review of the Literature Published during 1993

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Preface

In Prefaces to previous Volumes I have commented on the increasing activity in the field of carbohydrate chemistry and also on the increasing complexity of many current research papers. With these continuing trends the need for Reporters to this Series to abstract more selectively is growing, and the chapter writers also have to abstract the first synopses ever more severely because we must work within space-determined limits. The density of data in succeeding Volumes is therefore increasing rather rapidly as is illustrated by the observation that Volumes 16 and 26 (1982 and 1992 literature) contained 13 and 31 pages of author indexes, respectively, while the overall page numbers only increased by 25%. The rather severe distillation processes now required inevitably increase the chances of imprecision - not least as far as impressions given of papers are concerned - and we can visualise authors' views of our maltreatments when their masterpieces are dismissed in a line or so. Readers should be aware of this severe limitation in our methods and are advised to consult primary sources as appropriate.

A notable feature this year has been the increase in the number of ingenious developments from which far-reaching consequences could come, and while this is illustrated in several Chapters, the topic of glycosidation procedures illustrates it particularly well. To be able to "switch on" one glycosylating agent in the presence of another (for example, phenylseleno compounds in the presence of phenylthio analogues), to incorporate a concurrent 2-deoxy generating step into a glycosylation reaction and to synthesize a trisaccharide from its constituents in selective one-pot reactions are indeed ingenious. The number of "smart" developments is on the increase!

As the boundaries of the subject expand more choices have to be made in determining which research papers should be abstracted. This year, it seems the following question has emerged: should papers on the syntheses of "marginal carbohydrates" e.g. acyclic nucleosides, cyclitols, deoxynojirimycin be abstracted when non-carbohydrates are the starting materials used? Yet another guideline will be required.

This Volume sees the last contributions by Tim Gallagher, and I thank him warmly for his work on some of the more demanding parts of the writing task. For their work and cooperation the staff of the Royal Society of Chemistry - especially Mr A G Cubitt and his artwork colleagues - are also thanked sincerely.

R J Ferrier

May 1995

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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[3.3.1]nonane
Bn	benzyl
Boc	t-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
c.d.	circular dichroism
Cer	ceramide
c.i.	chemical ionization
Cp	cyclopentadienyl
Cyt	cytosin-1-yl
Dahp	3-deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate
DAST	diethylaminosulphur trifluoride
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	dicyclohexylcarbodi-imide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	di-isobutylaluminium hydride
DMAD	dimethylacetylene dicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
Dmtr	dimethoxytrityl
e.e.	enantiomeric excess
Ee	1-ethoxyethyl
e.s.r.	electron spin resonance
Et	ethyl
f.a.b.	fast-atom bombardment
Fmoc	9-fluorenylmethylcarbonyl
Fru	fructose
Fuc	fucose

Gal	galactose
GalNAc	2-acetamido-2-deoxy-D-galactose
g.l.c.	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	hexamethylphosphoric triamide
HMPT	hexamethylphosphorous triamide
Ido	idose
Im	imidazolyl
i.r.	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
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
Mem	methoxyethoxymethyl
Mmtr	monomethoxytrityl
Mom	methoxymethyl
m.s.	mass spectrometry
Ms	methanesulphonyl (mesyl)
n.m.r.	nuclear magnetic resonance
NAD	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NeuNAc	*N*-acetylneuraminic acid
NIS	*N*-iodosuccinimide
NMNO	*N*-methylmorpholine-*N*-oxide
o.r.d.	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
s.i.m.s.	secondary-ion mass spectrometry

TASF	tris(dimethylamino)sulphonium (trimethylsilyl)difluoride
Tbdms	*t*-butyldimethylsilyl
Tbdps	*t*-butyldiphenylsilyl
Tf	trifluoromethanesulphonyl (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
Tms	trimethylsilyl
TPP	triphenylphosphine
Tps	tri-isopropylbenzenesulphonyl
Tr	triphenylmethyl (trityl)
Ts	toluene-*p*-sulphonyl (tosyl)
Ura	uracil-1-yl
UDP	uridine diphosphate
UDPG	uridine diphosphate glucose
Xyl	xylose

1

Introduction and General Aspects

As always, an extensive range of reviews and symposia proceedings of general interest in the field has appeared. A novel approach to molecular modelling of carbohydrates uses the averages of intra- and inter-molecular bonding energies and potential energy functions, and apparently allows very efficient computation of the energetics and conformational properties of carbohydrates in aqueous solution.[1] A symposium was held on important characteristics of hydrogen bonding in molecular recognition undertaken by sugars,[2] and an analysis has been undertaken of the effects of stereochemistry on carbohydrate hydration.[3]

Two symposia reports have appeared on issues associated with sweetness, the first[4] dealing with natural and artificial sweetners, which included consideration of theoretical, structural and physical chemical correlations,[4] while the second focused on the sweetness of halogenated sugar derivatives.[5] A lecture on the synthesis of glycothanes as receptors in novel compounds derived from α,α-trehalose has been published.[6]

A review on protective group strategies in carbohydrate synthesis has appeared which included consideration of the preparation of phosphate and sulphate esters of heparin oligosaccharides,[7] and a related article covered the detailed consideration of the binding domains associated with the heparin-antithrombin 3 complex.[8]

A survey of the C-homologenation of sugars involving the use of thiazoles in aldol condensations has appeared,[9] and another covers a diverse range of synthetic methods for synthesizing carbohydrate derivatives from acyclic precursors.[10]

Free radical chemistry continues to be of importance in the field and a survey has been published on polar and enthalpic effects in free radical reactions.[11] A further short review dealt with free radicals, carbenes and nitrenes at the anomeric centre of carbohydrates.[12] A useful survey has appeared of the application of carbohydrate based chiral auxilliaries in stereoselective syntheses which covers a range of reactions, for example cycloaddition processes, reductions and Strecker reactions.[13]

Considerable interest continues to be shown in the application of enzymes in synthesis of carbohydrate compounds, and a review has appeared on the use of aldolases, glycosyl transferases and subtilisin.[14] Other reviews have concentrated on aldolases applied in the synthesis of C-C bonds.[15-18] Another deals with the synthesis of optically active carbohydrates by biooxidation of chlorinated aromatic compounds using *Pseudomonas putida*.[19] Enzymes may be also used to affect the hydroxyl groups of carbohydrates, and a review on the protection of such groups and deprotection has appeared.[20]

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2
Free Sugars

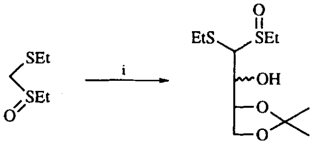
1 Theoretical Aspects

The chemical reactivity at different sites in α-D-glucopyranose and β-maltose has been examined by use of AM1 molecular orbital calculations with a view towards an understanding of the reactivities of glucans.[1] AM1.PM3 molecular orbital calculations on D-xylopyranose[2] and harmonic dynamics calculations on both anomers of glucose in the crystalline state[3] have been reported. Predictions, by means of UNIFAC, of liquid-solid phase diagrams for aqueous sugar systems, (*e.g.*, sucrose/glucose-, sucrose/fructose-, or xylose/mannose-mixtures) compared favourably with experimental data.[4]

The interactions between the surfaces of some heterogeneous catalysts and monosaccharides, *e.g.*, between gallium(I) and glucose in DMSO, have been described.[5]

2 Synthesis

Transketolase (EC 2.2.1.1), which catalyses condensations between aldehydes and hydroxypyruvic acid with loss of CO_2 (see Vol. 25, Chapter 2, Ref. 9) has been produced in relatively large quantities from an over-expressed *E. coli* transformant carrying the transketolase gene. This enzyme was fairly non-specific with respect to the aldehyde component, although best results were achieved with α-hydroxyaldehydes.[6]

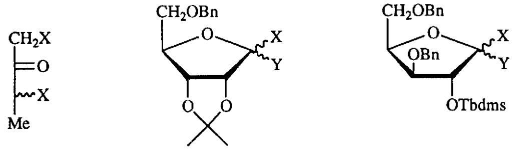


Reagents: i, 2,3-*O*-Isopropylidene-D-glyceraldehyde, Bu^{n}Li

Scheme 1

2.1 Trioses to Hexoses.- A kinetic analysis of the formose reaction has led to the conclusion that the carbonyl rearrangement and retro-aldol reaction steps play a substantial role in the autocatalytic process.[7] The condensation of D-glyceraldehyde acetonide with racemic alkyl (alkylthiomethyl) sulfoxides proceeded with high selectivity to produce diastereomeric 1-alkylsulfinyl-1-alkylthio-3,4-*O*-isopropylidene-D-tetroses with a predominance of *erythro*-products. An example is given in

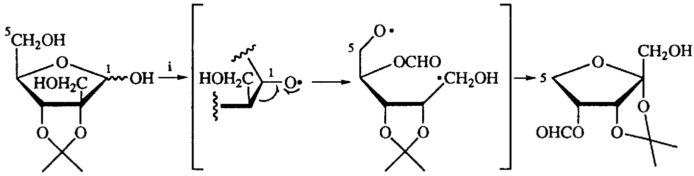
Scheme 1.[8] 4-Deoxy-D,L-*glycero*-tetrulose (**4**) has been synthesized from butanone (**1**) *via* dibromide **2** and diacetate **3**. The acetyl groups were hydrolysed by use of a lipase.[9]



1 X = H
2 X = Br
3 X = OAc
4 X = OH

5 X, Y = O **8**
6 X, Y = CH$_2$ **9**
7 X, Y = CH$_2$OH, H **10**

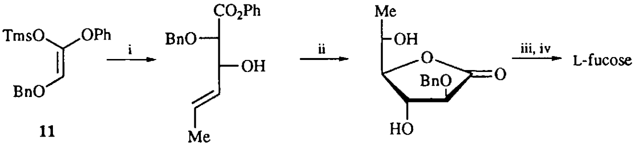
The preparation of acyclic 3,4:5,6-di-*O*-isopropylidene-D-glucose from 1,2:3,4:5,6-tri-*O*-isopropylidene-D-gluconate is referred to in Chapter 6. L-Glucose derivatives have been synthesized from D-glucose *via* 2,3,4-tri-*O*-benzyl-6-*O*-*t*-butyldimethylsilyl-D-glucono-1,5-lactone, following a modification of Shiozaki's method (see Vol. 25, Chapter 2, Ref. 15), and from 2,3,5-tri-*O*-benzyl-L-arabinofuranose by use of phenyldimethylsilylmagnesium chloride in a highly stereoselective Grignard reaction.[10] Methylenation of protected D-ribono- and D-xylono-1,4-lactone **5** and **8**, respectively, with Tebbe's reagent was inefficient, but exposure to Cp_2TiMe_2 gave alkenes **6** and **9** in 95% and 75% yield, respectively. Dihydroxylation with osmium tetroxide/NMO furnished mainly the β-anomers of D-psicofuranose and D-sorbofuranose derivatives **7** and **10**.[11] The fragmentation/rearrangement of carbohydrate anomeric alkoxy radicals formed on treatment of free sugars with iodosylbenzene has been investigated, in particular its application to the synthesis of ketoses from precursors with a free hydroxyl group at C-5 and a hydroxymethyl-branch at C-2. An example is shown in Scheme 2.[12,13]



Reagents: i, PhIO, I_2, CH_2Cl_2

Scheme 2

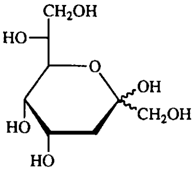
A new route to monosaccharides employing catalysed asymmetric aldol condensation has been illustrated by the preparation of L-fucose from crotonaldehyde and ketene silyl acetal **11** (Scheme 3) in 4 steps and 49% overall yield.[14] The preparations of D-tagatose 1,6-diphosphate and of (3*S*/4*R*)-configurated ketose 1-phosphates by use of aldolases are covered in Chapter 7.



Reagents: i, CHO, Sn(OTf)$_2$, (*S*)-1-methyl-2[(*N*-1-naphthylamino)methyl]pyrrolidine;
ii, OsO_4, NMO; iii, DIBAL; iv, H_2, Pd/C

Scheme 3

2.2 Chain-extended Compounds.- A review (50 pp., 75 refs.) on aspects of modern higher carbon sugar synthesis has been published.[15] A further report on the preparation of sedoheptulose by spinach transketolase-mediated condensation between D-ribose and hydroxypyruvic acid has appeared (see Vol. 25, Chapter 2, Scheme 1).[16] The hexulose phosphate synthetase-promoted aldol condensation between ribulose 5-phosphate and acetaldehyde gave a mixture of (5*R*/6*S*)- and (5*R*/6*R*)-7-deoxy-4-heptulose. The (*R*)-stereochemistry at C-5 was ascertained by extensive n.m.r. analysis, especially n.O.e. experiments. The configurations of two 7,8-dideoxy-4-octuloses prepared previously from ribulose 5-phosphate and propanal (see Vol. 25, Chapter 7, Ref. 45) and originally assigned as (5*S*) have now been corrected to (5*R*).[17] Condensation of D-ribose with dihydroxyacetone phosphate under catalysis by rabbit muscle aldolase, followed by exposure to phosphatase (see Vol. 20, Chapter 2, Ref. 33), gave octulose **12** in good yield.[18]



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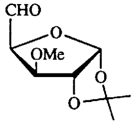

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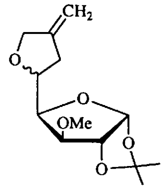
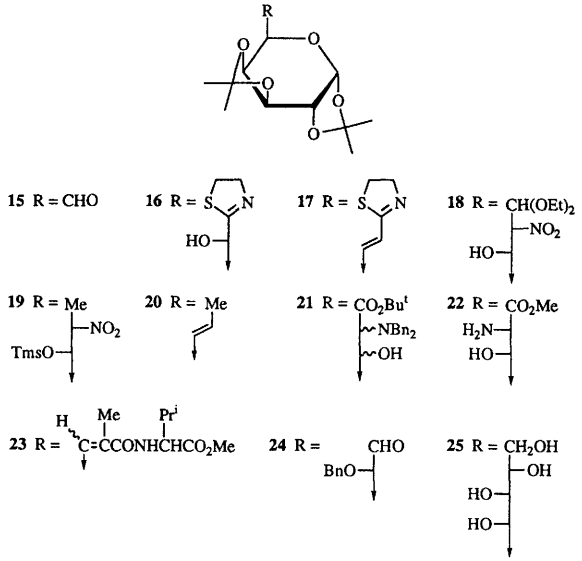


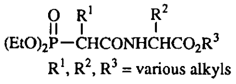
14

2.2.1 Chain-extension at the "Non-reducing End".- Sugar aldehyde **13** was one of a range of substrates which were condensed with 2-(chloromethyl)-3-(trimethylsilyl)-1-propene in the presence of boron trifluoride etherate, followed by DBU-promoted cyclization, in order to generate methylenetetrahydrofurans, in this case **14**.[19] 1,2:3,4-Di-*O*-isopropylidene-D-galacto-dialdose (**15**) has been subjected to a considerable number of chain-extension reactions: a variant of Dodoni's method (see Vol. 23, Chapter 2, Ref. 15) gave thiazoline **16** and its diastereomer in 95:5 ratio and 58% combined yield.[20] Use of a thiazole-based Wittig reagent allowed a two-carbon chain-extension *via* alkenyl thiazoles **17**.[21] Nitro-sugars **18** and **19** were obtained by application of modified, trialkylsilyl chloride-promoted Henry reactions to aldehyde **15**. The former product was transformed to the corresponding aminodeoxy-sugar by hydrogenation over Raney nickel,[22] the latter to the unsaturated trideoxy-octose **20** in three steps involving Barton radical chemistry.[23] The reaction of **15** with *t*-butyl dibenzylaminoacetate and LDA proceeded with little diastereoselectivity to give *syn*/*anti* mixtures of glycosyl-α-aminoesters **21**. Pure *anti*-product **22** was, however, obtained by use of reagent **26** and potassium *t*-butoxide. Similar reactions have been carried out with other dialdose derivatives.[24] Precursors, such as compound **23**, of pseudoglycopeptides were produced by condensation of **15** with diethylphosphonates **27** and LDA.[25] A standard Wittig reaction and subsequent osmium tetroxide hydroxylation have been used to convert the known heptodialdose derivative **24** to its nonose analogue **25**.[26]



$Ph_2C{=}NCH_2CO_2Me$

26

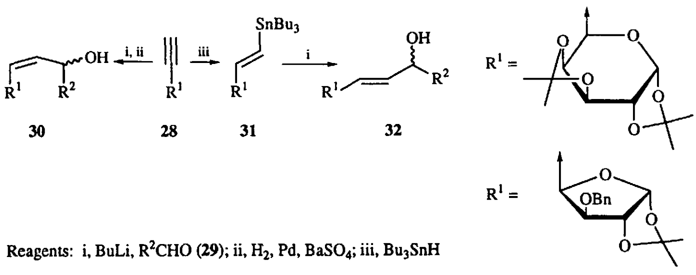


$(EtO)_2\overset{O}{\overset{\|}{P}}-\overset{R^1}{\overset{|}{C}}HCONH\overset{R^2}{\overset{|}{C}}HCO_2R^3$

R^1, R^2, R^3 = various alkyls

27

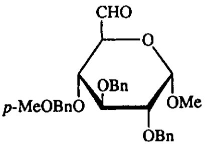
The diastereomeric C_{12} (*Z*)-allylic alcohols **30** [(*R*/*S*) 1:2] have been obtained by addition of lithiated alkyne **28** to dialdose derivative **29**, followed by partial hydrogenation of the triple bond, and the two (*E*)-isomers **32** [(*R*/*S*) 7:3] were formed when the lithiated alkene derived from tributylstannane **31** was used as nucleophile (Scheme 4).[27]



Reagents: i, BuLi, R^2CHO (**29**); ii, H_2, Pd, $BaSO_4$; iii, Bu_3SnH

Scheme 4

Chain-extension at C-6 of hexodialdose derivative **33** was involved in the synthesis of the linear *C*-8-*C*-8-linked dipyranyl dimer **34**,[28] and the diastereomeric alcohols **35**, obtained by Grignard reaction on the corresponding *C*-6-aldehyde, were used as glycosyl donors in the preparation of *C*-6-methylated analogues of disaccharide **36** and of a related trisaccharide.[29]



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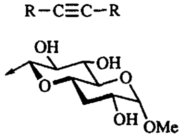

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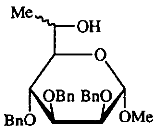
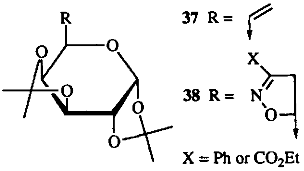


35

D-Man*p*-(1→6)-α-D-Man*p*OMe

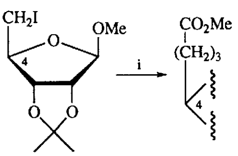
36



X = Ph or CO_2Et

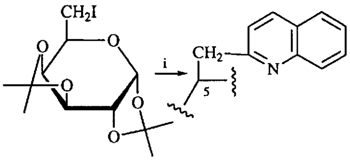
The dipolar cycloaddition of nitrile oxides to terminal sugar alkenes (see Vol. 23, Chapter 10, Scheme 18; Vol. 25, Chapter 2, Scheme 11) has been applied to the preparation of the D-*glycero*-D-*galacto*-configurated isoxazolines **38** from hept-6-enose **37**,[30] and two methods for the chain-extension of primary iodides, both presumed to involve radical mechanisms, have been reported; examples are given in Schemes 5[31]and 6.[32]

2.2.2 Chain-extension at the Reducing End.- Reaction of the four unprotected D-aldopentoses with the stabilized ylid $Ph_3P{=}CHCO_2Me$, in the presence of copper(II) acetate to suppress cyclization to furanose derivatives, gave (*E*)-alkenes **39** (isolated as the tetraacetates or diacetonides) in



Reagents; i, CO_2Me , Zn, $FeCl_3$, NaI, Py

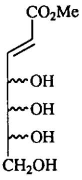
Scheme 5



Reagents; i, Quinoline, $(BzO)_2$

Scheme 6

up to 60% yields.[33] (*E*)-Alkenes, *e.g.* **40**, were also formed, in yields around 80%, when pyranoses or furanoses, protected at all except the anomeric positions, were exposed to arsenic ylids. Cyclization to β-*C*-glycosides (*e.g.* **40** → **41**) was brought about by heating with zinc bromide in benzene.[34]



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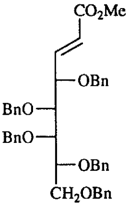

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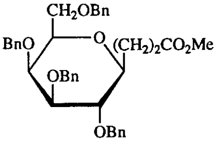

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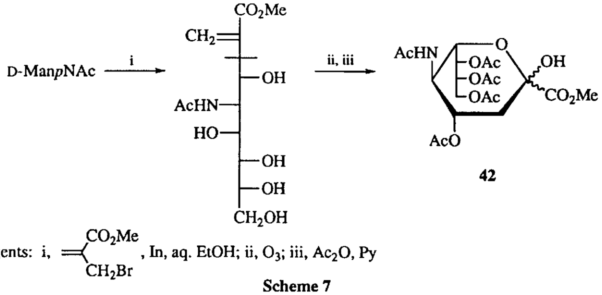
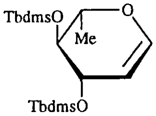
Allylation of unprotected aldoses in aqueous media has previously been carried out with allyl bromide and tin (see Vol. 25, Chapter 2, Ref. 31). This method has now been improved by replacement of tin with indium, and extended to substituted allylic bromides. Its usefulness is impressively demonstrated by the conversion of 2-acetamido-2-deoxy-D-mannose to neuraminic acid derivative **42** in 3 steps and 45% overall yield, as shown in Scheme 7.[35]



Reagents: i, , In, aq. EtOH; ii, O_3; iii, Ac_2O, Py

Scheme 7

3,7-Dideoxyheptulosonic ester **46** has been synthesized from glycal **43** by way of lactone **44** and dithiane **45**,[36] and KDN has been obtained by condensation of D-mannose with oxalacetic acid under basic conditions.[37] Stereocontrolled synthesis of polyol chains employing 2-acetylthiazole as



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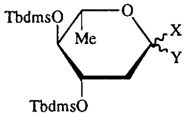
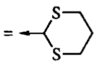


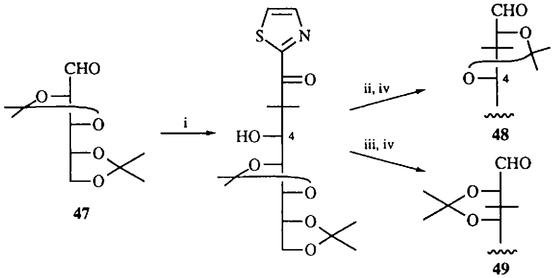
44 X, Y = O

45 X = OH, Y =



46 X = OH, Y = CO_2Me

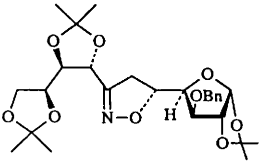
lactaldehyde equivalent gave 3-deoxyoctose derivatives from 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**47**) (Scheme 8). Stereoselective reduction was achieved with tetramethylammonium borohydride or DIBAL to give the D-*glycero*-D-*galacto*- **48** or the D-*glycero*-D-*talo*-isomer **49**, respectively.[38] A stereocontrolled route to 6-deoxyundecoses involved intermolecular nitrone-olefine cycloaddition between two sugar-derived components to give, for example, isoxazoline **50**.[39]



Reagents: i, 2 Acetylthiazole, Bu^{t}OLi; ii, Me_4NBH_4; iii, DIBAL; iv, $Me_2(COMe)_2$, camphorsulfonic acid

Scheme 8

The diastereomeric spirooxirans **52** were formed when glycosylideneaziridine **51** was irradiated in the presence of cyclohexanone.[40] Cycloaddition reactions of 1-thionoglyconolactones and the preparation of carboranyl aldoses from protected aldono-1,4- and -1,5-lactones are referred to in Chapters 11 and 17, respectively.



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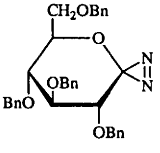

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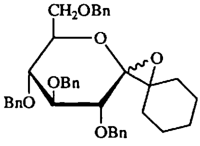

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3 Physical Measurements

The glass transition temperatures, fusion temperatures and the heats of fusion of a number of pentoses, hexoses, alditols, and disaccharides have been determined by differential scanning calorimetry.[41] In the course of an investigation aiming at a rigorous description of the thermal events occurring when frozen saccharide glass-ice mixtures are warmed, a supplemented phase diagram has been constructed based on new measurements of the glass transition temperatures for dilute and concentrated aqueous fructose solutions and literature data.[42] In a quantitative study, by FT-IR spectroscopy, of the composition of aqueous fructose solutions a considerable increase in the percentage of keto form with increasing temperature has been observed, whereas the pH dependence was negligible.[43] Vibrational Raman optical activity studies on 15 monosaccharides are referred to in Chapter 22.

The electro-osmotic transport of D-glucose across progesterone membranes has been investigated.[44]

4 Isomerization

The mutarotation of α-D-glucose has been studied in aqueous solutions of boric acid,[45] in ethanol/water under microwave activation,[46] and in DMSO under γ-irradiation.[47] A molecular dynamics investigation of the conformational and anomeric equilibria of D-glucose in aqueous solution is referred to in section 1 of this Chapter.

Previous studies on the Ni(II)- and Ca(II)-complex-catalysed C-2 epimerizations of aldoses by use of ^{13}C-enriched substrates have been reviewed (19 refs.).[48] Amphiphilic complexes between Ni(II) and long-chain *N*-alkyl ethylenediamines gave rise to "metallomicelles" which coordinated with aldoses which then underwent epimerization (see Vol. 25, Chapter 2, Ref. 51); short-chain complexes had little activity.[49] The epimerization of aldoses by Ca^{2+} in basic aqueous or alcoholic solution, which proceeds by molecular rearrangement (see Vol. 24, Chapter 2, Ref. 47), has now been developed into a preparative method for converting glucose and xylose to mannose and lyxose, respectively.[50]

The molybdate ion-promoted formation of ketoses from aldopentoses and aldotetroses has been investigated,[51] and physicochemical data for both directions of the heptamolybdate ion-catalysed xylose-lyxose epimerization have been published.[52]

D-Ketohexose-3-epimerase, a new enzyme isolated from *Pseudomonas* sp., catalysed the epimerization between D-tagatose and D-sorbose, D-fructose and D-psicose, D-xylulose and D-ribulose, and between L-xylulose and L-ribulose.[53]

5 Oxidation

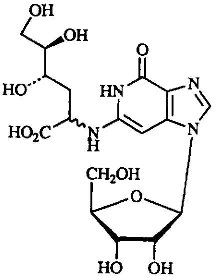
Studies on the oxidation of D-glucose on palladium electrodes in alkaline media,[54] on electrodeposited platinum electrodes,[55] and on single-crystal platinum electrodes[56] have been undertaken.

The catalysis of the oxidation of D-glucose by native and by recombinant glucose oxidase, mediated by one-electron redox co-substrates, has been monitored by cyclic voltammetry.[57] A study on the effect of pH on the Pd-catalysed oxidation of D-glucose revealed that in acidic media the product, free D-gluconic acid, reversibly inhibits the oxidation process.[58]

The oxidation of aldoses and sugar phosphates by Cr(VI) has been reviewed (23 refs.).[59] The kinetic behaviour and the relative reactivities of several trioses, tetroses, pentoses and hexoses, amino sugars, and methylated sugars towards potassium permanganate in perchloric acid solution have been examined.[60] Mechanisms have been proposed for the oxidation of arabinose and xylose by iodine in alkaline solution[61] and by alkaline NBS under Ru(VIII)-catalysis.[62] For the oxidation of monosaccharides by sodium *N*-bromobenzenesulfonamide in alkaline media, reaction *via* 1,2-enediol intermediates has been postulated.[63] 1:1 Stoichiometry has been observed in the oxidation of D-fructose with PCC.[64]

6 Other Aspects

The hydrothermolysis (27.5 MPa, 290 - 400 °C) of D-fructose furnished 5-hydroxymethyl-2-furaldehyde, furfural, and 1,2,4-benzenetriol.[65] The epimeric compounds **53**, separable by h.p.l.c., have been isolated in high yields from the reaction of D-glucose with guanosine under physiological conditions.[66] An analysis of the aroma compounds produced on exposure of rhamnose to cysteine under roasting conditions (200 - 220 °C) revealed the presence of *ca.* 180 compounds, mostly derivatives of furan, pyrrole, and thiophene, 125 of which have been identified.[67]



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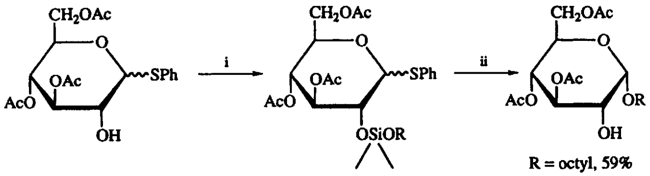
3
Glycosides and Disaccharides

1 *O*-Glycosides

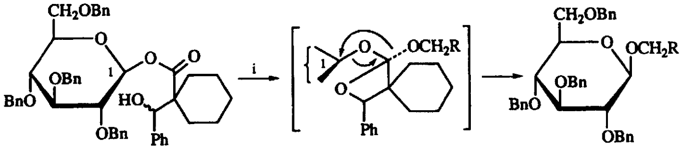
1.1 Synthesis of Monosaccharide Glycosides.-A detailed section on *Methods of Organic Chemistry* has been devoted to this topic;[1] a valuable, extensive *Chemical Review* on recent progress in *O*-glycosylation methods, and applications in natural product synthesis has been published,[1a] and Fraser-Reid has reviewed his work on 4-pentenyl glycosides, covering their use in synthesis and theoretical and mechanistic aspects.[2] A review in Japanese has dealt with thioglycosides as glycosylating agents,[3] and a further review in this language deals with glycosyl fluorides activated by metallocene dichlorides or silver salts in the synthesis of *O*- and *C*-glycosides.[4] A detailed lecture by Vasella dealing with novel approaches to glycosides by use of glycosylidene carbenes has been published.[5] Much interesting chemistry is dealt with in detail.

The important topic of the intramolecular approach to glycoside synthesis has been given further attention with Bols describing an interesting approach to α-glucopyranosides as illustrated in Scheme 1 (see also Scheme 7).[6] An ingenious new approach has been reported by Schmidt which involves the synthesis of the orthoester intermediates **1** and their collapse to give β-glucosides with anomeric



Reagents: i, $ClSiMe_2OR$, Py; ii, NIS, TfOH

Scheme 1

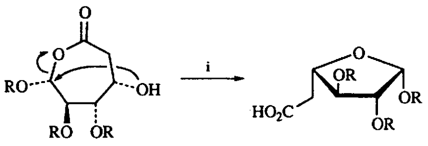


1

Reagents: i, NaH, crown ether, RCH_2 OTf

Scheme 2

selectivity 8:1(Scheme 2). Similar operations in the α-series give preferentially α-glycosides but with less selectivity.[7] An entirely different approach which results in the formation of 5-deoxyhexofuranuronic acid glycosides involves intramolecular rearrangement of compounds **2** (Scheme 3)

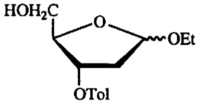


2

Reagents: i, TsOH, CH_2Cl_2

Scheme 3

which can be made by Baeyer-Villiger oxidation of corresponding cyclohexanone derivatives. These in turn are derivable from hex-5-enopyranosyl compounds. While of restricted applicability,the method nevertheless, was used to synthesize products with the β-D-*gluco*- and the α-L-*ido*-configurations, some carrying glycosyl groups at O-3.[8]



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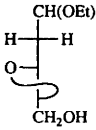

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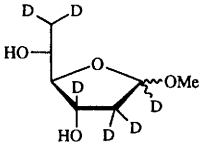

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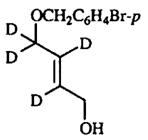


6

The ethyl furanoside **3** has been made from the epoxide **4** following ring opening with acyloxytris(isopropoxy)titanium reagents, the starting material being prepared from crotonaldehyde by Sharpless epoxidation, and ring opening occurring with high regioselectivity.[9] The related deuterated methyl glycosides **5** have been made from the deuterated alkene **6**.[10]

Schmidt has reported on the anomeric *O*-alkylation of unprotected pentoses and hexoses using sodium hydride as catalyst in an aprotic solvent with allyl bromide, benzyl bromide and didecyl sulfate. About 60% yields of glycosides were produced from glucose, mannose, *N*-benzoylglucosamine and xylose, the pyranosides being formed with α,β-ratios varying from 1:10 to 2.5:1. Galactose, on the other hand gave α-furanosides only, and arabinose gave mixtures of pyranosides and furanosides.[11] In somewhat related work, sugars substituted at all hydroxyl groups except the anomeric were treated with allyl ethyl carbonate and related allyl carbonates in the presence of palladium compounds to give high yields of glycosides. With 2,3,4,6-tetra-*O*-benzylglucose no anomeric selectivity was found, but with furanosyl compounds bearing acetal rings at C-2,3-diols, high selectivities of products having the aglycon *trans* to O-2 were obtained.[12]

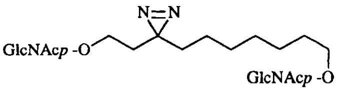
2,3,5-Tri-*O*-benzyl-D-ribose together with trimethylsilylated alcohols, [catecholato(2-)-

O,*O*′]oxotitanium and triflic anhydride gives rise preferentially to glycosides of the β-configuration (β:α 10:1). Lithium perchlorate as catalyst, however, gives mainly α-products (ratio 1:4). In both cases yields are of the order of 70%.[13] An interesting looking new approach involving starting materials of similar nature uses 1-hydroxy compounds and receptor alcohols in the ratio 1:1.2, and methoxyacetic acid and ytterbium triflate as promoters. Excellent yields are reported, but stereoselectivities were not high when tetrabenzylglucose was used. 2,3,5-Tri-*O*-benzyl-D-ribose, however, gave β-products with high selectivity.[14] The same authors have worked on 1-methoxyacetyl esters of carbohydrates and find they can convert them to *O*- and *S*-glycosides using zinc(II) as catalyst[15] or lanthanide(III) triflates.[16]

Various esters remain of interest as glycosyl donors. Glycosyl dimethylphosphites react with alcohols in the presence of different promoters, for example zinc chloride, copper triflate, boron trichloride and NIS/triflic acid, the α/β selectivities depending upon the promoter used.[17] *O*-Benzylated glycosyl dimethylphosphinothioates, in the presence of an equivalent of iodine and catalytic trityl perchlorate, give moderately good yields of glycosides with the 1,2-*cis*-isomers being somewhat favoured.[18]

Mukaiyama continues to contribute in the area of glycoside synthesis from glycosyl esters and has found means of using *O*-benzylated glucosyl (2-methoxyethoxy)acetyl esters in such a way that high yields of α- or β-products may be obtained. With trimethylsilylated alcohols and tin(IV) chloride and silver perchlorate α-products are claimed with 96% selectivity. On the other hand, silicon tetrachloride and silver perchlorate yield β-glycosides with better than 90% selectivity.[19] Applied with *O*-acetylated 2-amino-2-deoxy-α-D-glucopyranosyl acetate the tin(IV) chloride, silver perchlorate reagent gives the α-products which are formed by way of the β. The method is applicable in the galactosamine series and to the preparation of *O*-glycosylated amino acid derivatives.[20]

The tetra-*O*-acetyl derivative of 2-deoxy-2-phthalimido-β-D-glucose has been used in orthodox synthesis of compound **7**.[21] Reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose with various alcohols led, following debenzoylation, to β-ribofuranosides which were used to test the ability of horse liver alcohol dehydrogenase to act as an oxygen transferase from *t*-butyl hydroperoxide. Phenyl and cyclohex-3-enyl glycosides were produced, but surprisingly the reaction failed with cyclohex-2-enol, the product being the β,β-linked non-reducing disaccharide.[22]



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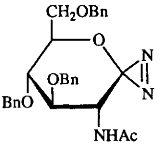

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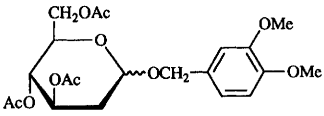
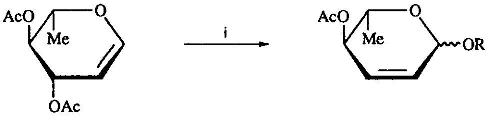


9

Vasella's group has reported a series of new glycosylidene diazirines, for example **8**, which undergo thermolysis in methanol to give methyl glycosides. Kinetic studies indicate the importance of conformational and electronic factors in controlling the heterolytic C-N bond cleavage.[23]

Dimethoxybenzyl glycosides, for example **9**, on treatment with DDQ in the presence of an alcohol in acetonitrile, degrade oxidatively to give the corresponding benzaldehyde compound and a carbocation which results in the formation of glycosides. Yields are in the 60-95% range, but the stereoselectivity is not high.[24]

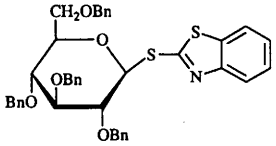
Glycosylthio compounds remain important as glycoside precursors; compound **10**, for example, reacting with alcohols in dichloromethane containing methyl iodide under high pressure to give α-glucosides with yields of about 80% and α/β ratios of the order of 9:1.[25] 2-Pyridyl 1-thioglycosides have again been used to make 2-azidoethyl α-glycosides as potentially useful compounds with spacer arms. Methyl iodide in dichloroethane was again used as activator.[26]



Reagents: i, ROH, DDQ, MeCN

Scheme 4

A new way of converting acylated glycals into 2,3-unsaturated glycosides involves treatment with alcohols in acetonitrile in the presence of catalytic amounts of DDQ (Scheme 4). Efficiencies are good and the anomeric selectivities (mainly α) seem to be very similar to those obtained when this type of reaction is conducted with Lewis acid catalysts.[27] Di-*O*-acetyl-L-rhamnal is the source of the glycosylating agents **11**, suitable furanoid compounds for making ristosamine related products.[28]



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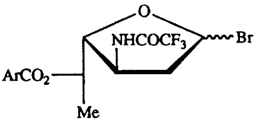
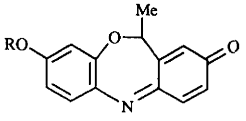


11

In the area of glycosyl trichloroacetimidates *O*-unsubstituted compounds have been described following deacetylation of their peracetates. This makes them a most unusual type of glycosylating agent. Reaction with alcohols in acetonitrile in the presence of trimethylsilyl triflate gave glycosides, the yields and α/β ratios of products being dependent upon reaction conditions. (1→6)-Linked glycobioses were also produced.[29] A glycosyl trichloroacetimidate of a uronic acid ester has been used in the production of aryl glycosides of β-D-glucuronic acid.[30] Also in the area of aryl glycosides, derivatives of 3-*n*-alkylcatechols have been prepared,[31] hydroquinone monoglycosides have been alkylated using radioactively labelled methyl iodide,[32] and an extensive range of hydroxybenzophenone glycosides and products of carbonyl reduction of these have been reported as potential antithrombotic agents.[33] Various *N*-acetyl-glucosaminides of 2′,7′-dichlorofluorescein have been successfully tested as potential chromogenic substrates for *N*-acetyl-β-D-glucosaminidase.[34,35] Compound **12**, derived from 8-hydroxy-11-methyl-11*H*-dibenz([b,e][1,4]oxazepin-2-one has been made as a β-galactosidase substrate.



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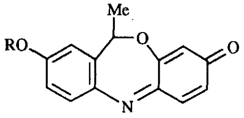
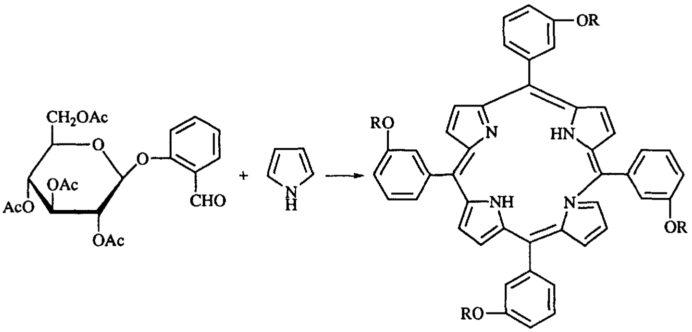


13

R = β-D-Gal*p*

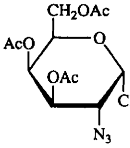
Together with its isomer **13**, it represents a new chromogenic substrate for the enzyme.[36] The glycosylated porphyrins indicated in Scheme 5 have good solubility in neutral aqueous solution. The complexing of zinc by these compounds was studied,[37] and similar derivatives having α-D-xylose and lactose as the sugars have been used in studies of photochemical hole burning spectroscopy.[38]



R = β-D-glucose, -maltose

Scheme 5

As always, a range of new compounds prepared using acylated glycosyl halides have been reported and the reactions involved have been submitted to detailed study. Thus the acceleration of *cis*-glycosylation with the galactosamine derivative **14** by ultrasonic radiation with various solid promoters has been described,[39] and particular attention has been given to the stereoselectivity of D-mannopyranosylation with the α-D-glycosyl chloride having allyl or n-propyl *O*-protection. To achieve enhanced β-selectivity, silver ion complexing in solution is recommended, but yields of β-products were never greater than 50%.[40] 2-(Trimethylsilyl)ethyl α-D-mannopyranoside has been prepared in 72% yield using an α-glycosyl chloride, the nature of the *O*-protection of which was important, and the 3,4,6-tri-*O*-acetyl-2-*O*-benzoyl derivative proved most satisfactory.[41]



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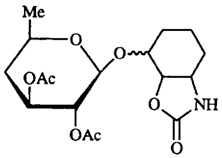
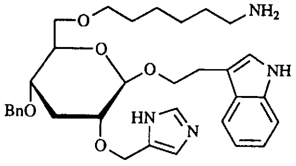


15

In the area of deoxy-sugars several α-fucosyl glycosides and disaccharides with *p*-methoxybenzyl *O*-protection were made from the corresponding chloride; the protecting groups are removable by selective oxidation.[42] In this way non-participating protecting groups were present which were suitable for use with glycosides having aglycons which were sensitive to hydrogenation. Use of the appropriate glycosyl bromide allowed preparation of compounds **15** of unspecified stereochemistry in the aglycon.[43] Application of the Koenigs-Knorr reaction to the synthesis of several 8-aminooctyl glycopyranosides has been reported and the products were condensed with acid residues to form poly-L-glutamic acid derivatives.[44] An extensive range of non-peptide peptidomimetics of somatostatin have been made and studies of the binding of these compounds with somatostatin receptors led to the preparation of compound **16** which proved to be the best binder tested.[45]



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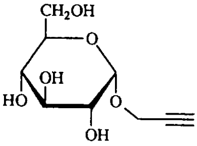
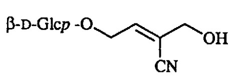


17

Enzymes continue to be recognized as important means of preparing glycosides. Thus the stereospecific synthesis of alkyl β-D-mannopyranosides from 4-nitrophenyl β-D-mannopyranoside by use of snail β-D-mannosidase gave a range of alkyl glycosides. The yields decreased with the hydrophobicity of the alcohol and with steric crowding of the hydroxyl group. Various disaccharides were also produced.[46] Transfer of monosaccharides from disaccharides has been used as a strategy for the preparation of β-D-galactopyranosyl and α- and β-D-glucopyranosyl propargylic glycosides, for example **17** and its anomer.[47]

1.2 Synthesis of Glycosylated Natural Products.–Sarmentosin **18** which is a potent glutamic-pyruvic transaminase inhibitor has been made from an acetylated glycosyl glycerol derivative.[48]

Several further examples have been reported of glycosylated amino acids which were then elaborated to glycosylated peptides. These include a glucosylated serine which was converted into a glucosyl cyclic peptide, glycosylated peptides, some of which have blood clotting characteristics - these include a xylobiosyl glucosyl serine based compound[49] and a serine derivative carrying 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranose.[50] An alanyl serine dipeptide carrying a β-D-xylopyranose unit on serine has been enzymically incorporated into a tetrapeptide derivative.[51] In the course of this work several glycosylamine linked peptides were reported. There is considerable interest in linking galactosamine to threonine and thence to peptides. A 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-galactose unit has been linked to a threonine derivative and then incorporated into a hexapeptide glycoside,[52] and the same sugar attached to a threonine unit of a tetrapeptide has been subjected to the action of lipase and thereby liberated from a 2-(*N*-morpholino)ethyl ester.[53] In the same area of interest 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-galactopyranosyl acetate has been used to link the sugar to a protected threonine compound.[50] Acetobromoglucose in the presence of silver triflate has been condensed with a protected tyrosine compound to give the β-linked glycoside **19**, and similarly a maltosyl β-linked compound was produced. Benzoylated protected glycosylating sugars on the other hand, and a change of solvent from dichloromethane to acetonitrile, gave 1:1 mixtures of α,β-glycosides.[54]



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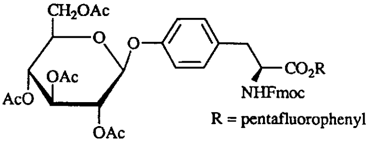

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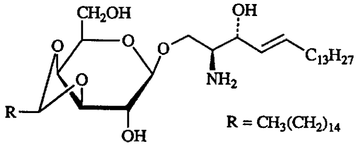
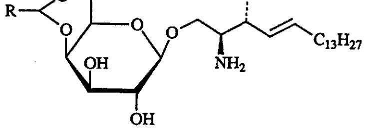


20

In the area of glycosyl ceramides, the plasmalopsychosines **20** and **21** have been synthesized for purposes of study of their biological activity; the analogue **22** was also produced.[55] In related work,



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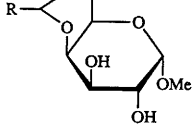

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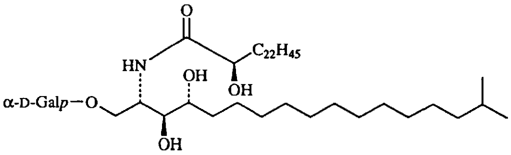
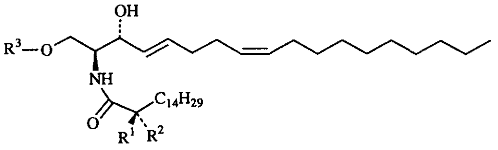
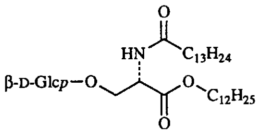


23

the α-galactosyl ceramide **23**, which has been isolated from a Japanese sponge, was prepared by use of a benzylated glycosyl fluoride.[56] Compounds **24**-**28** were synthesized, and their calcium ion binding abilities determined. These compounds are analogues of soya-cerebroside II. Synthesis was by way of the glycosyl imidate method.[57] Compound **29** and its D-*galacto*-analogue have been reported, their preparation also being by way of the trichloroacetimidate procedure.[58] When sphingenine-like compounds are converted to *N*-diphenylmethylene imines the neighbouring primary hydroxyl group is activated towards glycosylating reagents. Several mono- and di-saccharide derivatives including lactosides were made.[59]



	R^1	R^2	R^3
24	H	H	β-D-Glc*p*
25	OH	H	β-D-Glc*p*
26	H	OH	β-D-Glc*p*
27	OH	H	β-D-Gal*p*
28	is 8, 9-dehydro **25**		



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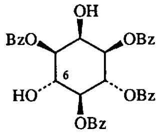
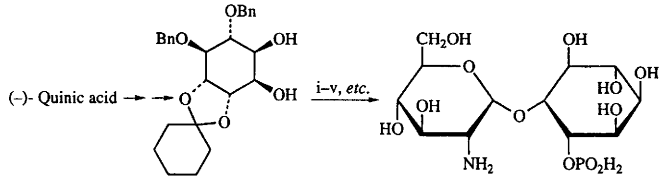


30

Enzymic glycosylation of *myo*-inositol afforded 4-*O*-α-glucopyranosyl-*myo*-inositol, the absolute configuration of which was established by selective glycosylation using tetra-*O*-benzyl-D-glucosyl fluoride at the equatorial O-6, of the inositol derivative **30**.[60] In Scheme 6 the synthesis from (-)-quinic acid of 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol **31**, an insulin second messenger, is illustrated.[61] A somewhat different approach to glycosylcyclitols is treated in Chapter 18 which records the synthesis of a disaccharide involving a *pseudo*-sugar related to kedarosamine. The method used involved building the cyclitol unit from a 1-glycosyloxybutadiene derivative,[62] and Chapter 18 also refers to the synthesis of a glycosylcyclitol by rearrangement of a glycosyl 6-deoxyhex-5-enose derivative. The licorice saponin A3 (compound **32**) has been prepared from glycyrrhizin by Koenigs-Knorr glycosylation,[63] and the structure/haemolitic activity relationships for 15 synthetic methyl

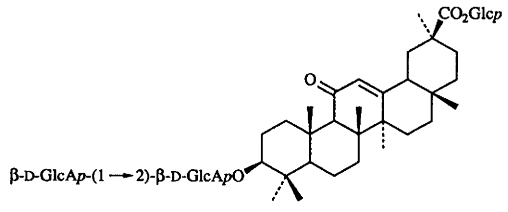


31

Reagents: i, Bu_2SnO; ii, BzCl, iii, $MeOC_6H_4CH_2OC(=NH)CCl_3$; iv, K_2CO_3, MeOH; v, 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-*p* -D-glucopyranosyl trichloroacetamidate

Scheme 6

glycyrrhetate glycosides has been reported.[64] Similarly haemolytic, antibacterial and antifungal activities of 15 synthetic methyl ursolate glycosides have been examined,[65] and use of hepta-acetyl cellobiosyl trichloroacetimidate has allowed the preparation of the tiqueside **33**.[66] In related work a study of structure-activity relationships of medicagenic acid saponins (that is those having antifungal activity) was carried out on a set of glycosides varying in their mono- and di-saccharide components.[67] A standard approach to uronosylation has given rise to an α/β mixture of the steroidal uronosides **34**.[68]



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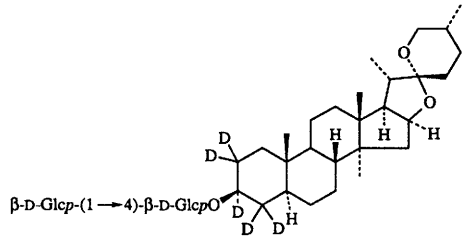
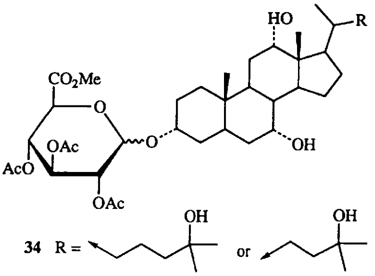


33

Also in the area of steroid glycosides, β-D-xylopyranosides of cholestan-3α- and 3-β-ol were prepared and used as models for n.m.r. comparisons with naturally occurring tetralinyl xylopyranosides.[69] The syntheses of isoflavone glycosides as potential β-galactosidase inhibitors have been reported[70] as has the use of sucrose phosphorylase from *Leuconostoc mesenteroides* to catalyse transglycosylation from sucrose to give the catechin glycoside **35**.[71] The same compound has been made by glycosylation using



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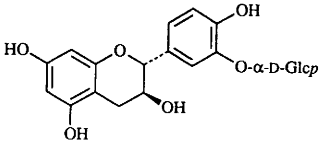
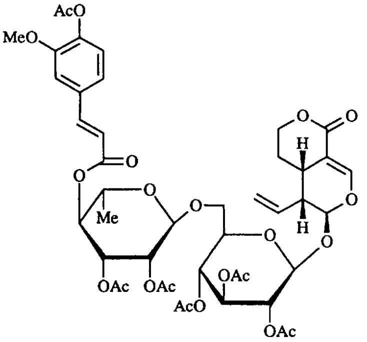


35

soluble starch in the presence of cyclodextrin glucano-transferase. The product was tested as an inhibitor of tyrosinases.[72]

The newly discovered iridoid glycoside **36** has been made as its hexa-acetate by condensation of the appropriate 6-trityl ether with the required 1,2-cyanoethylidene acetal.[73] Condensation of trimethylsilyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside with the corresponding alcohol in the presence of boron trifluoride resulted in the production in 80% yield of the acetylated glycoside of the podophyllum lignan **37** with an α,β-ratio of 5:95.[74]



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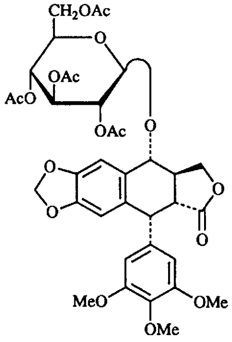
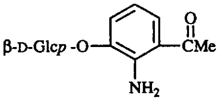


37

1.3 *O*-Glycosides Isolated from Natural Products.–As usual only compounds showing special features, usually within the sugar moieties, are dealt with in this section.



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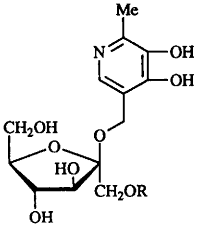
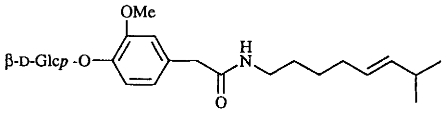


39 R = H
40 R = β-D-Fru*f*

Amongst relatively simple unusual compounds to have been reported are: ethyl 2-acetamido-2-

deoxy-β-D-glucopyranoside which was found in a yeast extract,[75] the acetophenone derivative **38**, which is a new fluorescent compound obtained from human lens insoluble protein,[76] the β-fructofuranosyl derivatives of pyridoxine **39** and **40** which were isolated from culture filtrates of *Aspergillus niger* when it was grown in a medium containing sucrose and pyridoxine,[77] and similarly the glucoside **41** was obtained from a cell suspension of *Coffea arabica* when it was grown in the presence of the aglycon.[78]



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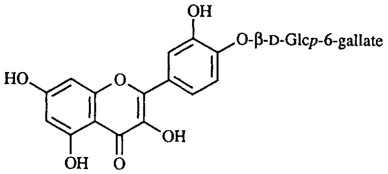
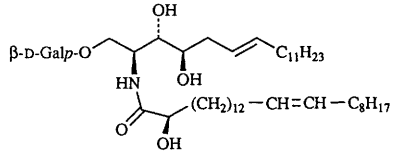


42

The structure-sweetness relationship has been established for a set of saponins from *Glycyrrhizae Radix*.[79] The relationship between structures of 16 synthetic tigogenyl glycosides and their haemolytic and antifungal activity has been reported,[80] and compound **42** was the most effective antioxidant and



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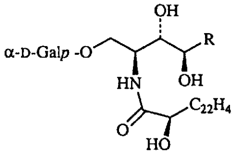
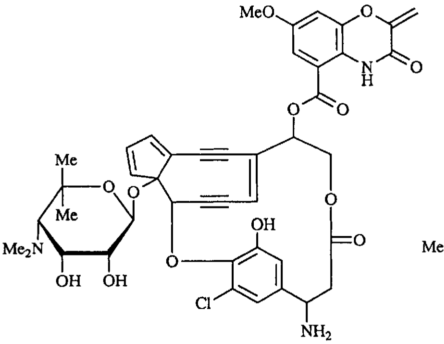


44 $R = C_{12}H_{25}$, $C_{13}H_{27}$, $C_{11}H_{22}CHMe_2$, or $C_{11}H_{22}CH(Me)CH_2Me$

had the highest superoxide dismutase activity of a set of nine active tannin and flavonoid compounds isolated from *Eucalyptus rostrata*.[81]



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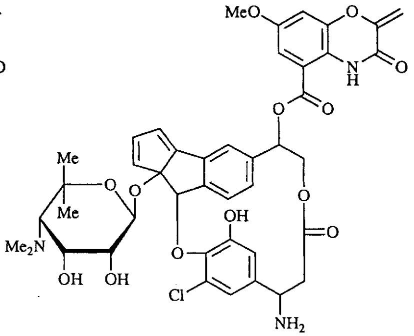


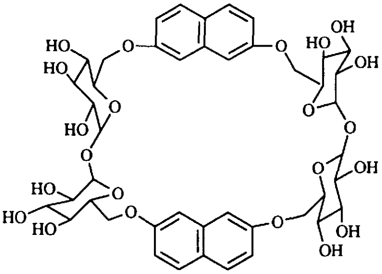
46

Compound **43** is a new glycosphingolipid from the red alga *Corallina pilulifera*. It is the first such compound to be isolated from a seaweed and is unusual in having a C-6 double bond.[82] Compounds of the set **44** are novel agelasphin ceramides isolated from a marine sponge. They are the first α-linked galactosyl such compounds.[83]

The delicate enediyne compound **45** has been obtained from a *Streptomyces globosporus* C1027 broth filtrate.[84] On treatment with such mild reagents as methanol or dioxane it aromatizes to give compound **46** which has been analysed by n.m.r. methods. The absolute configuration was not determined.[85]

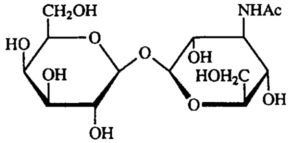
1.4 Synthesis of Disaccharides and their Derivatives.-In the field of non-reducing disaccharides isotopically labelled forms of sucrose were produced by chemical or enzymic methods having C-1, C-2, C-3 and C-6 of their fructofuranosyl ring ^{13}C labelled. ^{1}H-^{1}H, ^{13}C-^{1}H And ^{13}C-^{13}C spin coupling constants were then used to assess the furanose ring conformation and the glycosidic bond orientation.[86] α,α′-Trehalose has been prepared by biochemical methods having both C-1 positions ^{13}C labelled,[87] and ^{14}C trehalose has also been made by biochemical procedures from ^{14}C-labelled glucose, and β-glucose 1-phosphate by use of trehalose phosphorylase.[88] An investigation of the anomalous hydration of trehalose and several oligosaccharides containing α-D-glucopyranosyl units has been reported.[89]

The very interesting glycophane **47** has been synthesized from a trehalose 6,6′-ditriflate and found to display specific carbohydrate-carbohydrate interactions with some glycosides.[90]



47

Several novel non-reducing disaccharides have been reported. A practical isolation of trehalulose (1-α-D-glucopyranosyl α-D-fructopyranoside) from a novel strain of *Agrobacterium* has been described,[91] as has a chemico-enzymic synthesis of α-D-glucopyranosyl 6-deoxy-α-L-sorbofuranoside.[92] A new type of galactosyl transferase reaction has been discovered by which UDP-glucose in the presence of UDP-glucose epimerase with 3-acetamido-3-deoxy-glucose and a transferase gave β-D-galactopyranosyl 3-acetamido-3-deoxy-β-D-glucopyranoside **48**.[93] Several other novel non-reducing disaccharides containing amino-sugars have been made by chemical procedures starting from acosamine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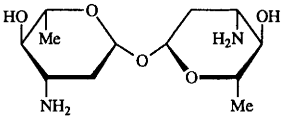
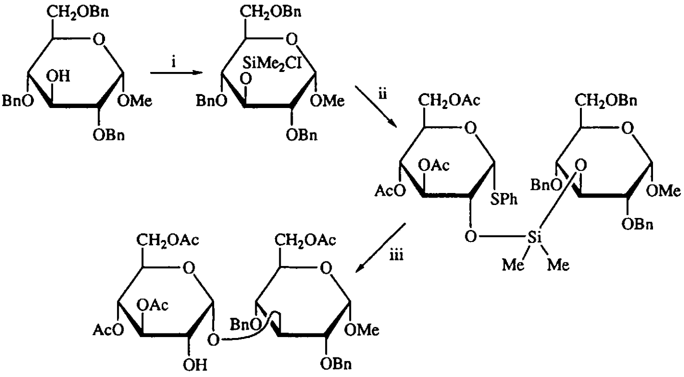

49

and ristosamine; a range of compounds, for example **49** and its α,α- and α,β-isomers, were produced.[94]

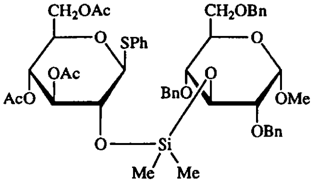
In the area of reducing disaccharides, several reports have appeared on the modification of disaccharide derivatives in ways which make them subject to further reaction, for example conversion to higher saccharides. Thus peracetylated glycosyl fluorides can be made from the corresponding peracetates with pyridinium poly(hydrogen fluoride).[95] 2-(Trimethylsilyl)ethyl glycosides, on treatment with acyl anhydrides in the presence of boron trifluoride, give the corresponding glycosyl β-esters which, in the case of the 4-pentenoyl compounds, are glycosyl donors.[96] 2-(Benzylthio)ethyl glycosides, on the other hand, can be cleaved by oxidation to corresponding sulfones which, with base, undergo hydrolysis. In this way, for example, disaccharides fully *O*-benzylated, other than at the anomeric position, can be produced.[97] Enzymic hydrolysis of peracetylated disaccharides can occur selectively at the anomeric position; for example β-octa-acetyl cellobiose gives the 1-hydroxy compound on treatment with a lipase from *Aspergillus niger*. β-Maltose octa-acetate and α/β-lactose octa-acetates are similarly selectively deacylated, and the method is reported as being preferable to chemical deacylation at the anomeric centre.[98]

As usual several reports have appeared on aspects of methodology which lead to better glycosylation procedures. The use of dibenzyl *N*,*N*′-diethylphosphoramidate for the preparation of dibenzyl glycosyl phosphites has been described together with their subsequent transformation to phosphates. This methodology can result in the preparation of otherwise unprotected glycosyl phosphates. With receptor sugar alcohols in the presence of trimethylsilyl triflate the intermediate dibenzyl phosphites can be used as useful glycosylating agents. A specific example is given below in the *N*-acetylneuraminic acid section.[99] The Bols procedure (Scheme 1) applied in disaccharide synthesis gave the 2-α-linked glucobiose,[100] and a minor modification involving the preparation of the silicon-bridged dimer by way of a chlorosilyl ether held in the aglycon is illustrated in Scheme 7.[101] In this reaction the propensity of silyl iodides to cause debenzylation can lead to irregular compounds; thus a significant product formed from the bridged disaccharide **50** is the tricyclic ether **51**.[100] The synthesis of simple glycosides from glycosyl methoxyacetyl esters is mentioned above,[15,16] and the approach can also be applied to disaccharide syntheses. For example tetra-*O*-benzyl-α-D-glucopyranosyl methoxyacetate, treated with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside in the presence of ytterbium triflate, gave the 1,6-linked disaccharides in 94% yield with, however, no strong



Reagents: i, Me_2SiCl_2, Et_3N; ii, *S*-phenyl-3,4,6-tri-*O*-acetyl-1-thio-α-D-glucopyranoside, Py; iii, NIS, $MeNO_2$

Scheme 7



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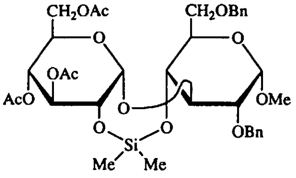


51

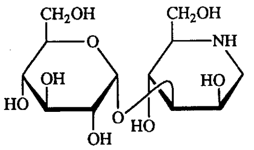
stereoselectivity. The α/β ratio was 30:70. With 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl methoxyacetate a similar high yield was produced but only the β-linked compound was formed.[102] For Mukaiyama coupling of glycosyl acetates it has been found that trityl groups are suitable activators of the aglycons whereas silyl ethers are not. Use of 2,3,4,6-tetrabenzyl-D-glucopyranosyl acetate with 6-*O*-tritylglucoside derivatives and silver triflate/tin tetrachloride resulted in 84% of 1,6-linked dimer which impressively was specifically the α-anomer.[103] Reaction of *O*-benzylated α-glycosyl chlorides with primary or secondary monosaccharide alcohols is significantly catalysed by 0.1 mol. equiv. of zinc *p*-*tert*-butyl benzoate in the presence of 2-methyl-2-butene. Yields were in the range of 40-100% and β-selectivities were extremely high. Studies in the D-glucose, D-galactose and L-rhamnose series were reported.[104] A critical evaluation of *S*-ethyl thioglycosides and nitrophenyl thioglycosides as glycosylating agents has extended the armed,disarmed concept. Thus the ethylthio group can be activated selectively with IDCP. Likewise, benzylated and benzoylated analogues are considered to be "less armed" and "more disarmed" variants.[105] *S*-Phenyl 2,3,4,6-tetra-*O*-benzyl or *O*-benzoyl-1-thio-β-

D-glucopyranoside electrolysed in an undivided cell in dry acetonitrile with primary or secondary carbohydrate alcohols give good yields of mainly β-linked disaccharide products.[106]

Dextransucrase from a *Streptococcus*, besides forming polymers, can be used as a glycosylating catalyst to transfer glucose units to acceptor substrates. Methyl α-D-glucopyranoside is thereby converted into the 1,6-α-linked dimer and methyl 6-bromo-6-deoxy-α-D-glucopyranoside is glycosylated by way of a α-1,3-linkage.[107]

As always, considerable attention has been given to disaccharides and disaccharide derivatives containing glucose at the non-reducing terminal position. These include several glucosamine derivatives having β-1,6-glucosylation,[108] cellobiose and maltose, as well as several monosaccharides, linked by way of a glycosylamine bond to asparagine,[109] various disaccharides *O*-linked to serine, which were made by enzymic coupling of sugars,[110] several 3-*O*-D-glucopyranosyl mannose derivatives with variations in structure at C-1 and C-2 of the mannose unit, which were prepared as potential mannosidase inhibitors. The compounds with O-1 removed from the mannose analogue, and the 1,2 double bonded analogue, that is the glycal, were found to inhibit the enzyme.[111] β-1,4-Linked glucosylallose and the corresponding galactosylallose were made by way of the corresponding glycosyl glucoses by inversion at C-3.[112] 6-*O*-α-D-Glucopyranosyl-D-fructose has been produced by biological methods from sucrose,[113] and 4-*O*-β-D-glucosyl- and -galactosyl-D-gluconic acid have been used to prepare synthetic glycolipids linked through amide bonds.[114] β-1,2-Linked glucobioses, galactobioses and corresponding uronic acid analogues were used to make the corresponding glycosides of glycyrrhetic acid,[115] and several common disaccharides have been linked to methyl ursolate and the haemolytic and antifungal activities were determined. Some were potent haemolytic agents.[65]

Special interest has been shown in the *endo*-mannosidase inhibitor **52** which is a glucosyl mannose disaccharide analogue. An extensive range of monodeoxy derivatives and monomethyl ethers with variations in the glucose moiety were produced, as well as analogues with galactose and xylose in place of glucose, by coupling the modified glucose units as glycosyl chlorides with the suitably protected base.[116] Likewise a set of analogues modified in the basic moiety were prepared.[117] It was concluded that all of the hydroxyl groups and the NH group in the latter ring were important for binding. Likewise the hydroxyl groups at 3 and 4 in the glucose unit were necessary, but the 2- and 6-hydroxyl groups were not important. Fleet and Dwek's groups have combined to report a further synthesis of



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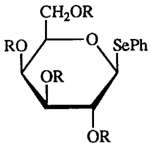
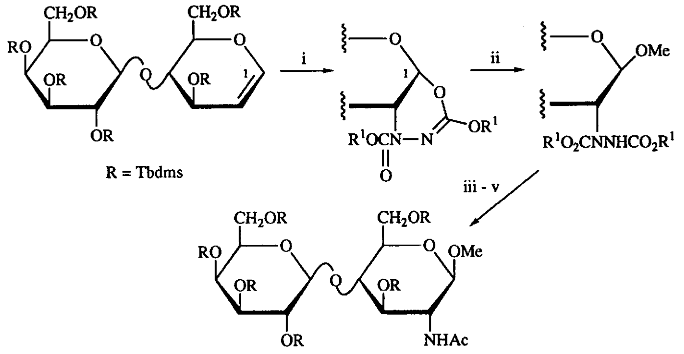


53 R = Bn
54 R = Bz

compound **52** together with the isomer of an α-D-mannopyranosyl analogue similarly linked to the basic unit.[118]

In the field of galactosyl disaccharides, the glycosylating properties of phenyl selenoglycosides **53** and **54** were assessed. While the "armed" former compound and IDCP led to good yields with primary and secondary acceptors, and α/β mixtures with α-selectivity increasing with steric hindrance, "disarmed" donor **54**, together with NIS/TfOH, gave β-products only. As a generalization the selenoglycosides are more reactive than the corresponding ethyl 1-thioglycosides.[119] A systematic investigation of the use of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-cyanobenzylidene)-α-D-galactopyranoses as glycosyl donors has been undertaken, the product ratios being found to be dependent on electron donors and acceptors on the benzene rings. The proportion of 1,2-*trans*-related products was highest with electron releasing groups and with trityl triflate as promoter. In each case the alcohol receptors were used as their trityl ethers.[120] The rather striking observation has been made that 1,2-cyanoethylidene acetals in the α-D-*galacto*- and β-D-*manno*-series, on treatment with 4,6-ditrityl ethers of otherwise substituted methyl galactosides and methyl glucosides, respectively, gave 1,4-β and 1,4-α-linked compounds as major products. When 2,6-ditrityl ethers were used as glycosyl acceptors 2-substituted disaccharides were the main products.[121] The β-1,2-linked galactobiose has been synthesized as its 2-trimethylsilyl ethyl glycoside,[122] and a β-galactosidase was used in the preparation of the β-1,2-linked galactobiose as its *N*-protected serine glycoside.[123] In efforts to prepare compounds with inhibitory activity against tumor cell colonization, the β-lactosyl group has been attached to various peptides through spacer arms.[124] Benzoylation of 3′,4′-*O*-isopropylidene β-lactosides with 4.2 equivalents of benzoyl chloride led to high yields of the 2,2′,6,6′-tetrabenzoates which were prepared for use as standard intermediates for making sialyl Lewis X analogues.[125]

Glycosyl transfer from *p*-nitrophenyl β-D-galactopyranoside to 6-*O*-acetyl-D-glucal or -D-galactal with a β-galactosidase occurs with high selectivity at the allylic 3-positions. Standard glycal additions then led to the 1,3-linked galactosyl 2-acetamido-2-deoxy-glucose and -galactose disaccharides. *N*-Acetylglycosamine transfer from UDP GlcNAc then caused glycosylation at the 6-position of the galactosamine residue to give the branched trisaccharide.[126] Lactosaminides can be prepared using a β-galactosidase which can transfer β-D-galactose from lactose to O-4 of *p*-nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside provided the concentration of DMSO or acetonitrile in the reaction medium is high. In an aqueous medium the 1,6-linked product is formed. The enzyme will also transfer this sugar to the 4-position of *N*-acetylgalactosamine.[127] Toepfer and Schmidt have demonstrated an ingenious new way of alkoxyaminating substituted glycals and thus preparing *N*-acetyllactosamine (Scheme 8).[128] A continuous enzyme-mediated synthesis of this compound in an enzyme-membrane reactor has been reported,[129] and it has been made with linkage to a serine dipeptide by enzymic methods.[130] 4-*O*-α-D-Galactopyranosyl-D-glucuronic acid has been made as a propyl glycoside by way of the trichloroacetimidate technique, the product representing a structural element of a capsular

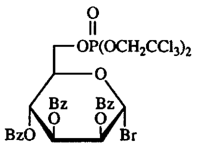


Reagents: i, $R^1O_2CN{=}NCO_2R^1$, Δ; ii, MeOH, $BF_3.Et_2O$; iii, BnOH, NaH; iv, Raney Ni, H_2; v, Ac_2O

Scheme 8

polysaccharide of *Streptococcus pneumoniae* Type 8,[131] and the benzyl β-glycosides of the analogous β-linked disaccharides carrying sulfate ester groups at O-4′ or O-6′ or at both these positions have been studied by n.m.r. methods as part of the conformational investigation of chondroitin sulfate-related compounds. This paper also investigated sulfates derived from dimers having the uronic acid and the hexose parts interchanged.[132]

For the preparation of mannosyl disaccharides 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl fluoride can be condensed with sugar alcohols in the presence of a complex derived from dibutyltin dichloride and silver perchlorate to give disaccharides with mainly the α-configuration.[133] The enzyme α-1,2-mannose transferase has been overexpressed by molecular biological processes, and by its use α-1,2-linked mannobiose linked to a peptide has been converted to the corresponding trisaccharide, also linked to the peptide. A multi-enzyme system was developed which included a GDP-Man regeneration step, this being the source of the D-mannose for transfer.[134] In related purely chemical work the glycosylating agent **55**, on condensation with 1,3,4,6-tetra-*O*-acetyl-β-D-mannose in the presence of



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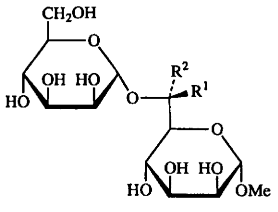
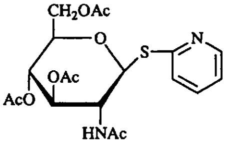


56 $R^1 = H$, $R^2 = Me$
57 $R^1 = Me$, $R^2 = H$

silver triflate, also led to the α-1,2-mannobiose compound which was then coupled, by way of the corresponding glycosyl bromide, with a protected threonine.[135] Use of **55** with *S*-phenyl 2,3,4-tri-*O*-benzoyl-1-thio-α-D-mannopyranoside led to the α-1,6-mannobiose which was also coupled to a threonine compound prior to conversion into a disaccharide tripeptide.[135] The analogues **56**, **57** of α-1,6-linked mannobiose were prepared starting from a 6-aldehydo derivative which was treated with a methyl Grignard reagent and then mannosylated. The 2-amino-2-deoxy analogue of the parent disaccharide was also produced.[136] A range of α-D-mannopyranosides was produced by treatment of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl acetate or *p*-nitrobenzoate with primary or secondary alcohols, the reactions being promoted by zinc triflate and trimethylsilyl chloride in acetonitrile. Yields were in the 70-90% range and α/β ratios upwards of 97:3. By this procedure methyl 6-*O*-α-D-mannopyranosyl-D-glucoside was produced.[137] α-L-Mannopyranose has been linked separately to each of the hydroxyl groups of methyl D-glucopyranosides and O-6 of D-galactose and O-5 of methyl β-D-glucofuranoside to give compounds to act as substitutes for naringinase.[138]

Enzymolysis of levan has led to the isolation of levanbiose [β-D-Fru*f*-(2→6)-D-Fru].[139]

Normally 2-pyridyl 1-thioglycosides with an acetyl group at O-2 are not activated as glycosyl donors by methyl iodide. The glucosamine analogue **58**, however, is so activated and gives rise to 1,2-*trans*-linked glycosides and disaccharides.[140] Access to 1,2-*cis*-analogues can be obtained by use of 1,2-*trans*-2-azido-2-deoxyglycosyl thiocyanates as donors, trityl ethers of the acceptor alcohols and trityl perchlorate as activator.[141] D-Glycosyl phosphite **59**, with trimethylsilyl triflate as catalyst, has afforded the β-1,6-linked glucosaminobiose in 63% yield. A related β-glycosyl phosphite also led to β-1,6-linked products which were used in making lipid A.[142] Compound **60** and some related aza-analogues of glucosaminyl muramic acid disaccharides have been prepared as potential anti-bacterial agents.[143]



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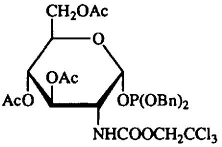

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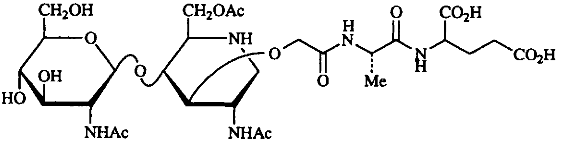

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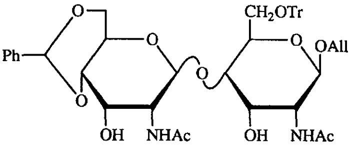
An enzymic method for preparing chitobiose in hundred gram quantities from chitin has been developed and the product was converted into the disaccharide **61** which is based on the carbohydrate component of the insecticide allosamidin.[144] The further allosamine-containing disaccharide derivative



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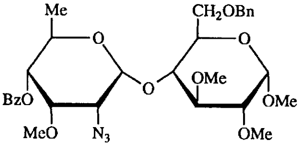
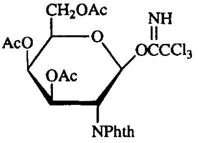


62

62 has been synthesized using the trichloroacetimidate procedure.[145] In the galactosamine series the trichloroacetimidate **63** has been 1,4-linked to 4-hydroxy-3-benzoxy-bearing D-galactose derivatives with boron trifluoride as catalyst. Moderate yields were obtained of both α- and β-linked products, and also 1,3-linked products following benzoyl migration within the aglycon. Better results were obtained by use of silver triflate as activator. Yields were then in the 80-90% region with almost exclusive β-coupling. No products of benzoyl migration were detected.[146]



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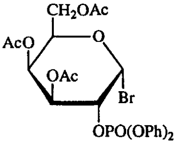

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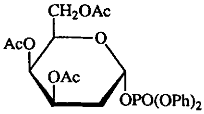
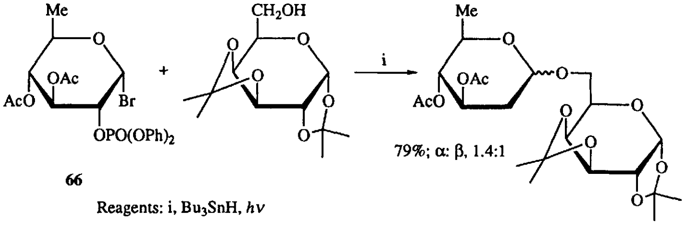


65

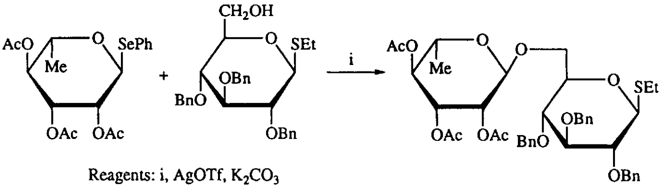
Considerable further interest is being shown in deoxysugar disaccharides. Coupling of the 2-deoxyglycosyl phosphate **65** (made by tributyltin hydride reaction of the bromide **64**) using magnesium perchlorate as activator, has been used to give the disaccharide having 2-deoxygalactose linked 1→6 to D-glucose, the yields and α,β-ratios being 53% and 3.8:1. A very impressive consequence of the work is that bromide **66** can be used directly to produce 2-deoxy-glycosyl products with remarkable efficiency as illustrated in Scheme 9.[147] The ingenious way of making 2-deoxyglycosides from 1,2-*trans*-related



Reagents: i, Bu_3SnH, *hν*

Scheme 9

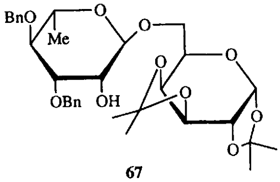
S-phenyl 2-*O*-phenoxythiocarbonyl-1-thioglycosides (Volume 26, p 32, Scheme 15) has been further assessed. While ethyl thioglycosides are better donors, phenyl thioglycosides yield products which are more readily desulfurized.[148] Seven monodeoxy derivatives of 2-(trimethylsilyl)ethyl β-lactoside have been made, the 2-, 3-, and 6-deoxy compounds by galactosylation of suitable deoxyglucosides, and deoxygenation at positions 2′, 3′, 4′, and 6′ being effected at the disaccharide level.[149] In the L-rhamnose series the interesting reaction illustrated in Scheme 10 gave 80% yield of product, the



Reagents: i, AgOTf, K_2CO_3

Scheme 10

"disarmed" phenyl selenoglycoside being activated selectively in the presence of the "armed" thioglycoside. The phenyl selenoglycosides, however, were deactivated by bases such as collidine, and glycosyl bromides activated preferentially relative to phenyl selenoglycosides by silver triflate in the presence of collidine. The selectivities of glycosylating agents are thus extended usefully by these findings.[150] α-L-Rha*p*-(1→3)-α-D-Glc*p*-OMe has also been made.[151] Other L-rhamnosyl disaccharides to have been reported are compounds **67**, prepared by way of the 1,2-anhydro-L-rhamnose ether,[152] and



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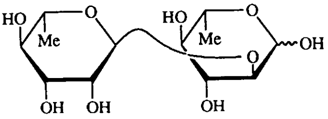
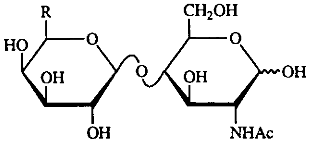
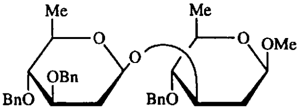


68

68, which was converted into its α-acetobromo derivative as part of a programme investigating the preparation of hesperetin sweetening agents.[153] Extensive study of the reaction of 2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl bromide under Helferich conditions (mercury cyanide/mercury bromide, acetonitrile) with a range of mono- and di-hydroxy sugar derivatives has been undertaken.[154] UDP-6-Deoxy-D-galactose and UDP-6-Deoxy-6-fluoro-D-galactose have been prepared chemically and used for enzymic



69 R = Me **70** R = CH_2F

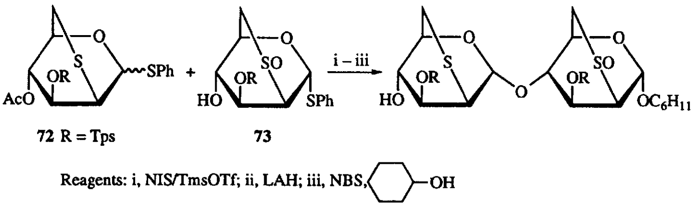


71

glycosyl transfer to carbohydrates; D-lactosamine analogues **69** and **70** were produced in this way.[155] α-L-Fuc*p*-(1→2)-β-D-Gal*p*-O$(CH_2)_7$Me, which is an acceptor disaccharide for both transferases responsible for the biosynthesis of A and B blood group antigens, has been made by standard methods together with the six possible deoxy- and deoxy-fluoro analogues modified in the galactose unit.[156]

Several *O*-methylated 6-deoxyhexosyl disaccharides have been described in connection with studies of natural products: 2-*O*-Me-α-L-Fuc*p*-(1→3-)-L-Rha*p*-OMe,[151] a component of a bacterial lipopolysaccharide; 3,4-di-*O*-Me-α-L-Rha*p*-(1→2)-3,4-di-*O*-Me-α-L-Rha*p*, a component of a glycotetrapeptide of the core of a *Mycobacterium* glycopeptidolipid;[157] and 2,3-di-*O*-Me-α-L-Fuc*p*-(1→3)-2,4-di-*O*-Me-β-D-Xyl*p*, the carbohydrate component of a novel glycosylated macrolide from a red alga.[158]

Several reports have appeared on the topic of disaccharides based on 2,6-dideoxyhexoses, the field attracting some very ingenious chemistry. Scheme 11 illustrates another case of preferential arming/disarming, the sulfide-based thioglycoside **72** being activated in the presence of the sulfoxide analogue **73** to give a product which was reducible to the 2,2′,6,6′-tetradeoxy disaccharide of the

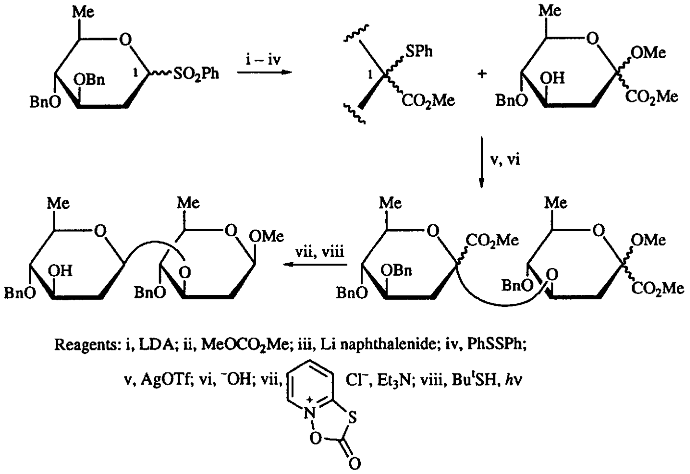


72 R = Tps

73

Reagents: i, NIS/TmsOTf; ii, LAH; iii, NBS, –OH

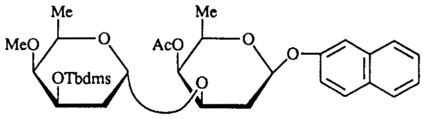
Scheme 11



Reagents: i, LDA; ii, $MeOCO_2Me$; iii, Li naphthalenide; iv, PhSSPh;
v, AgOTf; vi, ^-OH; vii, Cl^-, Et_3N; viii, Bu^tSH, *h*ν

Scheme 12

avermectins.[159] The β-1,3-linked compound **71**, the C′, D′ disaccharide of aureolic acid, has been made by more conventional methods involving glycal addiction reactions.[160] In Scheme 12 a quite different approach involving radical technology is illustrated for use in a synthesis of the olivomycin A disaccharide,[161] and an NIS-promoted glycal addition reaction was used in the key step of the preparation of the related dimer derivative **74**.[162] Compounds **75** and **76** were made, respectively, by use of the glycosyl bromide **77**[163] and by coupling of **78** with **79** followed by a Mitsunobu inversion at C-3.[164] Other related compounds to have been synthesized by use of the glycopyranosyl dimethylphosphinothioate **80** are the L-anhydro-sugar derivative **81** and **82** which were formed in 79% yield with α/β ratio 76:24 (Scheme 13).[165] 2,6-Dideoxy-α-L-*arabino*-hexose (the sugar of which **79** is a derivative) has been bonded to O-3 of methyl β-D-glucopyranoside and O-2 of methyl α-L-rhamnopyranoside.[166]



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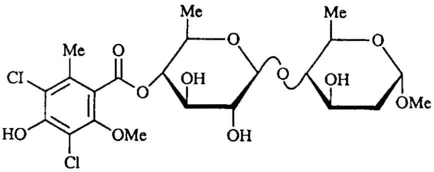

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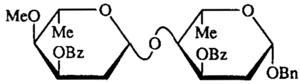

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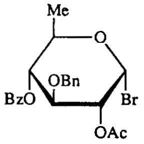

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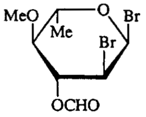

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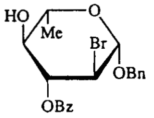

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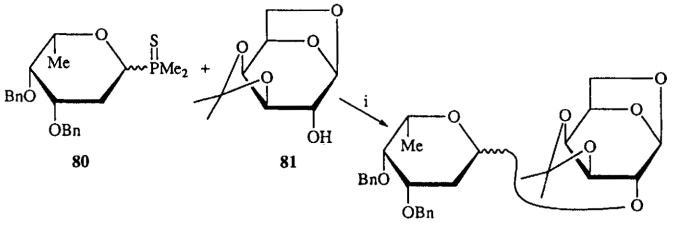
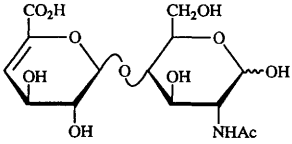


80 **81** **82**

Reagents: i, $AgClO_4$, molec. sieve

Scheme 13

In the field of uronic acid disaccharides, enzymic digestion of heparin gave the unsaturated disaccharide **83**,[167] and the related compound **84**, named lepidimoide, which has been isolated from germinating cress seeds, promotes shoot growth and inhibits root growth. It has been synthesized to determine its absolute configuration.[168] The artificial 2-acetamido-2-deoxy-β-D-mannuronic acid-



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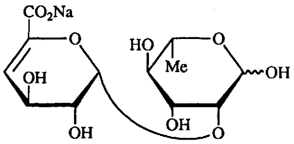
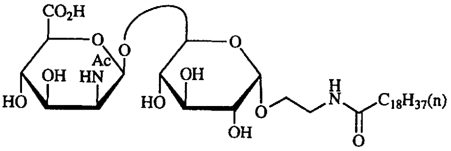


84

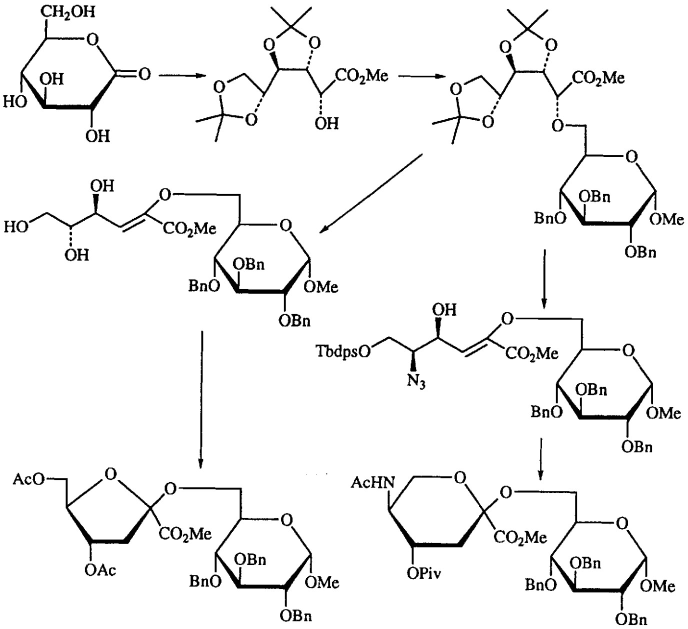
containing glycolipid **85**, which corresponds to the repeating unit of a teichuronic acid from



85

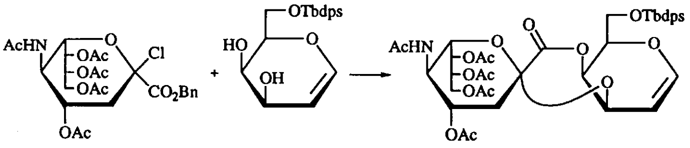
Micrococcus luteus, has been synthesized.[169]

Much interest continues in the chemistry of ulosonic acids and Scheme 14 shows the synthesis of



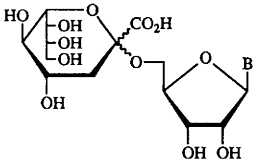
Scheme 14

some hexulosonic acid disaccharides in outline. The key steps were base-catalysed eliminations to give the alkenes and phenylselenyl halide-induced ring closures followed by tributyltin hydride deselenations.[170] Allyl 6-*O*-(α-D-*glycero*-D-*talo*-2-octulopyranosyl)-onate-2-acetamido-2-deoxy-β-D-glucopyranoside, which is a derivative of the core constituent of the lipopolysaccharide from *Acinetobacter calcoaceticus*,[171] and the α-2,8-linked dimer of 3-deoxy-D-*manno*-2-octulopyranosylonate have also been prepared, together with some disaccharides having other monosaccharide substituents on the ulosonic acid residue.[172] A *trans*-sialidase from *Trypanosoma cruzi* can be applied to the synthesis of oligosaccharide chains containing the α-Neu5Ac-(2→3)-Gal terminal sequence.[173] Chemical methods have been used to synthesize α-D-Neu5Ac-(2→2)-D-Gal linked to a ceramide unit, and the same paper describes the condensation of the sialylating reagent **86** and the glycal **87** which gave the tricyclic **88** (Scheme 15) and hence afforded a route to a (2→3)-sialylated galactoceramide.[174] Koenigs-Knorr conditions were used to prepare the nonulosonic acid-substituted nucleosides **89**,[175] and the branched chain sugar glycoside **90**. The latter was synthesized starting from a hexos-4-uloside derivative and is a mimic for the Lewis X determinant which blocks the interaction of the lectin domain of E-selectin.[176] The novel disaccharide analogue **91**, comprising *N*-acetylneuraminic acid and deoxynojirimycin, as well as the D-*galacto*-analogue, have been prepared. Minor products in which the carboxylic acid groups are free and the ring nitrogen atoms are methylated were produced.[177]

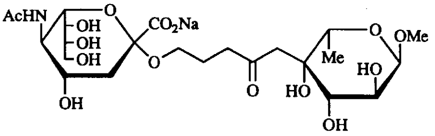


86 **87** **88**

Scheme 15



89 B = Ura, 5-F-Ura, or Cyt



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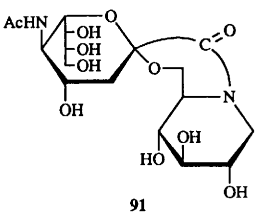
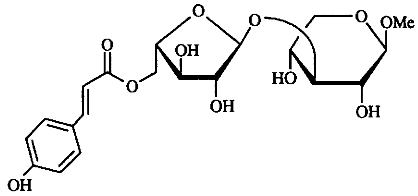


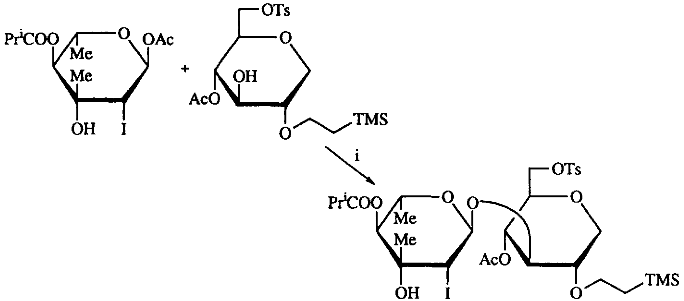
91



92

The feruloyl ester **92** and the corresponding 5-*O*-coumaroyl disaccharide derivative, as well as analogous compounds with 1→2 linkages, have been produced.[178] Mukaiyama, using silver triflate, silver perchlorate, and Lawesson's reagent or alternatives and the required 2,3,5-triether, has developed a β-ribofuranoside synthesis applicable to disaccharides which is highly efficient and highly selective, yields being greater than 90% with anomeric selectivities in the same range.[179] Alternatively, using 2,3,5-tri-*O*-benzyl-D-ribosyl iodoacetate and trimethylsilylated alcohols he obtained high β-selectivity when using similar coupling reagents to the above, but with silver perchlorate together with lithium perchlorate, α-selectivity in the region of 88% was claimed.[180]

3'- And 4'-deoxyfluoro derivatives of lactose and their ceramide glycosides have been produced using (trimethylsilyl)ethyl glycosides as intermediates.[181] Some other fluorinated analogues of disaccharides are referred to above. Disaccharides based on olivomycosides have been produced, the key step being as indicated in Scheme 16, the iodine atom being deemed to have participated in the reaction.[182]



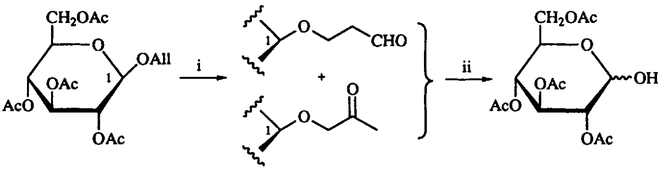
Reagents: i, TmsOTf

Scheme 16

Disaccharides based on 5-thio-D-arabinopyranose are referred to Chapter 11.

1.5 Hydrolysis and Other Features of Glycosides and Disaccharides.

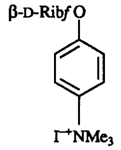
-Deslongchamps has presented a comprehensive review on the stereoelectronic effects applying during the hydrolysis of glycosides.[183]



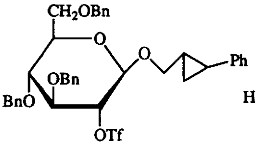
Reagents: i, PdCl$_2$, CuCl, O$_2$, DMF, H$_2$O; ii, *h*ν, Et$_3$N

Scheme 17

Allyl glycosides can be cleaved under mild conditions (Wacker oxidation) as illustrated in Scheme 17.[184] The quaternary ammonium salt **93** is a UV-active substrate for the study of DNA glycosylases. The kinetics of its hydrolysis have been studied over the pH range 0-12.[185] The acid-sensitive aglycon can be released from glycoside **94** using pyridine and aqueous DMF at 160 °C, and the carbohydrate product is a 2,5-anhydrohexose triether. Aspects of the stereochemistry of the ring contraction reaction were examined.[186] Enzymic hydrolysis of the secoiridoid glucoside **95** occurs with rearrangement of the ester alkoxide group and gives jasmolactone **96**.[187]



93



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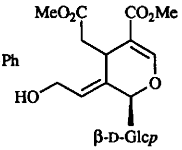
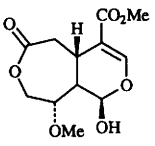


95



96

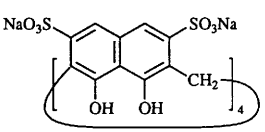
Monosaccharide monolayers have been implanted on a gold electrode already coated with thioamines by use of *p*-isothiocyanatophenyl α-D-*manno*-, β-D-*gluco*- and α-D-*gluco*-pyranosides which bind to the amines. The kinetics of binding of a modified protein (concanavalin A) to the modified electrodes were followed by cyclic voltametry and the binding could be photoregulated.[188] Stability constants for the 1:1 complexes formed between the cyclic tetramer **97** and some simple carbohydrates were determined by proton spectroscopy. Free sugars do not complex but methyl pyranosides do.[189] In related work the binding of octyl glycosides with cyclic resorcinol tetramers was examined; the complexing is dependent upon sugar-sugar interactions which are dependent upon sugar stereochemistry. Binding strengths decrease in the order glucosides, mannosides, galactosides, pentosides.[190]

The liquid crystal properties of *p*-alkylphenyl D-glucopyranosides have been considered.[191]

A conversion of isomaltulose to α-D-glucopyranosyl-oxymethylfurfural which is applicable on an industrial scale is based on heating in DMSO in the presence of H^+-form resin.[192] The same compound can be degraded efficiently in air with potassium hydroxide to give potassium 5-*O*-α-D-glucopyranosyl-D-arabinonate.[193]

2 *S*- and *Se*-Glycosides

Several references to such compounds as precursors of *O*-glycosides have been made in Section 1; see e.g. **10**, **50** **53**, **83**, Scheme 10, 11.



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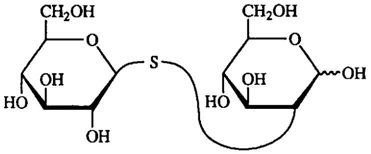
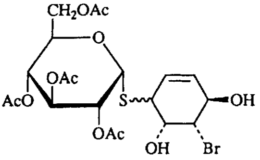
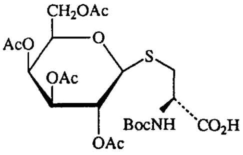


98

Free sugars protected at all centres except the anomeric, on reaction with aryl disulfides, and tributylphosphine or triethylphosphine (but not triphenylphosphine) give aryl thioglycosides. A typical yield is 80%. For example, 2:3,5:6-di-*O*-isopropylidene-D-mannose gives such aryl thioglycosides in 80% yield and with an α/β ratio of 1:2.5. In the case of tetrabenzyl aryl thioglucosides, treatment with C_8K in THF at -10°C gives tri-*O*-benzyl-D-glucal in 81% yield.[194] Treatment of 1-thioglucose as the sodium salt with 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-D-*arabino*-1-hexenitol gave access to 2-thiosophorose **98**.[195] In related work 2,3,4-tri-*O*-acetyl-1-thio-α-L-fucopyranose has been used as nucleophile to make sulfur-linked disaccharides involving α-L-fucose linked to the 2-position of allyl-β-D-galactopyranoside, the 3-position of propyl 2-acetamido-2-deoxy-β-D-glucopyranoside, the 4-position of allyl 2-acetamido-2-deoxy-β-D-glucopyranoside and the 6-position of the same glycoside. Sulfur-carbon bonds were formed by 2,3-epoxide ring opening for the first of these, 2,3-aziridine ring opening for the second, and tosylate displacement for the third and fourth.[196] The pseudo thiodisaccharide derivatives **99** and **100** were prepared as potential affinity reagents for trehalase by ring opening of a racemic cyclohexane epoxide.[197] (See Vol 24, p 43 for similar work.) The cystine thiogalactoside derivative **101** has been made from the acetobromo sugar for studies of conformational aspects of resulting glycosylated peptides,[198] and the glycolipid thioglycoside derivative **102** of the muramic acid compound has been made from the free sugar.[199] The disaccharide thioglycosides **103** and several related compounds were made from the corresponding glycosyl β-peracetate, and used in the synthesis of derivatives of helper T-cell stimulating glycopeptides.[200] In the area of neuraminic acid derivatives, compound **104** has been prepared from the *O*-acetylated 2-hydroxy compound by use of dithiocarbonate technology and used in reactions which involve the synthesis of *O*- and *C*-glycosides. In most cases the displacements were accompanied by elimination reactions.[201] In related work compound **105** was



99 *R*-isomer; **100** *S* -isomer



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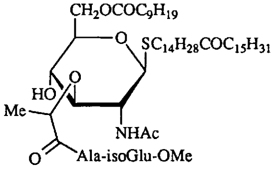

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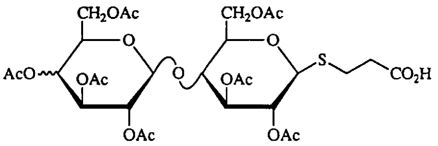

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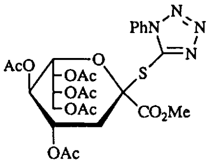
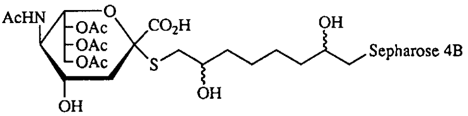


104

made in a five step reaction from the neuraminic acid 2-thioacetate. It was used as an affinity adsorbent for sialidase.[202] 5-Thioglucose β-penta-acetate was converted to the corresponding glycosyl bromide, thence by use of thiourea treatment to the corresponding 1-thiol; *p*-nitrophenyl and *p*-nitrobenzyl thioglycosides were then prepared and the intermediate thiol was also used to obtain 5-thio-analogues of glucosinolates.[203] Compounds **106**, which are further analogues of glucosinolates, have been



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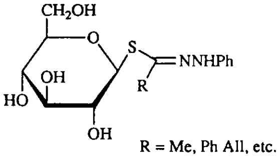
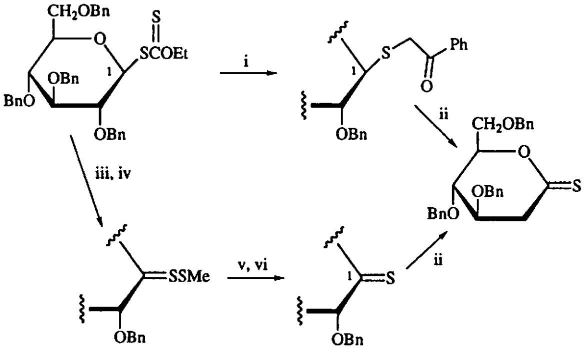


106

prepared by use of tetra-*O*-acetyl-1-thio-D-glucose and hydrazonoyl halides.[204]

As usual, thioglycosides have been used on several occasions in the preparation of *O*-glycosides and disaccharide derivatives and several instances have been noted in section 1 of this Chapter. *N*-Bromosuccinimide and *t*-butylammonium triflate or diphenyliodonium triflate promote activation of thioglycosides for such purposes. With *S*-methyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside



Reagents: i, NaOMe, BnCOCl; ii, *hv*; iii, NaOEt; iv, $MeS\overset{+}{S}Me_2$ BF_4^-; v, MCPBA; vi, Δ

Scheme 18

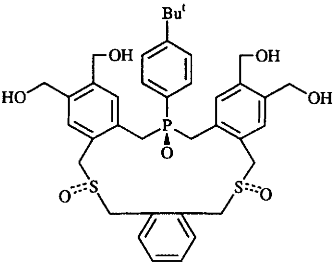
high yields and high β/α ratios for products were reported.[205]

The various reactions of tetrabenzyl-β-D-glucopyranosyl ethylxanthate leading to gluconothiolactone and its 2-deoxy analogue are illustrated in Scheme 18.[206] The reaction of glucosyl thiohydroximates to *spiro*-oxa-thiazol compounds, which are derivatives of aldonolactones, is reported in Chapter 16. The binding of several *p*-*t*-butylphenyl 1-thiohexopyranosides within the macrocycle **107** has been studied and evidence for interaction between the hydroxyl groups and the macrocycle suggests that these lead to the stable bound states. The work on these artificial receptors is of relevance to the interaction of proteins and carbohydrates.[207]

Two papers have reported on the addition of diphenyl diselenide to tri-*O*-acetyl-D-glucal and -D-galactal which gives rise to 1-phenylseleno 2-azido-2-deoxy glycosides as reported in Chapter 10. See ref. 119 for a comment on phenyl selenoglycosides as glycosylating agents.

3 *C*-Glycosides

3.1 Pyranoid Compounds.-The novel cascarosides which are *C*-glucosides **108** and **109** have been isolated from cascara bark,[208] and the 3,6,8-tri-*C*-xylopyranosyl apigenin **110**, which is unusual in having three *C*-glycosidic substituents, is produced by *Asplenium viviparum*.[209] Biosynthesis studies on the angucycline B group of antibiotics **111** have been reported.[210]



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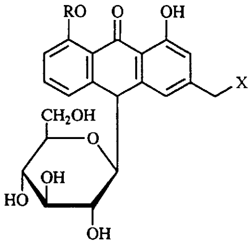
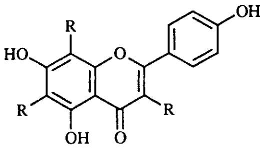
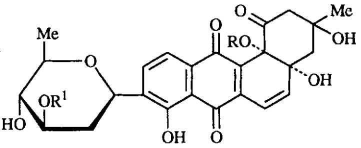


108 X = OH, R = β-D-Glc*p*
109 X = H, R = β-D-Glc*p*



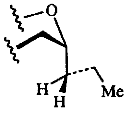
110 R = β-D-Xyl*p*



111 R = R¹ = H
R = rhodinose, R¹ = olivosylrhodinosyl

A theoretical study by *ab initio* quantum mechanics on the origin of the *exo*-deoxyanomeric effect (which is the term given to the preference for the gauche O-C_1-C_{exo}-C dihedral angle) in the structural feature **112** has been published. This is the *C*-glycoside equivalent of the "*exo*-anomeric effect".[211] A review has appeared on the preparation of *C*-glycosides,[212] and a further one by Kishi on the conformations adopted by *C*-glycosides and their *O*-linked analogues. The paper includes discussion of stereochemical features of palytoxin.[213] An assessment has been made of the configurational analysis of α- and β-*C*-glycosides using ^{1}H and ^{13}C nOe spectral methods. Irradiation of H-1′ is a particularly reliable means of configurational assessment since it can lead to specific enhancement of the *cis*-H-5 signal in *C*-glycopyranosides or that of *cis*-H-4 in *C*-glycofuranosides.[214]

As is now usual, a considerable range of methods have been used to prepare *C*-glycosides. Photolysis of the diacyloxyiodo benzene **113** in the presence of phenylvinylsulfone gave the phenylsulfonyl *C*-glycoside **114** by a free radical mechanism. The reaction, however, was unexpectedly sensitive to the anomeric configuration of the starting material. Thus **113** gave **114** as the predominant product, while from the α-anomer a 2:1 mixture of β- and α-products was formed.[215] *O*-Protected glycosyl halides, treated with allyldiisobutylaluminium, can be used to give allyl *C*-glycosides,[216] and the paper also discusses the reaction of organoaluminium reagents with D-gluconic acid 1,5-lactone. The glycosyl free radical obtainable from acetobromoglucose adds to *O*-benzylformaldehyde oxime, and unexpectedly the ester group from C-2 migrates on to the aglycon to give compound **115** as the product.[217]



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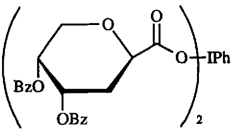

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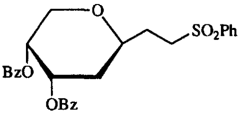
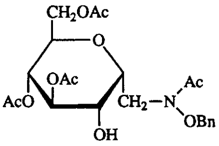


114

Condensation of D-ribose 5-phosphate with dihydroxyacetone phosphate under the influence of rabbit muscle aldolase gives D-*glycero*-D-*altro*-octulose which exists mainly in the pyranose ring form, and on treatment with triethylsilane is reduced to the *C*-glycoside **116**, that is, a 2,6-anhydro-octitol.[218]



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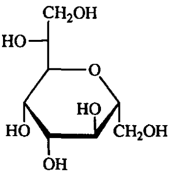

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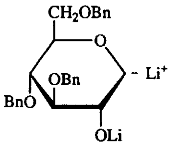
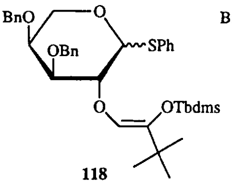


117

Treatment of 3,4,6-tri-*O*-acetyl-1,2-anhydro-D-glucose with dimethyl- or diphenyl-copper lithium gave, following acetylation, the β-*C*-methyl or *C*-phenyl glycosides. The same chemistry applied to 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannose again led to glycosides and in this case α-*C*-glycosides were formed and a free hydroxyl group was again released at C-2. Deoxygenation at this position is therefore possible.[219] Preparations of several *C*-D-glycopyranosyl methylamines, that is 1-amino-2,6-anhydro-1-deoxy-heptitols, have been effected from the corresponding nitriles. They show only weak glycosidase inhibitory activity.[220]

Treatment of 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride with butyllithium in THF at -100°C followed by lithium naphthalimide led to the interesting di-lithio derivative **117** which, with electrophiles such as aldehydes and methyl iodide, afforded α-*C*-glycosides with free hydroxyl groups at C-2, and thus the normal elimination which occurs when a C-1 anion is generated in the case of fully substituted sugars was avoided.[221] An interesting intramolecular *C*-glycosylation reaction occurred when the L-arabinose phenyl thioglycoside derivative **118** was treated with silver triflate, the product being the bicyclic derivative **119**.[222] The 2,6-anhydroheptitol compound **120** was converted by standard procedures to the corresponding amino-substituted benzyl α-*C*-glucosides **121** and **122**, and compound **123** was produced by a Beckmann rearrangement process, compounds **121** and **123** being good α-glucosidase inhibitors.[223] Treatment of the acetylenic *C*-glycoside **124** with dicobalthexacarbonyl gave the complex **125** which, under acid conditions, epimerized to the β-analogue, and this afforded efficient means of producing the β-epimer **126** of compound **124**. A number of similar examples were given.[224] The outline of a synthesis of a racemic β-*C*-guloside derivative is given in Scheme 19.[225]



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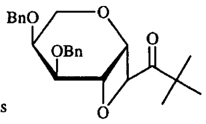

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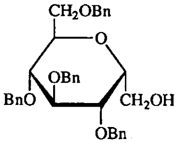

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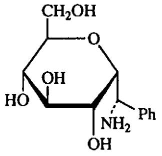
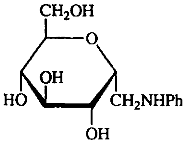


121 *R*- isomer
122 *S* - isomer



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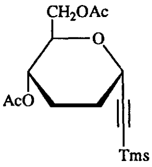

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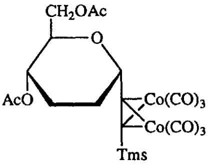

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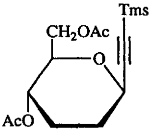

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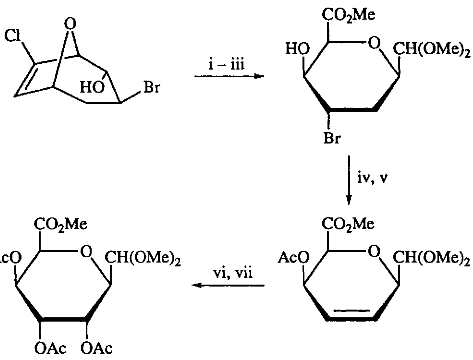
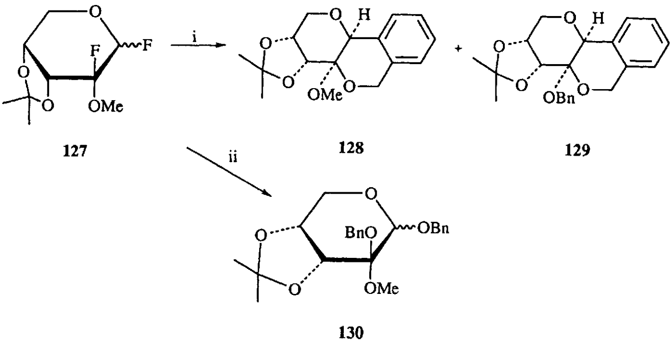


Reagents; i, O_3; ii, Me_2S; iii, $HC(OMe)_3$; iv, Ac_2O, Py; v, BzONa, DMF,
vi, OsO_4, H_2O_2; vii, Ac_2O, Py

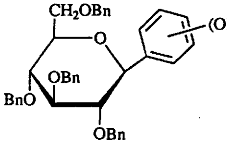
Scheme 19



Reagents: i, BnOH, Cp_2HfCl_2, $AgClO_4$; ii, BnOH, Cp_2ZrCl_2, $AgClO_4$

Scheme 20

Treatment of the difluoride **127**, made from the methyl pentos-2-uloside, with benzyl alcohol and dicyclopentadienyl hafnium dichloride in the presence of silver perchlorate, gave compounds **128** and **129** (82%, 7:10) as shown in Scheme 20. With dicyclopentadienyl zirconium dichloride, however, the same reaction resulted in a direct displacement of both fluorine atoms by benzyloxy groups, 89% of benzyl glycosides **130** being produced.^{226} Reaction of the appropriate *O*-benzyl glucosyl α-trichloroacetimidate with various electron-rich phenols in the presence of trimethylsilyl triflate resulted in β-aryl glycosides e.g. **131** which can be de-*O*-protected by hydrogenolysis. Less reactive phenols give *O*-glycosides.^{227} Treatment of an aromatic steroid with tetra-*O*-benzyl-β-D-glucopyranosyl trifluoroacetate under acid catalysis gave first the *O*-glycoside, which then underwent the known rearrangement to a *C*-linked product.^{228} *O*-Substituted 2-deoxy-aldonolactones can be converted either to phenyl *C*-glycosides or analogous 1,2-unsaturated compounds as illustrated in Scheme 21. In the D-glucose series 2-deoxy-β-D-glucoside was produced.^{229} A reaction of the 1,8-dihydroxyanthracenone with acetobromoglucose resulted in the 9-*C*-linked product **132**.^{230}



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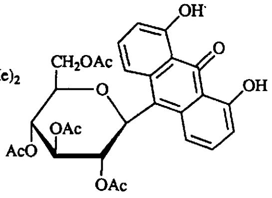

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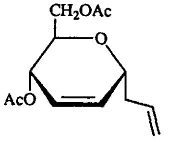

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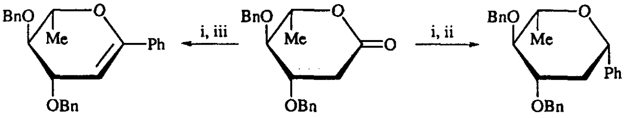
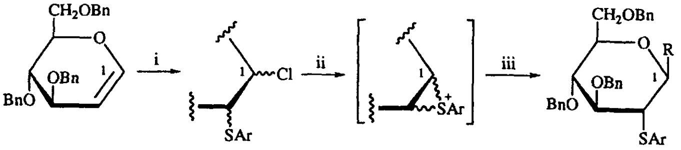


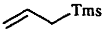
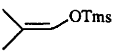
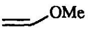
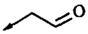
Reagents: i, PhMgCl, THF; ii, NaCNBH$_3$, EtOH; iii, Ph$_2$[OC(CF$_3$)$_2$Ph]$_2$

Scheme 21

Tri-*O*-acetyl-D-glucal treated with allyltrimethylsilane in the presence of DDQ gave 83% of compound **133** with the α/β ratio being 16:1. In the L-rhamnal series again the α-anomer was produced with high stereoselectivity. It should be noted that DDQ is a neutral activator for this reaction.^{231} The same glycals treated with the Reformatsky reagent ^{t}BuO$_2$CCH$_2$ZnBr in the presence of trimethylsilyl triflate gave the corresponding 2,3-unsaturated glycosyl acetic acid esters as α/β mixtures. Tetra-*O*-acetyl-2-hydroxy-D-glucal did not take part in this reaction.^{232} Addition of aryl sulfenyl chlorides to tri-*O*-benzyl-D-glucal gave 2-(arylthio)-glycosyl chlorides which, with tin tetrachloride, afforded 1,2-

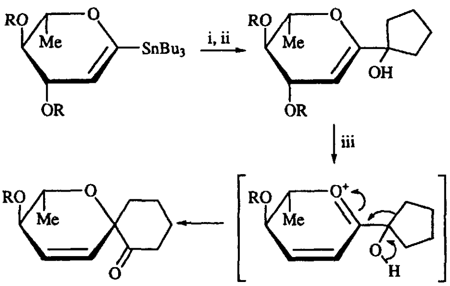
episulphonium species; these in the presence of nucleophiles gave *C*-glycosides as shown in Scheme 22.[233] A new way of gaining access to glycosyl *spiro*-cycloalkanones is illustrated in Scheme 23. Tri-*O*-silyl protected D-glucal by similar means led to compound **134**, but the cyclobutyl *C*-glycoside **135** under acid conditions, rearranged to give **136** by a pinacol-like process rather than by allylic rearrangement.[234]



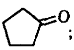
N	R	*yield*	α : β
TmsCN	CN	88	1 : 19
		79	1 : 19
		73	1 : 10
		63	1 : 19
PhMgBr	Ph	60	1 : 19

Reagents: i, ArSCl; ii, $SnCl_4$; iii, Nucleophilic reagent (N)

Scheme 22

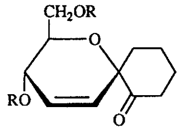


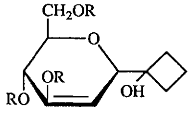
R = Tbdms (assumed from the abreviation TBS in the original)

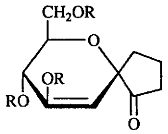
Reagents: i, BuLi; ii, ; iii, camphorsulfonic acid

Scheme 23

Considerable interest continues to be taken in the production of *C*-linked disaccharides, most attention being given to linking sugars via carbon bridges to primary positions of other sugars. Further reference to these compounds is made in Chapter 24. *C*-Iodomethyl 3,4,6-tri-*O*-benzyl-α-D-





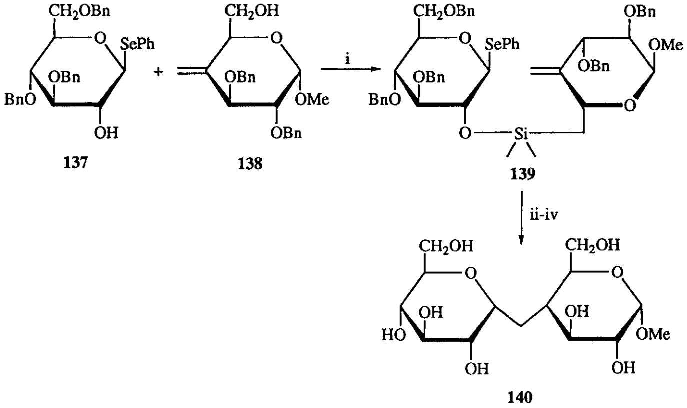


R = Tbdms (assumed from the abbreviation TBS in the original)

134 **135** **136**

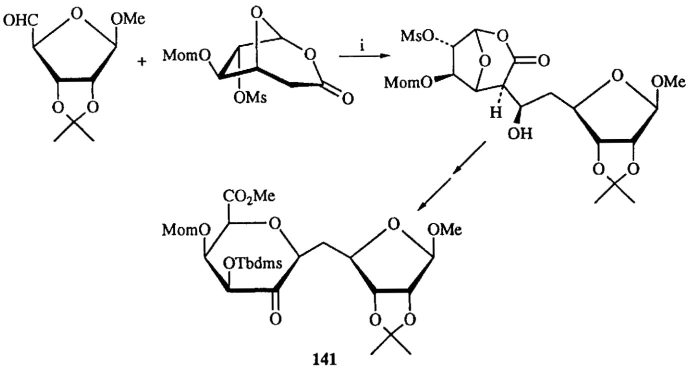
glucopyranoside was converted to a cobalt-containing analogue and condensed with a glucoside carrying a 6-deoxy-6-nitro group by radical coupling to give a 1,6-linked analogue of gentiobiose with a nitro group at C-6.[235] In somewhat reciprocal manner, β-D-glucopyranose has been glycosidically linked through a methylene group to C-6 of D-galactose by use of a glucosylnitromethane and 1:2,3:4-di-*O*-isopropylidene-D-galacto-dialdose.[236]

Sinäy and colleagues have linked compounds **137** and **138** to give **139** and thence caused an intramolecular radical reaction to afford the maltose analogue **140** (Scheme 24).[237] A 1,4-α-mannopyranosyl glucose analogue has been produced by similar methodology.[238] A further paper on *C*-linked sucrose has been published (cf. Vol. 22, p. 38), the X-ray of its octaacetate being measured and a conformational study undertaken.[239] The undeculofuranosiduronic acid derivative **141** related to herbicidins has been prepared by Vogel's group as outlined in Scheme 25.[240] The dipyranyl disaccharide **143**, having the two units linked through an alkyne group, may well represent the longest chain sugar derivative known; there are 18 carbons linearly set out in the structure. It has been



Reagents: i, Me_2SiCl_2; ii, Bu_3SnH,AIBN; iii, HF, THF; iv, H_2, Pd/C

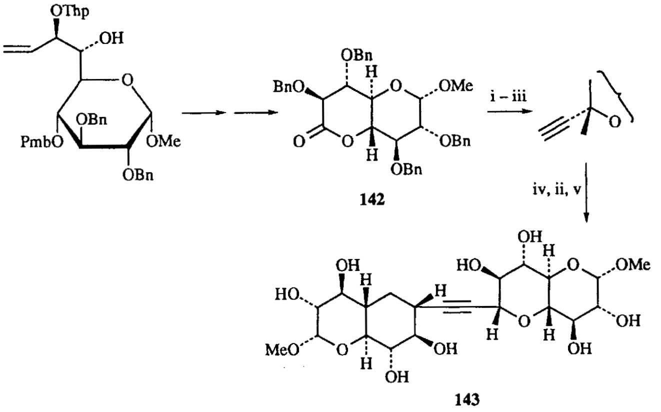
Scheme 24



Reagents: i, $(Tms)_2NLi$

Scheme 25

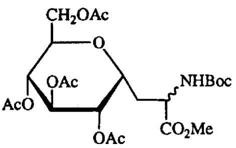
synthesized by an acetylene coupling procedure (Scheme 26).[241]



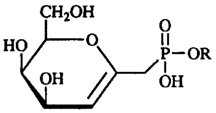
Reagents: i, Tms ——≡ , BuLi; ii, Et_3SiH, $BF_3•Et_2O$; iii, Bu_4NF; iv, BuLi, **142**; v, EtSH, BF_3

Scheme 26

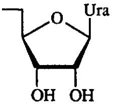
Several compounds which are *C*-glycosyl analogues of compounds of interest in biology have been prepared. For example the glycosyl amino acid derivatives **144** and **145** have been produced from the corresponding α-*C*-allyl D-glucoside.[242] Compounds **146** and **147** were produced as transition state analogues for inhibition of β-galactosyl transferase,[243] and in related work the disaccharide phosphonate derivative **148** with structural features closely related to a peptidoglycan unit and also a unit of moenomycin A has been produced. It is thus a potential antibiotic and also inhibitor of



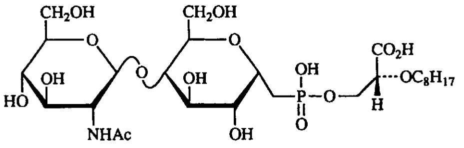
144 *R*-isomer
145 *S*-isomer



146 R = Na or $\overset{+}{\text{H}}\text{NEt}_3$
147 R = ← O$_2$PO—



transglycosylase.[244] Compound **149**, n=0 is etoposide, and now analogues with n=1,2 have been produced together with others having the β-configuration at C-4 of the aglycon. Glycosylalkanols were condensed with the 4-hydroxy compounds under acid conditions.[245]



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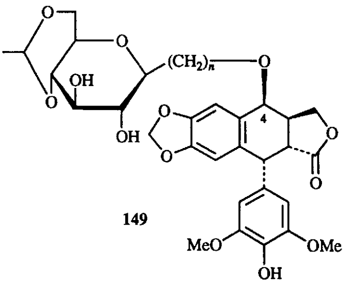
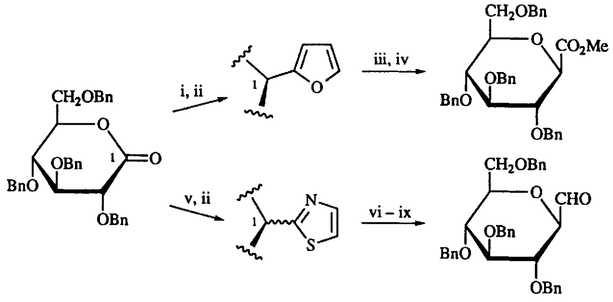
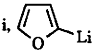
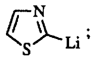


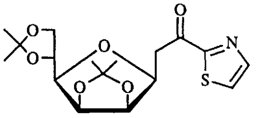
149



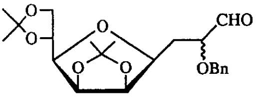
Reagents: i,  ; ii, Et$_3$SiH; iii, O$_3$; iv, CH$_2$N$_2$; v,  ;
vi, MeOTf; vii, NaBH$_4$; viii, HgCl$_2$, H$_2$O; ix, Et$_3$N

Scheme 27

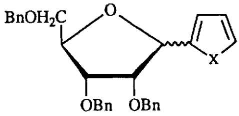
3.2 Furanoid Compounds.-A set of fluoromethylene and fluoromethyl *C*-glycosides have been derived from D-gulono-1,4-lactone,[246] and some glycosyl carboxylic acids[247] and aldehydes[248] have also been produced from lactones as shown in Scheme 27; the two reactions involved may also be used in the pyranose series and adaptations can give rise to α-anomers. 2:3,5:6-Diisopropylidene-D-mannose, treated with the appropriate Wittig reagent, gave a high yield of the β-linked *C*-glycoside **150**. Initially the α/β ratio was 1:2 but treatment with base gave a final equilibrium ratio of 15:85. The product can be refunctionalized to the anhydrononose derivative **151**.[249] The furan and thiophene *C*-glycosides **152**



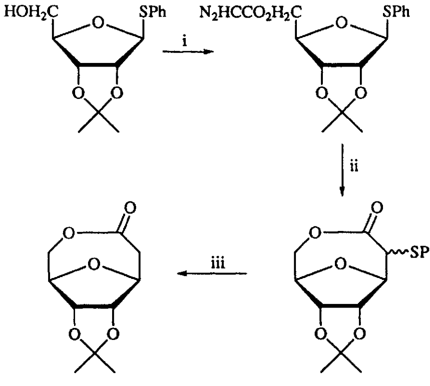
150



151



152 X = O
153 X = S



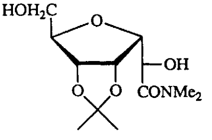
155 **154**

Reagents: i, $\mathrm{H{-}\overset{\overset{\displaystyle NNHTs}{\|}}{C}{-}COCl}$; ii, $\mathrm{Rh(OAc)_4}$; iii, RaNi

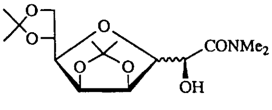
Scheme 28

and **153** were produced from 2,3,5-tri-*O*-benzyl-D-ribose following treatment with the 2-lithio derivatives of the heterocycles. The α-products were formed first and then isomerized to β-anomers.[250]

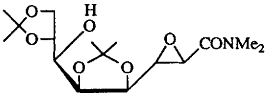
The α-thiophenyl lactone **154**, prepared as indicated in Scheme 28 by an intramolecular carbene insertion reaction, gave **155** which is a lactone intermediate suitable for *C*-nucleoside synthesis.[251] Use of the ylid reagent $Me_2\overset{+}{S}\overset{-}{C}HCONMe_2$ with aldehydosugars has led to a new approach to *C*-glycosides. For example 2,3-*O*-isopropylidene-D-ribofuranose gives compound **156** in 85% yield. On the other hand, 2:3,5:6-di-*O*-isopropylidene-D-mannose gave the *C*-glycosides **157** and **158** in 38 and 12% yield, respectively, as well as the epoxide **159** (40%) which is an intermediate formed en route to the *C*-glycosides.[252]



156



157 α-anomer
158 β-anomer



159

Further references to *C*-glycosides are made in Chapter 24.

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4
Oligosaccharides

1 General

As previously, this Chapter deals with specific tri- and higher oligosaccharides, most references relating to their synthesis by specific chemical and, increasingly, enzymic or combined methods. Chemical features of the cyclodextrins are noted separately.

The synthesis of e.g. pentasaccharides is dealt with under that heading, and the required preparations of constituent parts are assumed and are not normally dealt with in their respective sections. Frequently, specific derivatives e.g. glycosides, of the named compounds are involved, and this fact is often not recorded in the formulae used or the names listed.

A review of the determination of the 3-dimensional structure of oligosaccharides discusses a wealth of n.m.r. and other data published in the preceding year.[1]

Several catalysts – TmsOTf, $BF_3.Et_2O$, TmsOMs, $EtSO_3H$, $TmsOCOCF_3$, $TiCl_4$ – which can be used for the partial cleavage of polysaccharides to di- and trisaccharides were compared in their reactions with permethylated methyl glycosides. β-Anomers anomerize faster than the α-analogues, and $TiCl_4$ did not cause any anomerization of α-compounds. On the other hand, TmsOMs and $BF_3.Et_2O$ together (5:1) caused rapid anomerization.[2]

Danishefsky has developed a solid phase oligosaccharide synthesis strategy based on glycals which are bonded to a polystyrene copolymer *via* silyl ether bonds and coupled to other glycals. The products were released by use of tetrabutylammonium fluoride.[3]

A review has been published on the synthesis of blood group I- and i-active oligosaccharides,[4] and one on the preparation of β-D-mannoside- and 2-amino-2-deoxy-D-mannoside-containing oligosaccharides by use of 2-oximinoglycopyranosyl bromides[5] has appeared. For making oligosaccharides containing α-D-glucopyranosyl linkages, methyl 2,3,4,6-tetra-*O*-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside has been recommended.[6]

In the area of D-glucosamine-containing oligosaccharides a simple, sensitive ultra-violet-based method has been developed for determining the degree of de-*N*-acetylation.[7] In related work, *N*-acetylchito-oligosaccharides of size greater than the hexaose have been shown to be active as elicitors of phytoalexins in rice cells. Smaller compounds and *N*-deacetylated derivatives are inactive.[8]

2 Trisaccharides

Compounds in sections 2.1 - 2.3 are categorized according to their non-reducing end sugars.

2.1 Linear Homotrisaccharides.–Non-reducing trisaccharides of this category are rather unusual but β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p* together with trehalose has been found in a yeast extract,[9] and β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1↔1)-α-D-Glc*p* has been isolated following the reaction of α-cyclodextrin and lactose in the presence of a cyclodextrin glucanotransferase.[10]

In the field of reducing trimers β-1,3-linked oligomers of D-glucose, which are constituent parts of laminarin, have been prepared by use of 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-chloroacetyl-β-D-glucopyranosyl chloride. The trimer and oligomers up to octamer were described.[11]

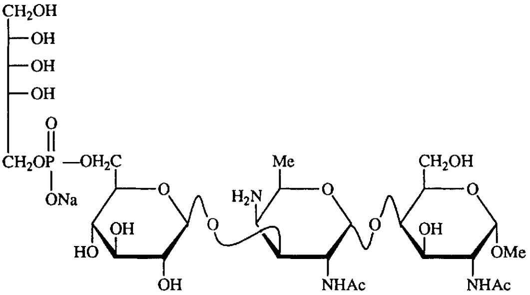
A 1:1 complex of maltotriose and L-tryptophanyl-L-tryptophan has been reported.[12]

The cyanogenic disaccharide glycoside amygdalin has been converted into its 6′-*O*-trityl peracetate derivative and thereby used with acetobromoglucose to give the β-(1→6)-linked trimer,[13] and α-(1→6)-β-(1→6)-glucotriose linked through a glycosylamine bond to a long chain peptide is the key part of the compound nephritigenoside which is described in Chapter 9.

By use of cellulase, β-D-lactosyl fluoride has been condensed with methyl-β-D-cellobioside and thereby a galactosyl glucotriose derivative was made. From this the galactose was enzymically cleaved and methyl β-cellotrioside resulted. Repetition of these two steps provided a route to methyl β-D-cellotetraoside.[14]

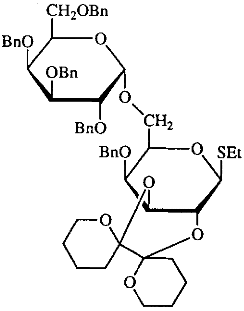
In the mannose series the α-(1→2)-linked trimer substituted onto a protein was produced using GDP-Man as mannose source and α-(1→2)-mannosyl transferase, which was overexpressed by molecular biological processes, as the catalytic enzyme. A multiple enzyme system was developed to produce the trimer-containing product.[15] α-D-Man*p*-(1→2)-α-D-Man*p*-(1→6)-D-Man has been made with Ley's "dispoke" protecting group used at O-3, O-4.[16]

2.2 Linear Heterotrisaccharides.–In this area many of the compounds produced are related to structural components of bacterial polysaccharides. β-D-Glc*p*-(1→3)-α-D-Rha*p*-(1→3)-β-D-Glc*p*-OMe is the terminal trimeric unit of the lipo-oligosaccharide from *Mycobacterium linda*;[17] 3,6-Di-*O*-Me-β-D-Glc*p*-(1→4)-2,3-di-*O*-Me-α-L-Rha*p*-(1→2)-3-*O*-Me-α-L-Rha*p*-O-C_6H_4-$NHCOCF_3$ is a derivative of the trimeric component of the *Mycobacterium leprae* antigen and was intended for conjugation with bovine serum albumin as an antigen to elicit antibodies to this bacterium.[18] Allyl 2,6-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzyl-D-glucopyranosyluronic)-α-D-galactopyranoside is a derivative of the repeating unit of *Klebsiella* type 8 bacterium capsular polysaccharide.[19] β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1→4)-D-Gal, which is a structural element of the capsular polysaccharide of *Streptococcus pneumoniae* Type 8, has been made using the glycosyl trichloroacetimidate procedure.[20] Compound **1** is the trisaccharide ribitol phosphate repeating unit of a cell wall associated complex polysaccharide from *Streptococcus pneumoniae* Type 1. Its synthesis has been described.[21]



1

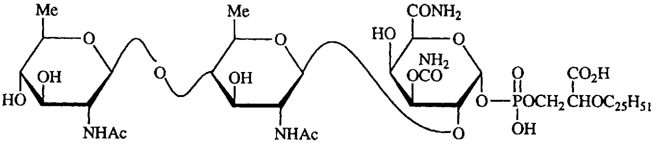
In a set of D-galactose-terminating oligosaccharides β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-OMe has been synthesized using β-lactosyl fluoride as donor, and methyl β-D-glucopyranoside, and a cellulase as catalyst,[22] the analogous trimer linked β-(1→4), β-(1→6) as a diacetate forms part of a cytoprotective steroid and has been synthesized,[23] and α-D-Gal*p*-(1→4)-β-D-Glc*p*A-(1→4)-D-Glc, which is a fragment of the capsular polysaccharide from *Streptococcus pneumoniae* Type 8 has been made by standard chemical methods.[24] α-D-Gal*p*-(1→6)-α-D-Gal*p*-(1→3)-α-D-Man*p*-SEt has been made by use of the novel glycosylating agent **2** and used in the synthesis of a tetrasaccharide inositol.[16] Chemical methods have also been used to synthesize β-D-Man-(1→4)-β-D-Man-(1→4)-β-D-Glc*p*-(1→1)Cer. [25]



2

The glucosamine-terminating trisaccharide α-D-Glc*p*NAc-(1→2)-α-D-Glc*p*-(1→2)-α-D-Gal*p*-

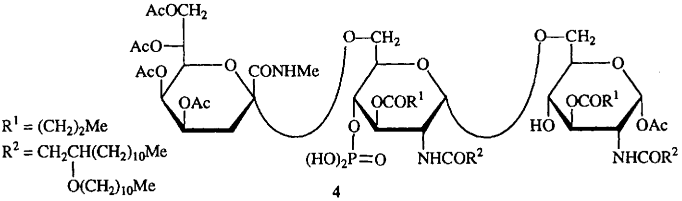
OMe has been chemically synthesized for studies of the core structures of the *Salmonella* lipopolysaccharide.[26] β-D-Glc*p*NAc-(1→2)-α-D-Man*p*-(1→6)-β-D-Glc*p*-O-All was made by transfer of Glc*p*NAc from UDP-GlcNAc to O-6 of the central sugar, and the contribution of the glucose unit in this reaction has been examined.[27] The work has been extended by the preparation of a set of analogues of this trimer having OMe, F, NH_2, NHAc and H in place of the hydroxyl group at C-4 of the non-reducing terminal sugar.[28] The dirhamnose-containing trimer β-D-Glc*p*NAc-(1→3)-α-L-Rha*p*-(1→2)-α-L-Rha has been prepared chemically for use as a donor as well as acceptor in the synthesis of a hexasaccharide related to the cell wall polysaccharide of the β-haemolytic *Streptococcus* group A.[29] Compound **3** is the smallest degradation product of the new moenomycin antibiotic (C_1) that retains activity.[30] Also in the field of deoxysugar trisaccharides, the following deoxy analogues of α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-β-D-Glc*p*NAc-OMe have been synthesized: 4-deoxy-, 6-deoxy-, 4′-deoxy-, 4″-deoxy-, 4′,4″-dideoxy-, 3″,4′-dideoxy-,[31] as have several chlorodeoxy derivatives.[32] The further analogue having 2-deoxy-α-L-rhamnopyranose 1,3-linked to 2-acetamido-2-deoxy-β-D-glucopyranose, 1,2-linked to methyl-α-L-rhamnopyranoside was reported.[33]



3

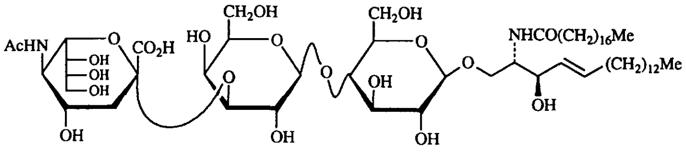
2,3-Di-*O*-Me-α-L-Rha*p*-(1→2)-3-*O*-Me-α-L-Rha*p*-(1→4)-2,3-di-*O*-Me-L-Rha was prepared by standard methods as a trimeric segment of a *Mycobacterium haemophilum* phenolic glucoside,[34] and similarly the trimer of the lipopolysaccharide of *Mycobacterium szulgai*, 2-*O*-Me-α-L-Fuc*p*-(1→3)-α-L-Rha*p*-(1→3)-L-Rha, has been made.[35]

Several trisaccharides terminating in sugar acids have been reported. β-D-GlcA*p*-(1→4)-β-D-Glc*p*-(1→4)-D-Glc is a component unit of the capsular polysaccharide of *Streptococcus pneumoniae* Type 8;[20] α-L-Ido*p*A-(1→4)-α-D-Glc*p*NAc-(1→4)-D-GlcA has been prepared as a trisaccharide component of a heparin tetramer,[36] the KDO-containing compound **4**, related to a



4

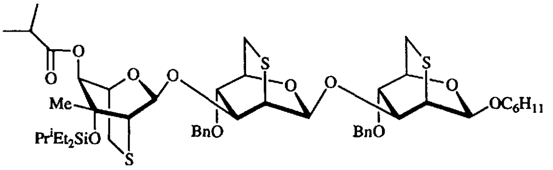
trisaccharide of lipid A, has been made,[37] and α-KDN-(2→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-*O*-Cer has been synthesized as an analogue of gangliosides GM_3 and GM_4 with 3-deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid (KDN) in place of Neu5Ac.[38] Much interest continues in trisaccharides containing neuraminic acid, and several synthetic products have been reported. Notably in this area two syntheses of the ganglioside GM_3 **5** have been described; both involve the making of a receptor lactose unit and transfer of the sialic acid by enzymic methods.[39,40] A related approach enzymically transferred N-acetylneuraminic acid to N-acetyllactosamine to give Neu5Ac-(2→6)-β-D-Gal*p*-(1→4)-GlcNAc,[41]



5

A paper has appeared on the structural analysis of compounds of the type which involves the selective reductive cleavage of the aldosidic bonds.[42]

The xylose-containing trisaccharide glycoside β-D-Xyl*p*-(1→2)-α-D-Man*p*-(1→3)-α-D-Man*p*-OR ($R=CH_2CH_2C_6H_4.NHCOCF_3$) has been prepared together with related compounds as parts of the repeating unit of the capsular polysaccharide of *Cryptococcus neoformans* serogroup A,[43] and for immunological work associated with lipopolysaccharides the L,D-heptose-containing trisaccharides L-α-D-Hep-(1→3)-L-α-D-Hep-(1→5)-α-KDO, L-α-D-Hep-(1→3)-L-α-D-Hep-(1→5)-β-KDO and L-α-D-Hep-(1→7)-L-α-D-Hep-(1→3)-L-α-D-Hep have been copolymerized with acrylamide.[44]



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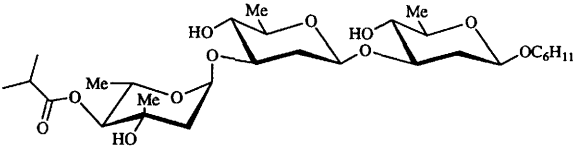
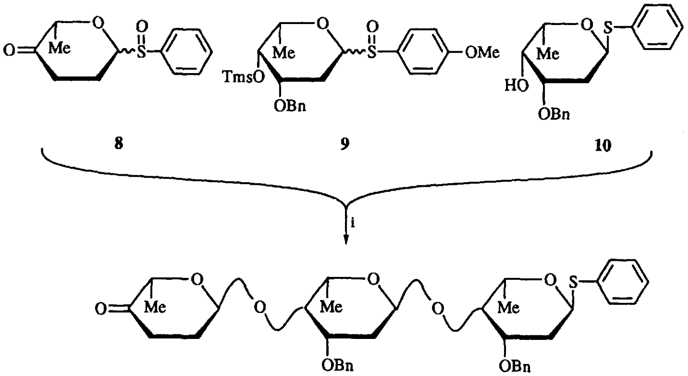


7

Compound **6** has been desulfurized to give access to **7**, which is the trisaccharide of olivomycin A.[45]. An outstanding example of the art of synthesis is represented in Scheme 1 which shows the preparation of a derivative of the trisaccharide of cyclamycin O. Compounds **8** to **10** were taken together and activated in such a way that **8** and **10** reacted together preferentially. This was followed by condensation at a slower rate of **8**, and the product trisaccharide was produced in a yield of 25%. This introduces almost a new level in relative activation of compounds, compound **9** being activated relative to **10** by the *p*-methoxy group. The concept of doing sequential glycosylation reactions in a one pot procedure heralds a new dimension in oligosaccharide preparations.[46]



Reagents: i, **8** (3.0 equiv.), **9** (2.0 equiv.), **10** (1.0 equiv.), $HC\equiv CCO_2Me$ (20 equiv.), TfOH (0.05 equiv.), −78 → −70 °C

Scheme 1

Two molecules of 2,6-dideoxy-3-*O*-methyl-*lyxo*-hexose separated by one of the *ribo*-isomer comprise the trisaccharide of the complex antibiotics the granefromycins.[47]

2.3 Branched Homotrisaccharides.–The branched trimer β-D-Glc*p*-(1→3)-[β-D-Glc*p*-(1→6)]-β-D-Glc*p*-OAll has been copolymerized in a radical procedure with acrylamide to give copolymers for immunological studies of schizophyllan.[48] D-Galactose, having β-D-galactopyranosyl substituents at O-2 and O-6 and phosphate esters at O-3 and O-4 was prepared and studied for insulin-like activity.[49]

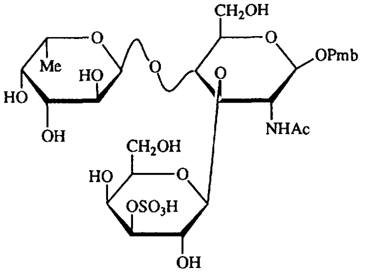
Because of their importance in naturally occurring glycoproteins attention has been given to several branched trimannoses. α-D-Mannopyranose has been prepared carrying α-D-mannopyranosyl substituents at O-3 and O-4 or O-6 in the form of long chain alkyl glycosides.[50] A further paper describes the methyl glycoside of the (1→6)(1→3) linked trimer having 2′,2″-

dideoxy-2′,2″-difluoro groups.[51]

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

A very extensive set of methyl α- and β-D-glucopyranosides substituted at O-2 and O-3 with a range of other sugars has been produced for computer-based structural analytical work. α-Linked D-mannopyranose, L-rhamnopyranose, L-fucopyranose, and β-linked D-galactose and L-fucose were the substituting sugars.[52,53]

The branched-chain galactoside having a spacer arm aglycon and carrying L-fucose and GalNAc substituents at O-2 and O-3, respectively, was made by enzymic transfer of the latter sugar in studies related to blood group substances.[54] In the area of *N*-substituted glucosamine-containing trisaccharides, α-L-Fuc*p*-(1→3)-[α-L-Fuc*p*-(1→6)]-β-D-Glc*p*NAc-O-All has been made by chemical methods,[55] and β-D-Gal*p*-(1→3)-[α-L-Fuc*p*-(1→4)]-D-Glc*p*NAc-OBn was made as an Le^a acceptor for a fucosyl transferase which introduces the sugar at O-2 of the galactose residue.[56] In related work, this Le^a trisaccharide has been synthesized by two groups in the form of the sulfate ester at O-3 of the galactose unit (**11**),[57,58] and likewise the Le^x trisaccharide, an isomer of the previous Le^a compound, has been prepared having the fucose and the galactose sulfate groups interchanged.[58] Electrospray mass spectrometry has been used to demonstrate a strong affinity of the Le^x trisaccharide and a ceramide derivative for calcium ions which may relate to their biological function as cell-surface carbohydrates.[59] The *N*-phthalimido glucosamine trisaccharide **12** has been made as a building block for the synthesis of xylose-containing carbohydrate chains of glycoproteins.[60] Purely enzymic methods were used to put together the trisaccharide β-D-Gal*p*-(1→3)-[β-D-Glc*p*NAc-(1→6)]-D-Gal*p*NAc: firstly β-galactosidase was applied to tri-*O*-acetyl-D-galactal and the product was converted to the (1→3)-linked *N*-acetylamino sugar disaccharide, and then *N*-acetylglucosamine was attached to the reducing



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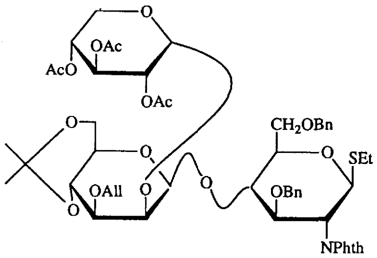
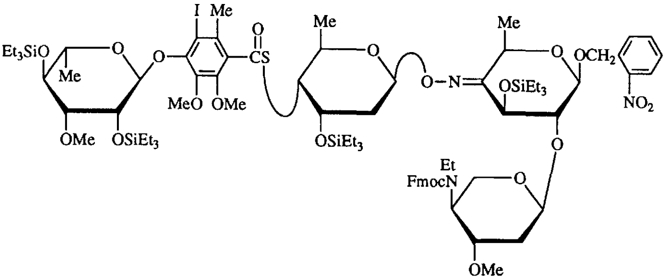


12

terminal sugar.[61] Related work was carried out on the disaccharide glycal produced by glycosylation of glucal 6-acetate.

α-D-Hep-(1→7)-[α- and β-KDO-(2→8)]-KDO-O-All (Hep = L-*glycero*-D-*manno*-heptose) and the analogue having α-D-mannose in place of this heptose were prepared in the course of work aimed at an immunological study using the core region of bacterial lipopolysaccharides.[62]

2.5 Analogues of Trisaccharides.–Full details have been published on the synthesis of the oligosaccharide fragment of Calicheamycin $\gamma_1{}^I$ (Vol 26, p. 65). This important compound contains the unusual hydroxylamine linking unit between two sugars.[63] Following this, the highly complex carbohydrate derivative **13** has been put together and used in the final coupling stages to the aglycon of calicheamycin $\gamma_1{}^I$.[64]



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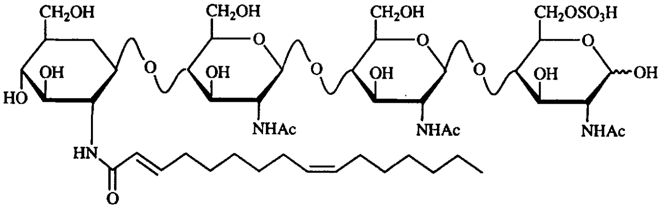
3 Tetrasaccharides

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

3.1 Linear Homotetrasaccharides.–Perbenzyl maltosyl and maltotriosyl fluorides have been coupled by α-(1→4) bonds to a partially protected trehalose derivative by use of trimethylsilyl triflate and, after deblocking, a tetra- and a penta-glucose linked α-(1→4) but terminating with a non-reducing unit were obtained.[65] An ingenious way of making cellotetraose involves coupling methyl cellotrioside with lactose under the influence of cellulase and then cleaving the galactose residue by use of a galactosidase.[66] A related approach to maltotetraose involved reaction of starch with deoxynojirimycin in the presence of a cyclodextrin glycosyl transferase. A set of oligosaccharides ending in the 5-amino-1,5-aminohexitol were thereby produced, and by amylase they were cleavable to give products which included high purity maltotetraose.[67] A set of β-(1→4)-linked glucosamine oligosaccharides ranging from the tetramer to the decamer has been described; they are thus the oligomers of chitosan.[68] The related sulfated cellotetraose derivative



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14, which is a nodulation signal compound involved in the symbiotic relationship between rhyzobia and alfalfa, has been prepared using the trichloroacetimidate method, with sulfation being effected using the sulfur trioxide pyridine complex on an otherwise protected compound.[69]

3.2 Linear Heterotetrasaccharides.–The ganglioside GD_3 which is α-Neu5Ac-(1→8)-α-Neu5Ac-(1→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-O-Cer has been produced by a straightforward route,[70,71] and a fully substituted derivative of β-D-Glc*p*NH_2-(1→4)-β-D-Glc*p*-(1→3)-β-D-Glc*p*-NH_2-(1→4)-D-Glc allows specific deprotection of the primary alcohol groups of the D-glucose moieties such that they can be oxidized to uronic acids.[72] A disaccharide *S*-phenyl thioglycoside derivative has given access to β-D-Gal*p*-(1→3)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-D-Glc[73] and the xylose-terminating tetramer found in the linkage region of heparan sulfate β-D-Glc*p*A-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-β-D-Xyl*p* has been described as a methyl[74] and a peptide[75] glycoside, and α-D-Glc*p*NAc-(1→3)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→2)-α-D-Gal, an α-galactose terminating tetramer which represents the repeating unit of the O-specific antigen of *Shigella dysenteriae* has also been reported.[76]

Several compounds terminating in glucosamine or *N*-substituted derivative have been reported: β-D-Gal*p*-(1→3)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→3)-β-D-Glc*p*NAc-*O*-$C_6H_4NO_2$;[73] β-D-Glc*p*-(1→2)-α-D-Man*p*-(1→6)-β-D-Glc*p*-(1→4)-D-Glc*p*-NAc.[77]

Compounds ending in a 6-deoxyhexose to have been made are α-L-Rha*p*-(1→2)-α-D-Gal*p*-(1→3)-α-D-Glc*p*NAc-(1→3)-α-L-Rha,[78] and the unusual 6-deoxy-L-talose compounds 4-*O*-Me-α-L-Rha*p*-(1→4)-2-*O*-Me-α-L-Fuc*p*-(1→3)-α-L-Rha*p*-(1→2)-6-deoxy-α-L-Tal*p*-$O(CH_2)_3NH_2$[79] and 2-*O*-Me-α-D-Rha*p*-(1→3)-2-*O*-Me-α-L-Fuc*p*-(1→3)-α-L-Rha*p*-(1→2)-6-deoxy-α-L-Tal*p*-O-C_6H_4-$NHCOCF_3$[80] which were required for studies of immunodiagnostic agents and synthetic vaccines in relation to the surface antigens of *Mycobacterium* serocomplexes.

In the area of tetramers terminating in acidic sugars, β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*A-(1→3)-β-D-Glc*p*-NAc-(1→4)-β-D-Glc*p*A-O-CH_2-C_6H_4-OMe, which is a dimer of the repeating unit of hyaluronic acid, has been described,[81] and α-D-Glc*p*-(1→3)-L-α-D-Hep*p*-(1→3)-L-α-D-Hep*p*-(1→5)-KDO, in which Hep is L-*glycero*-D-*manno*-heptose, has been isolated from the core region of the lipopolysaccharide of *Salmonella minnesota* and structurally characterized.[82]

3.3 Branched Homotetrasaccharides.–β-D-Glc*p*-(1→6)-[β-D-Glc*p*-(1→3)]-β-D-Glc*p*-(1→6)-α-D-Glc*p*-OMe has been prepared by use of ethyl thioglycoside methods in connection with phytoalexin elicitor studies.[83]

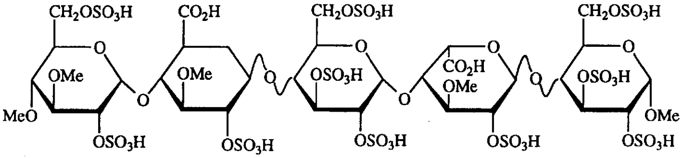
3.4 Branched Heterotetrasaccharides.–The sialyl Le^{x} epitope analogue in which the terminal Glc*p*NAc residue is replaced by glucose-carrying azido-containing alkyl aglycons {α-Neu5Ac-(2→3)-β-D-Gal*p*-(1→4)-[α-D-Fuc*p*-(1→3)]-β-D-Glc*p*-OR} has been made,[84] and in related work the further analogues α-Neu5Ac-(2→3)-β-D-Gal-(1→4)[α-L-Fuc-(1→3)]-β-D-Glc-OR and α-Neu5Ac-(2→3)-β-D-Gal-(1→3)-[α-L-Fuc-(1→3)]-β-D-Glc-OR have been prepared, the fucosyl residues having been introduced by enzymic methods.[85] Glycal technology involving glycose 1,2-anhydrides was used to put together the branched tetrasaccharide β-D-Xyl*p*-(1→3)-[β-D-Glc*p*-(1→2)]-β-D-Glc*p*-(1→4)-β-D-Gal*p* and then a full saponin of which it is a component.[86] Five monodeoxy analogues of tetrasaccharide β-D-Glc*p*NAc-(1→2)-α-D-Man*p*-(1→3)-[α-D-Man*p*-(1→6)]-β-D-Man*p*-O-$(CH_2)_7$Me were tested as substrates for *N*-acetylglucosamine transferase. These had deoxy groups at either positions 3, 4 or 6 in the 1,6-linked mannose unit and positions 3 or 6 in the 1,3-mannose residue.[87] The rhamnose terminating tetramer α-D-Glc*p*A-(1→3)-α-D-Gal*p*-(1→3)-[β-D-Gal*p*-(1→4)]-α-L-Rha*p*-OMe, which is the repeating unit of the antigen from *Klebsiella* type 83, has been prepared,[88] and further work on Lewis tetrasaccharides has resulted in the production of α-L-Fuc*p*-(1→2)-β-D-Gal*p*-(1→4)-[α-L-Fuc*p*-(1→3)]-β-D-Glc*p*NAc-OR [R=$(CH_2)_8CO_2Et$][89] and α-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-[α-L-Fuc*p*-(1→3)]-D-GlcNAc.[90] In related work β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→6)-[β-D-Gal*p*-(1→3)]-α-D-Gal*p*NAc-$OC_6H_4NO_2$ was prepared by use of *N*-acetyllactosamine in the form of a 2-phthalimido thioglycoside.[91]

3.5 Tetrasaccharide Analogues.–The *N*-methyldeoxynojirimycin-containing tetramer α-

Neu5Ac-(2→3)-β-D-Gal*p*-(1→3)-[α-L-Fuc*p*-(1→4)]-NMe-DNJ, which is a sialyl-Lewis A antigen analogue, has been reported.[92]

4 Pentasaccharides

4.1 Linear Pentasaccharides.–The chemical synthesis has been reported of the non-reducing β-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc, which, carrying acyl groups, forms the glycolipid of a *Mycobacterium*. In the natural product the terminal 1,3-linked unit carries a 4,6-pyruvyl acetal as does the adjoining glucose unit, and the former of these is also methylated at O-3.[93] An extensive set of novel 2-chloro-4-nitrophenyl β-D-maltopentaosides modified at positions 4 and 6 in the non-reducing terminal unit has been prepared for testing as substrates for human α-amylase,[94] and the same group published on further modifications in the same terminal unit, these including the introduction of a double bond at C-5 and converting the unit to the 3,6-anhydro moiety. Use of these substrates allowed the selective assay of two different human amylases.[95] In related work, *p*-nitrophenyl α-maltopentaoside was prepared with a thio-group at C-6 of the non-reducing terminal unit, and a variety of *S*-substituted further derivatives was reported.[96] The penta- and hepta-oligosaccharides HO_3S-3-β-D-Glc*p*A-(1→3)-[β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→3)]$_n$ -β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→1)-Cer, where n is 1 or 2, have been isolated from human peripheral nervous system.[97] A short synthetic route to biologically active heparin-like pentasaccharide **15**, which carries O-methyl groups and an additional sulfate ester on O-2 of ring 4, as well as sulfate groups instead of sulfamino groups, has been reported.[98] Research on the core and lipid A components of bacterial polysaccharides has led to the preparation of L-α-D-Hep-(1→3)-L-α-D-Hep-(1→5)-α-KDO-(2→6)-β-D-GlcNHR-(1→6)-D-GlcNHR in which the R-group protecting the amino function is 3(R)-hydroxymyristinoyl.[99]



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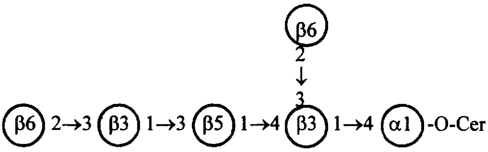
4.2 Branched Pentasaccharides.–β-D-Glc*p*NAc-(1→2)-α-D-6-deoxy-Man*p*-(1→6)-[β-D-Glc*p*NAc-(1→2)-α-D-4-deoxy-Man*p*-(1→3)]-β-D-Man*p*-O-$(CH_2)_7CH_3$ has been prepared as part of a study of *N*-acetylglucosaminyl transferase. The positions of the deoxy groups are chosen such that the compound should be mono-specific for GlcNAc transferase III.[100] The synthesis of Lewis^{A} pentasaccharide α-L-Fuc*p*-(1→4)-[β-D-Gal*p*-(1→3)]-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-D-Glc has been reported.[101] In related work the pentasaccharide which consists of galactose carrying β-*N*-acetyllactosamine at positions at 3 and 6 was made as a precursor to the monosaccharide with the sialyl Le^{x} tetrasaccharide at these positions.[102] Two groups have reported on the total synthesis of ganglioside GD2: α-Neu5Ac-(2→8)-α-Neu5Ac-(2→3)-[β-D-Gal*p*NAc-(1→4)]-β-D-Gal*p*-(1→4)-β-D-Glc*p*-1-Cer.[103,104] The branched mannose-based pentasaccharide β-D-Glc*p*NAc-(1→2)-α-D-Man*p*-(1→6)-[β-D-Glc*p*NAc-(1→2)-α-D-Man*p*-(1→3)]-β-D-Man*p*-O-$(CH_2)_7$Me and several of its mono-deoxy and mono-methyl ether analogues have been reported in studies related to substrate specificity for *N*-acetylglucosamine transferases.[105] UDP-6-deoxy-D-galactose and the 6-deoxy-6-fluoro analogue, prepared chemically, were used for glycosyl transfer in the preparation of pentasaccharide 6-deoxy-β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→2)-[6-deoxy-β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→6)]-D-Man and the fluorinated analogue.[106]

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*Ac**
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-glucose)**
⑬	**L-*glycero*-D-*manno*-heptose**				

5.1 Branched Hexasaccharides.–Compound **16**, which has been synthesized is the ganglioside GD1a; the pentamer without the neuraminic acid on the left of the structure being GM$_1$.[107] Compound **17** has been prepared from the corresponding pentasaccharide by linking the 1,4-bonded *N*-acetylglucosamine unit using a transferase and UDP GlcNAc as source.[100] In this hexamer the 1,6- and 1,3-linked mannose units were devoid of oxygen atoms at C-6 and C-4



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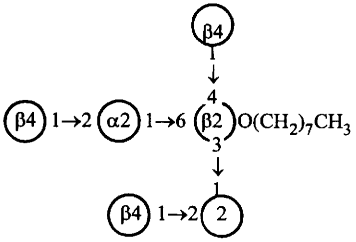

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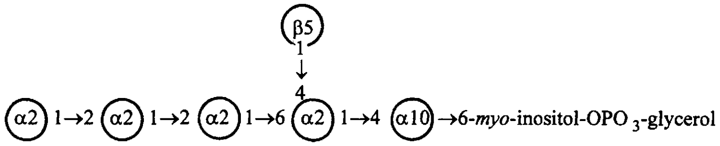
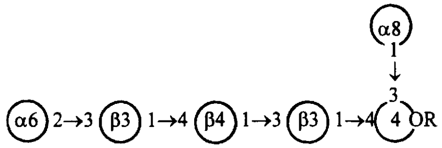


18

respectively. The high mannose-containing hexamer **18**, which also carries phosphate functions at two of the mannose units, corresponds to the GP1 membrane anchor of a rat brain glycoprotein, and it has been prepared by Fraser-Reid using his pentenyl glycoside procedures as well as glycosyl trichloroacetimidates.[108] Chemo-enzymic procedures of sialylation and fucosylation have led to the hexamer **19**,[109] but largely enzymic approaches were used in the preparation of **20**, the sialyl-Le^x hexasaccharide.[110] The xylose-containing hexamer **21**, having methyl groups at O-3 of the terminal glucose units and a 6-deoxyglucose in the 1,2-linked unit is the hexasaccharide moiety of a saponin and has been synthesized by Schmidt.[111]



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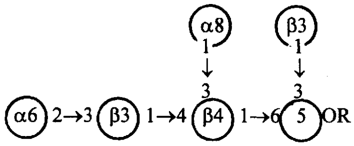
R=$(CH_2)_8CO_2Me$



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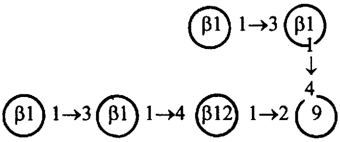

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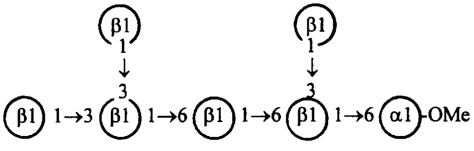
6 Heptasaccharides

The glucose heptamer **22**, which has been synthesized, is a phytoalexin elicitor of soya beans,[83] and compound **23**, which is the heptasaccharide moiety of ganglioside BGM$_1$ has been prepared as the methyl ester of the neuraminic acid moiety.[112] Compound **24** has been prepared and in the form of its glycosylamine linked to a pentapeptide to give a product which represents a unit of ovalbumin.[113]



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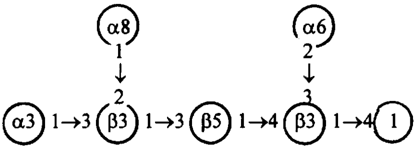

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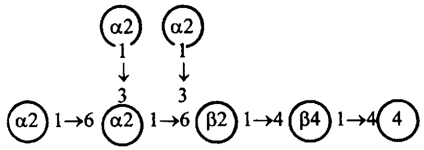

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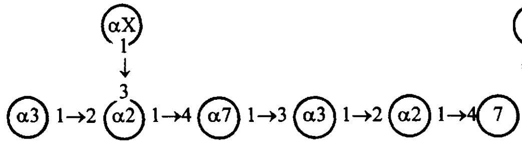

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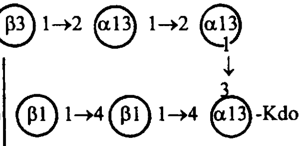

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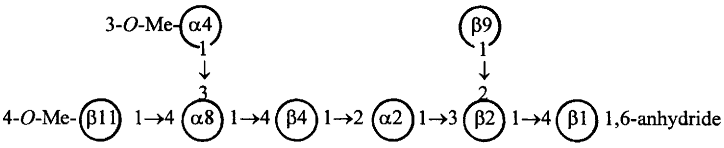
Compound **25**, in which X=3,6-dideoxy-D-*xylo*-hexose (abequose), and the isomer which has this sugar bonded to the mannose unit adjacent to the reducing centre, have been produced on mild acid hydrolysis of a bacterial *O*-antigen fragment octasaccharide which has the abequose at the mannose units second from each end of the octamer.[114] Heptasaccharide **26**, isolated by mild hydrolysis from the lipopolysaccharide of *Haemophilus influenzae*, has been structurally characterized.[115]

7 Octasaccharides

Octasaccharide **27** is a component derived from a novel mollusc glycolipid and has been prepared by 3+5 coupling using *S*-methyl 1-thioglycoside technology.[116]



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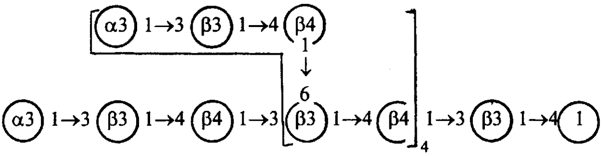
8 Higher Saccharides

Ethyl β-D-galactopyranoside with the Le^x tetrasaccharide {α-NeuAc-(2→3)-β-D-Gal*p*-(1→4)-[α-L-Fuc*p*-(1→3)]-β-D-GlcNAc} bonded to O-3 and O-6, is a bivalent sialyl Le^x monosaccharide and has been synthesized largely by enzymic methods and subjected to conformational studies.[102]

The linear β-D-glucan decasaccharide with alternating 1,3- and 1,4-linkages has been made in the fully C-deuterated form except for the central cellobiose residue. The undeuterated analogue was also obtained.[117] As seems appropriate, T. Ogawa appears to lead the way in terms of size and complexity of oligomers obtained by synthetic means. He has produced the glycan of a glycosyl ceramide obtained from rabbit erythrocyte membrane which consists of twenty five sugar units linked as indicated in **28**.[118]



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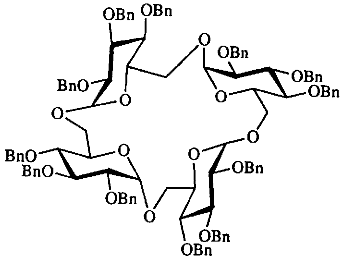
9 Cyclodextrins

Treatment of the hexa-*O*-benzyl derivative of 6′-*O*-tritylisomaltosyl acetate with silver perchlorate and tin tetrachloride in ether gave in 40% yield the novel cycloisomaltotetraose ether **29**.[119]



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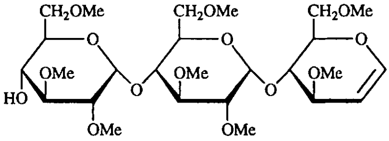
Three unusual cyclic isomaltosaccharides which were produced from the culture broth of a strain of *Bacillus sp. T-3040* were identified as the cyclo-heptaose, octaose and nonaose.[120] By use of appropriate glycosyl fluorides three lactose units were linked α-(1→4) in a cycloglycosidation process to give the heterocyclodextrin which has a trigonally shaped structure.[121] Iodonium-promoted cyclo-dimerization of the trimer **30** yielded a fully substituted α-cyclodextrin derivative



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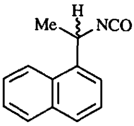
having deoxyiodo groups at C-2 of sugar units 1 and 4.[122] Kuzuhara has applied related technology to obtain monoiodo analogues in the α-, β- and γ-cyclodextrin series. Initial thiolyses broke the rings and gave oligomer phenyl thioglycosides. From these, corresponding glycals were produced and the addition reactions ensued.[123] Enzymic methods have been used to produce 6-*O*-(α-D-galactopyranosyl)cyclomaltoheptose, the approach being to epimerize at C-4 of the extra-cyclic unit of the commercially available glucosyl β-cyclodextrin.[124] In related work eighteen β-D-galactosylated branched cyclodextrins have been produced by transgalactosylation of α-, β- and γ-cyclodextrins bearing glucosyl and maltosyl side groups.[125]

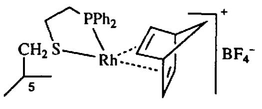
Considerable progress has been made with the derivativization of cyclodextrins. From the heptakis-(6-*O*-pivaloyl) derivative of β-cyclodextrin a benzylidine acetal with the group spanning O-2 of one sugar unit and O-3 of the neighbour has been described, and reductive ring opening of the acetal, as well as other hydroxyl group manipulation, afforded the perbenzylated derivative having one free hydroxyl group at O-2.[126] Further anhydro derivatives have been produced: thus from per-2-*O*-tosyl-cyclodextrins, cyclo-2,3-anhydro-α-D-mannopyranosyl compounds have been described,[127] and the octakis-3,6-anhydro derivative of the γ-compound has been prepared and found to bind large alkali metal ions.[128]

In the area of ethers of cyclodextrins, 2,2-dipyridyl has been linked to O-6 by way of a 3-methylene group in otherwise permethylated β-cyclodextrin. Metal ions can be trapped by the product, and the complexes produced were studied.[129] A chiral phosphinyl ferrocene compound has been tethered by way of a C-2 bridge to O-3 of heptakis-2,3-di-*O*-methyl-β-cyclodextrin.[130] Commercially available hydroxypropyl β-cyclodextrin of molecular weight about 1500 has been described, and therefore approximately six of the primary hydroxyl groups are substituted.[131] The four regioisomeric $6^1,6^n$-di-*O*-trityl-γ-cyclodextrins have been synthesized and separated by HPLC. For characterization purposes alkenes were produced at the 5,6-positions previously carrying trityl groups. The molecules were fragmented at that point and product analysis was done by FAB mass spectrometry.[132]

In the field of cyclodextrin esters, the *p*-(dimethylamino)benzoyl derivatives of α-, β- and γ-cyclodextrins have been reported as fluorescent sensors of molecular recognition. They show fluorescence derived from planar and intramolecular charge transfer excited states.[133] β- And γ-cyclodextrins bearing one ferrocene group linked by variable length ester chains to O-6 have been made and their binding of various guests has been studied.[134] The six possible monocarbamate derivatives obtained from β-cyclodextrin and the (R) and (S) forms of the isocyanate **31** were examined.[135] Polytosylation of γ-cyclodextrin gave the octakis-(6-*O*-tosyl) derivative, this compound also bearing a secondary ester group at O-2, and the heptakis product. These could be separated on silica gel columns carrying 3-aminopropyl groups.[136] By use of heptakis-(6-bromo-6-deoxy)-β-cyclodextrin and sodium 2-naphthol 6-sulfonate a sulfonated aromatic derivative was produced; a detailed photophysical study of it was undertaken to establish that the compound has a hydrophobic cavity capable of accepting a photozyme.[137] By way of the hepta-2-*O*-benzyl ethers, which had been made from the hepta-Tbdms ethers at O-6, β-cyclodextrin per-3,6-sulfates were prepared and shown to exhibit anti-HIV activity.[138]



31



32

Interest continues to be shown in 6-amino-6-deoxy-derivatives. The mono-derivatives of α- and β-cyclodextrin, prepared from monosulfonates by use of ammonia in dry DMF under pressure, were shown to be much more soluble in water than the parent compounds.[139] From the latter monoamine mono[6-deoxy-6-L-tyrosylamino]-β-cyclodextrin has been made,[140] and Leuenkephalin has also been linked to the amino group of this compound.[141] The complexing with inorganic anions formed using heptakis-(6-butylamino-6-deoxy)-β-cyclodextrin has been studied.[142]

A set of heptakis-(6-S-alkyl-6-thio)-β-cyclodextrins have been produced in connection with studies of thermotropic liquid crystals[143] and from monotosyl-β-cyclodextrin a phosphinyl rhodium complex with the structural feature **32** has been produced.[144]

Several cyclodextrin derivatives have been prepared as chiral stationary phases for the chromatographic resolution of racemates. Heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin on aminopropyl silica gel provided suitable HPLC material for resolution of various aromatic compounds under reverse-phase conditions,[145] and 3,5-dimethylphenylcarbamate derivatives of β-cyclodextrin have also been prepared as HPLC stationary phases.[146] For capillary gas chromatography, β-cyclodextrin carrying *O*-pentyl groups at the O-2 and O-6 positions and trifluoroacetyl groups at O-3 was prepared.[147] A related fully-substituted derivative of β-cyclodextrin, having methyl groups at O-2 and O-3 and *p*-allyloxyphenyl groups at O-6, and related alkene-containing derivatives, was bound to polymethylsiloxane to give chiral stationary phases for open tubular column chromatography. Separations of racemates of methyl mandelate, *trans*-1,2-cyclohexane diol and *trans*-2,4-pentane diol were illustrated.[148]

Partial enzymic hydrolyses of substituted β-cyclodextrins using bacterial α-amylase have been described. From the mono-6-tosylate maltotriose carrying the ester group at the non-reducing terminal position was obtained, and from the mono-2,3-anhydro-D-*allo*-compound the trimer bearing the anhydride ring in the central position was the product. This work is related to degradative studies with γ-cyclodextrin and a different amylase (Vol. 24, p. 60, ref. 20).[149]

The above describes chemical features of the cyclodextrins to have been reported. The complexing characteristics of them and their derivatives and a variety of guests have not been dealt with.

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5
Ethers and Anhydro-sugars

1 Ethers

1.1 Methyl Ethers. - During the course of studies on glucuronic acid-containing saponins, it has been discovered that the hydroxy groups of the sugar moieties can be partially methylated by prolonged treatment with diazomethane in methanol. Non-glucuronide saponins were not methylated.[1] Convenient syntheses of methyl 2-acetamido-2-deoxy-3-, 4-, and 6-*O*-methyl-α-D-glucopyranosides from methyl 2-acetamido-2-deoxy-α-D-glucopyranoside have been reported[2], and 2,3,4-tri-*O*-methyl-D-rhamnose has been prepared from D-mannose.[3]

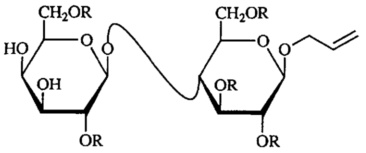
Analogues of the disaccharide α-D-Glc*p*-(1→3)-D-Man (which is released by a Golgi *endo* mannosidase), including the 4- and 6-*O*-methyl derivatives, have been synthesized as potential inhibitors of the mannosidase.[4] Also, analogues of the acceptor β-D-GlcNAc*p*-(1→2)-α-D-Man*p*-(1→6)-β-D-Glc*p*-*O*-$(CH_2)_7CH_3$ of *N*-acetylglucosaminyl transferase V, including the 4″-*O*-Me derivative, have been produced,[5] and similar work has involved the preparation of the 4-nitrophenyl glycoside of the above acceptor and its 4′-*O*-methyl and 4′,6′-di-*O*-methyl derivatives as potential inhibitors of *N*-acetylglucosaminyl transferase V.[6] Analogues of the mannosidase inhibitor 1,5-dideoxy-3-*O*-α-D-glucopyranosyl-1,5-imino-D-mannitol incorporating each of the mono-*O*-methyl glucose derivatives have been reported.[7] The synthesis of selectively methylated 1,5-anhydro-D-fucitols for use in glycosyl linkage analysis is discussed in Chapter 22, and some partially methylated oligosaccharides are mentioned in Chapter 4.

1.2 Other Alkyl and Aryl Ethers. - The synthesis of 3-*O*-(2-iodoethyl)-D-glucose has been described,[8] and other 3-*O*-alkyl and -haloalkyl-D-glucose derivatives are mentioned in Chapters 17 and 19. Some amphiphilic and mesogenic di-*O*- and tri-*O*-(n-alkyl)-D-glucose derivatives have been reported along with a study of their thermal behaviour.[9] An electrochemical method has been used for the mono-alkylation of some mono- and di-saccharides,[10] and a number of 4-*O*-alkyl-D-glucose compounds have been prepared[11] as well as 2-*O*-(2-nitrobenzyl)-D-glucose by standard methods.[12] The use of some carbohydrate ethers as chiral auxiliaries is discussed in Chapter 24, and an n.m.r. method for the determination of the relative stereochemistry of sugar 1-carboxyethyl ethers is outlined in Chapter 21.

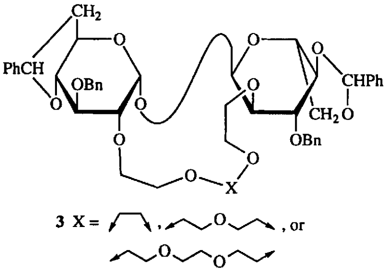
Organotin ethers continue to be employed in selective alkylations. In a study of the Bu_2SnO-mediated alkylation of lactosides **1** and **2** aimed at obtaining the 3′-*O*-ethers, the penta-benzyl ether **2** afforded better yields than the corresponding benzoate **1**,[13] and similar conditions have been employed for the regioselective benzylation of octyl β-D-galactopyranoside at *O*-3.[14] Dibutyltin dimethoxide has been used in place of dibutyltin oxide for selective alkylation of carbohydrate diols.[15]

Selective benzylation of some carbohydrate diols has been effected under phase-transfer conditions with the major products being those expected on steric grounds.[16] New debenzylating conditions have employed boron trichloride dimethylsulfide complex which apparently cleaves benzyl ethers in the presence of trityl ethers, silyl ethers, esters and aryl methyl ethers,[17] while acetolysis of benzyl ethers has been achieved using tin(II) bromide and acetyl bromide.[18] The effects of a deoxyfluoro group at C-2 or C-3 on the ratios of 4- and 6-benzyl ethers produced on LAH - aluminium chloride ring opening of methyl 4,6-*O*-benzylidenehexopyranosides have been assessed,[19] and some diphenylmethylene acetals have been reductively cleaved under the same conditions to afford diphenylmethyl ethers selectively.[20] Deprotection of allyl and propenyl ethers has been achieved under neutral conditions using palladium chloride, cuprous chloride and oxygen in aqueous DMF,[21] while TFA/TFA anhydride in dichloromethane leads to detritylation of 5′-*O*-trityl nucleosides by way of the trifluoroacetates which are cleaved with triethylamine.[22]

Some α,α-trehalose crown ether derivatives **3** have been prepared,[23] and also the furanoside- and pyranoside-based crown ethers **4** and **5**.[24]



1 R = Bz
2 R = Bn



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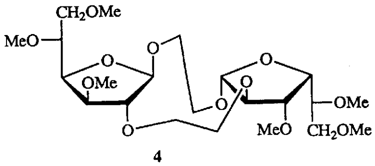

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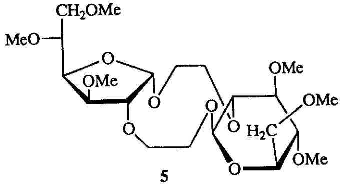

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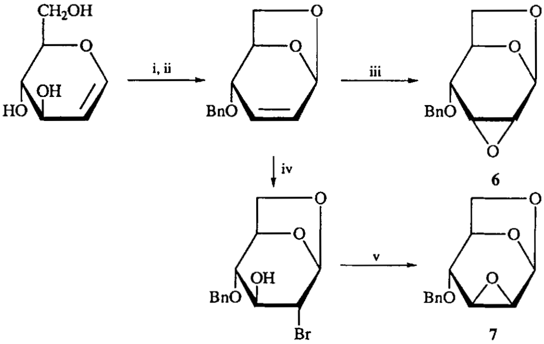
1.3 Silyl Ethers. - Regioselective silylation of lactose derivatives using dibutylstannylene acetals has afforded the 6′-*O*-silyl ethers in contrast to alkylations which give the 3′-*O*-ethers under the same conditions.[25] Some Tbdms ethers have been cleaved by absorption onto alumina and then irradiation in a microwave oven.[26] The silylation of 2′-deoxynucleosides is discussed in Chapter 20.

2 Intramolecular Ethers (Anhydro-sugars)

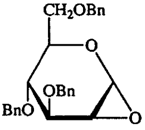
2.1 Oxirans. - Treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with a mixture of diethyl carbonate and potassium carbonate in DMF has afforded directly a new simple synthesis of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside. The corresponding 2,3-cyclic carbonate is postulated as an intermediate.[27] Some carbohydrate examples have been published of the use of sodium hydride and *p*-toluenesulfonyl chloride for the conversion of 1,2-diols to epoxides.[28] Simple routes to the Cerny epoxides **6** and **7** from D-glucal have been developed (Scheme 1).[29] In this scheme the first step involves a dehydration elimination with allylic rearrangement. Syntheses of methyl 2,3-anhydro-α- and β-L-erythrofuranoside have been reported.[30] Some nitro-sugar epoxides are mentioned in Chapter 10.



Reagents: i, $CuSO_4$, THF, Δ; ii, NaH, BnBr; iii, MCPBA; iv, AcOBr, then K_2CO_3, H_2O, 3 h; v, K_2CO_3, H_2O, 5 days

Scheme 1

The synthesis of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-talopyranose has been published,[31] as have syntheses of 1,2-anhydro-3,4-di-*O*-benzyl-β-L- and β-D-rhamnopyranose.[32] Some 2-*O*-Ts free sugar derivatives on treatment with base have afforded the 1,2-anhydro compounds **8-10**.[33] Conditions have been found for the conversion of tri-*O*-methyl-D-glucal into predominantly either the corresponding 1,2-anhydro-β-D-manno- or -α-D-gluco- compounds by way of 2-bromo-2-deoxy-hexopyranoses.[34] The formation of *C*-glycosides from 1,2-anhydro-sugars is discussed in Chapter 3. Selective opening of epoxide **11** with titanium reagents has afforded the 2-deoxyribose derivatives **12** (Scheme 2).[35]



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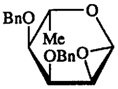

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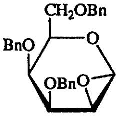

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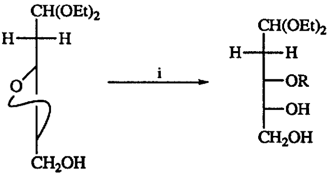
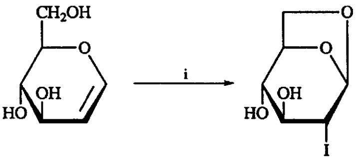


11 **12** R = Ac or toluoyl

Reagents: i, Ti(OPr^i)$_3$OR, CHCl$_3$

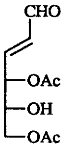
Scheme 2

2.2 Other anhydrides. - 1,6-Anhydro-2-deoxy-2-iodo-β-D-glucopyranose has been prepared directly from D-glucal (Scheme 3).[36] The conversion of levoglucosenone into 4-deoxy-D-*lyxo*-hexose is



Reagents: i, (Bu$_3$Sn)$_2$O, CH$_3$CN, then I$_2$

Scheme 3



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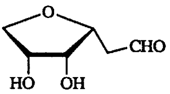

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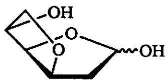

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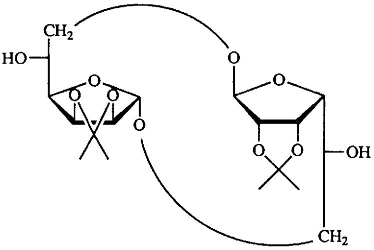
mentioned in Chapter 12 and into branched chain compounds is discussed in Chapter 14. Treatment of 2,3,6-tri-*O*-benzoyl-α-D-galactopyranosyl fluoride with Lewis acids has afforded 1,4-anhydro-2,3,6-tri-*O*-benzoyl-β-D-galactopyranose.[37] The unsaturated derivative **13** under basic conditions gives the 3,6-anhydro compound **14**, which exists in equilibrium with the 2-deoxy-furanose **15**.[38]

The product distribution from the pyrolysis of inulin has been compared with that from the pyrolysis of glucose and fructose under varying pH conditions. The major product from inulin was 2,6-anhydrofructofuranose.[39] A ring-opening polymerisation of 1,6-anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-β-D-mannopyranose, with phosphorus pentafluoride as the initiator, has afforded a 4-*O*-α-D-mannopyranosyl-(1→6)-α-D-mannopyranan.[40] A study has shown that the TFA hydrolysing conditions used for polysaccharide analysis converts some of any D-mannose present into 1,6-anhydro-β-D-mannopyranose. The synthesis is also reported of 2,3,5-tri-*O*-acetyl-1,6-anhydro-β-D-mannofuranose and of the 1,6′:1′6 dianhydride **16**.[41]



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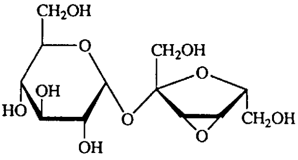

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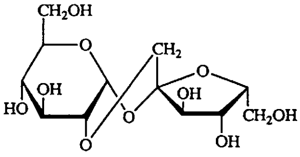

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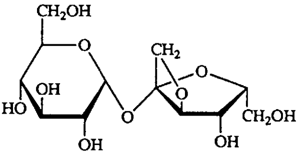

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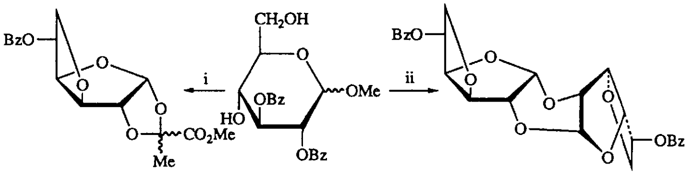

20 **21**

Reagents; i, $MeCOCO_2Me$, TfOH; ii, TfOH

Scheme 4

Methanolysis of epoxide **17** affords not only 4′-*O*-methylsucrose, but also the 2,1′-anhydride **18** by way of the oxetan **19**.[42] Attempts to prepare 4,6-*O*-pyruvate acetals from methyl 2,3-di-*O*-benzoyl-α,β-D-glucopyranoside using TfOH as catalyst led to formation of the 3,6-anhydroacetal **20** (Scheme 4). In the absence of the pyruvate reagent the 1,2′:1′,2-dianhydride **21** was formed.[43]

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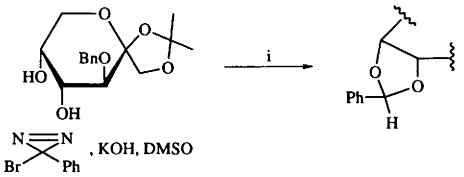
6
Acetals

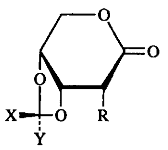
1 Isopropylidene and Benzylidene Acetals

The regioselective isopropylidenation of L-rhamnose dithioacetal is covered in Chapter 11. A new synthetic approach to benzylidene acetals from 1,2-*cis*-, 1,2-*trans*-, and 1,3-*cis*-diols under basic conditions by use of arylhalodiazirines has been developed; an example is given in Scheme 1.[1] A reinvestigation of the benzylidenation and isopropylidenation of D-ribono-1,4-lactone has confirmed that the 3,4-(*R*)-benzylidene-1,5-lactone derivative **1** is the thermodynamic product [benzaldehyde/HCl (conc.)], whereas the 2,3-*O*-(*R*)-benzylidene-1,4-lactone **5** prevails under anhydrous conditions (α,α′-dimethoxytoluene, $SnCl_2$, 1,2-dimethoxyethane). Acetonation with acetone/HCl (conc.) furnished a 1:2 mixture of isopropylidene derivatives **2** and **6**. From 2-deoxy-D-ribono-1,4-lactone, acetals **3** and **4** were obtained as the main products on treatment with benzaldehyde and acetone, respectively, in the presence of acid.[2] A modification of the original procedure (acetone/H_2SO_4/$CuSO_4$) for the preparation of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-gluconate (**7**) from D-glucono-1,5-lactone increased the yield from 24 to 64%; an even better yield (76%) was achieved by use of acetone and $ZnCl_2$. Compound **7** is a convenient precursor of the open-chain form **8** of

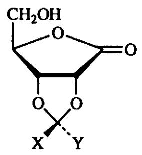


Reagents: i, , KOH, DMSO

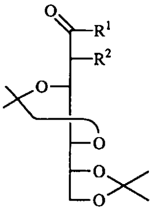
Scheme 1

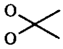


1 R = OH, X = H, Y = Ph
2 R = OH, X = Y = Me
3 R = H, X = H, Y = Ph
4 R = H, X = Y = Me



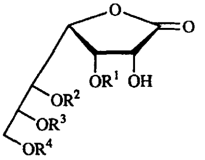
5 X = H, Y = Ph
6 X = Y = Me

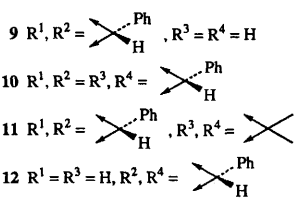


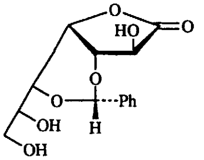
7 $R^1, R^2 =$ 

8 $R^1 = H, R^2 = OH$

D-glucose.[3] On treatment with benzaldehyde in the presence of hydrochloric acid, D-*glycero*-D-*gulo*-heptono-1,4-lactone afforded the highly crystalline 3,5-*O*-benzylidene derivative **9** in 97% yield. The dibenzylidene acetal **10** was obtained in modest yield on exposure of compound **9** to benzaldehyde in the presence of zinc dichloride. Isopropylidenation of **9** with 2,2-dimethoxypropane and *p*-toluenesulfonic acid, on the other hand, gave the mixed diacetal **11** quantitatively. The 5,7-monobenzylidene derivative **12** was available by Kiliani ascent from 4,6-*O*-benzylidene-D-glucose, and inversion of configuration at O-2 of **11** furnished, after selective hydrolysis of the acetonide, a further useful synthon, the D-*glycero*-D-*ido*-configurated heptono-1,4-lactone monoacetal **13**.[4]







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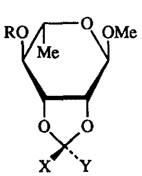
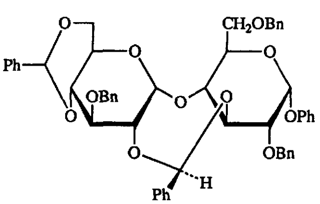


14 R = H, X = H, Y = Ph
15 R = H, X = Ph, Y = H
16 R = Bn, X = H, Y = Ph

Dioxolane-type *endo*-benzylidene acetals were the main products in the kinetically controlled reactions of several hexopyranosides carrying 2,3- or 3,4-*cis*-hydroxyl groups with dimethoxytoluene and *p*-tolenesulfonic acid without added solvent. It was noted that *endo*-*exo* isomerization was faster for derivatives with unprotected hydroxyl groups vicinal to the acetal; thus, methyl α-L-rhamnopyranoside gave a 1:1 mixture of **14** and **15**, while from the 4-*O*-benzylated starting compound the *endo*-product **16** was formed stereospecifically.[5]



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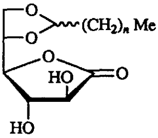
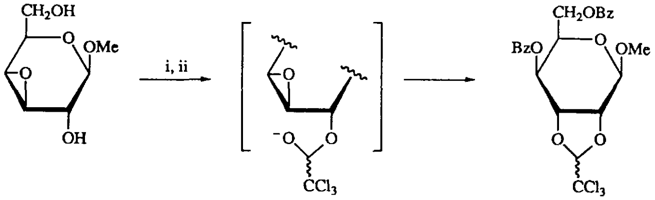


18 n = 4–6, 8, 10, 12

The synthesis of maltose derivative **17**, with a 3,2′-*O*-benzylidene acetal bridging the two glucose residues, and its behaviour under hydrolytic, reductive, and oxidative cleavage conditions have been described.[6] A similar, 8-membered, interglycosidic benzylidene group has been introduced into β-cyclodextrin heptakis-(6-*O*-pivaloate) by use of 2 molar equivalent of dimethoxytoluene in the presence of camphorsulfonic acid. Subsequent deacylation, perbenzylation and finally reductive acetal cleavage furnished a β-cyclodextrin derivative with one free O-2 position.[7]

2 Other Acetals

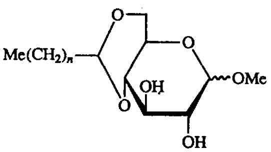
On treatment with a non-enolizable aldehyde and sodium hydride, *trans*-related α-hydroxyepoxides were converted to acetals. The reaction is thought to proceed by way of a hemiacetal salt, as illustrated in Scheme 2.[8] L-Galactono-1,4-lactone, a by-product of the sugar industry, furnished a diastereomeric mixture of 5,6-alkylidene acetals **18** in >60% yield on microwave irradiation in the presence of long-chain aldehydes and montmorillonite KSF as catalyst,[9] and 4,6-*O*-alkylidene derivatives **19** of D-glucose have been prepared by use of long-chain aldehydes and catalytic pyridinium *p*-toluenesulfonate in benzene under azeotropic removal of water.[10] Compounds **18** and **19** were of interest in liquid crystal studies.



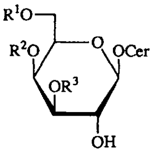
Reagents: i, Cl_3CCHO, NaH, imidazole; ii, BzCl, py

Scheme 2

Plasmalopsychosines **20** and **21**, previously isolated from human brain tissue, and the methyl α-glycoside analogue of **21** have been synthesized by employing 1,1-dimethoxyhexadecane/*p*-TsOH, for use in biological studies.[11]

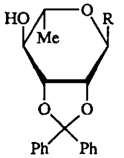


19 *n* = 4–8



20 $R^1 = H, R^2, R^3 =$ >—$(CH_2)_{14}Me$

21 $R^1, R^2 =$ >—$(CH_2)_{14}Me, R^3 = H$



R = OMe, OBn, SMe, SEt, or SPh

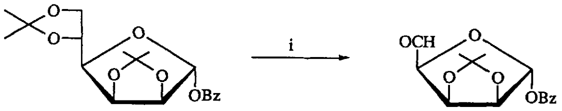
22

The preparation of dioxolane-type diphenylmethylene acetals **22** and **23**, some of which are new compounds, by use of dichlorodiphenylmethane in pyridine has been reported.[12] The synthesis of pyruvate acetal-containing disaccharides by the trichloroacetimidate method is covered in Chapter 3, and n.m.r. studies on 4,6-pyruvate acetals of α- and β-glucosides, -mannosides, and -galactosides are referred to in Chapter 21. Attempts to prepare the 4,6-*O*-pyruvate acetals of methyl 2,3-di-*O*-acyl-D-glucopyranosides by use of methyl pyruvate in the presence of triflic acid, rather then boron trifluoride etherate (see Vol. 26, Chapter 6, Ref. 13) led instead to the formation of 3,6-anhydrofuranose derivatives[13] (see also Chapter 5).

Several new acetals, such as compounds **24** and **25**, have been prepared from methyl α-D-glucoside and methyl α-D-mannoside by exposure to 1-methoxy-1,3-butadiene or 1-methoxy-3-buten-2-one, respectively, and catalytic pyridinium *p*-toluenesulfonate in DMF.[14] Protection of *trans*-vicinal diols by means of dispiroketals (see Vol. 26, Chapter 6, Ref. 19) has been applied to a series of methyl glycosides.[15]

3 Reactions of Acetals

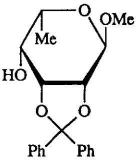
Further studies on the acetolysis of 2,4-*O*-benzylidene- and 2,4-*O*(4-methoxybenzylidene)-hex-5-enitols (see Vol. 26, Chapter 6, Scheme 4) have been reported.[16] Ethereal HIO_4 has been used to selectively remove terminal 1,2-*O*-isopropylidene groups with subsequent cleavage of the released diol in a one-pot process. An example is given in Scheme 3.[16a] The reductive cleavage of interglycosidic acetals is referred to in section 1 above and that of compounds **18**, **22** and **23**, and of 4,6-*O*-benzylidene-3-deoxyhexopyranosides with fluorine at C-2 or C-3 is covered in Chapter 5. Treatment of the mixed diacetal **26** with lithium aluminium hydride/aluminium trichloride afforded dibenzyl ether **27** as the main product, *i.e.*, both acetal groups were cleaved reductively[17].



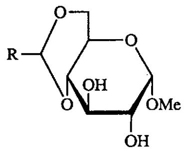
Reagents: i, HIO_4, ether

Scheme 3

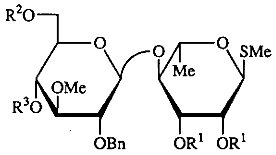
The behaviour of 6-(substituted methyl) ethers **28**, **30**, and **32** of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside and similar 4-*O*-derivatives of 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside during hydrogenolysis has been examined. The primary methylthiomethyl derivative **28**, for example, furnished the corresponding alcohol **29** on exposure to AlH_2Cl; treatment of the primary *p*-methoxybenzyl derivative **30**, with BH_3 in toluene on the other hand, gave the 6-methyl ether **31** quantitatively.[18]



23

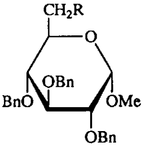


24 R = CH=CHMe
25 R = CH_2COMe

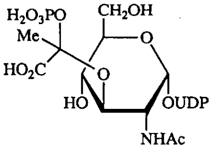


26 R^1, R^1 = Ph Ph, R^2, R^3 = Ph
27 R^1 = R^2 = H, R^3 = Bn

The isolation and structural elucidation of compound **33**, a tetrahedral intermediate in the UDP-*N*-acetyl-glucosamine enolpyruvyl transferase enzymatic pathway has been reported.[19] The use of acetal-protected 3-thio sugars as ligands in metal-catalysed asymmetric synthesis is referred to in Chapter 11.



28 R = OCH_2SMe
29 R = OH
30 R = $OCH_2OC_6H_4OMe$
31 R = H
32 R = OCH_2OBn, OCH_2OEt, or $OCH_2O(CH_2)_2Tms$



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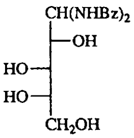
7
Esters

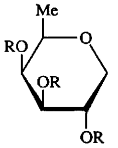
1 Carboxylic Esters

1.1 Synthesis and Reactions.- The formation of formates by β-scission of anomeric oxygen-centred radicals is covered in Chapter 2, and the unusual reduction of an acetyl group by LAH is referred to in Chapter 12. The ammonolysis of 1,2,3,4-tetra-*O*-benzoyl-L-arabinopyranose, which is known to furnish 1,1-bis(benzamido)-1-deoxy-L-arabinitol (**1**), has been investigated by use of ^{14}C-labelling. It was, surprisingly, found that the two benzoyl groups of **1** are those originally attached to O-3 and O-4 of the starting compound.[1]

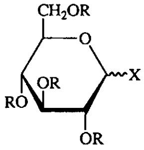
A simple, convenient procedure for the hydrolysis of carbohydrate and nucleotide acetates using IRA-400 (OH) resin in methanol has been described.[2] Methanolysis of acetylated or benzoylated alditols, aldoses, lactones, carbohydrate orthoesters, glycosides, and disaccharides has been carried out efficiently with tertiary amines in the absence of water at ambient temperature.[3] A study on the partial methanolysis and hydrazinolysis of acetylated and benzoylated methyl α- and β-D-xylopyranosides has been published; special attention was given to the influence of anomeric configuration and reaction medium on the course of the reactions.[4]



1



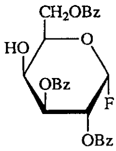
2 R = Me or Bz



X = α-OMe or β-OPh
3 R = Bn
4 R = Ac

The 32 possible derivatives of methyl α- and β-D-fructofuranosides bearing four chromophores, chosen from 4-bromobenzoate or 4-methoxycinnamate, have been prepared for c.d. studies.[5] All nine methylated/benzoylated derivatives **2** of 1,5-anhydro-D-fucitol have been synthesized by partial methylation (dimsyl lithium, DMSO, methyl iodide) followed by *in situ* benzoylation. The corresponding acetates were available by debenzoylation/acetylation of compounds **2**.[6]

Tetrabenzyl ethers **3** have been converted readily and in high yields to the corresponding tetraacetates **4** by treatment with acetyl bromide and catalytic quantities of tin(II) bromide in dichloromethane.[7] The preparations, by standard procedures, of several acylated and partially acylated glycosyl fluorides, such as compound **5**, and some of their reactions have been described.[8] Esterification of D-mannose and D-galactose with 6.2 molar equivalents of pivaloyl chloride in pyridine/chloroform at 35 °C gave the β-pyranose 1,3,4,6- and 1,2,3,6-tetraesters, respectively, in yields of 60%, whereas a *ca.* 3:4 mixture of the β-1,2,4,6- and β-1,2,3,6-tetrapivaloates was obtained from D-glucose under these conditions.[9] The pivaloylation of aldono-1,4-lactones with 3.3-3.6 molar equivalents of acid chloride in pyridine at 0 °C has been investigated. The D-gulono-**6** and L-mannono-derivative **7** gave the 2,5,6-tripivaloates in yields of 84 and 50%, respectively; the analogous benzoylations were less selective, and the D-galactono derivative **8** furnished complex mixtures of di- and tri-esters with either acylating agent.[10] In a study on the conventional benzoylation (benzoyl chloride/pyridine, -14 °C to room temperature) of *N*-(2,2-diethoxy carbonylvinyl)-β-L-rhamnopyranosylamine (**9**), the order of reactivity was found to be OH-3>OH-4≈OH-2.[11] The synthesis of digalloyl esters of 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol is referred to in part 1.2 below (Ref. 65).



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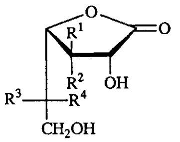
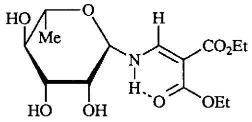
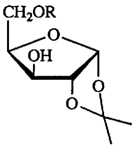


6 R^1 = R^3 = H, R^2 = R^4 = OH
7 R^1 = R^4 = H, R^2 = R^3 = OH
8 R^1 = R^4 = OH, R^2 = R^3 = H

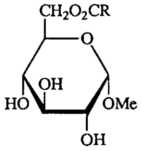


9

Use of acetyl chloride in dichloromethane in the presence of 2,4,6-collidine or some other bulky base allowed selective esterification at primary sites; the 5-*O*-acetate **11**, for example, was obtained in 91% yield from the 3,5-diol **10**.[12] Bis(2-oxo-oxazolidin-3-yl)phosphinic chloride (BOP-Cl), a new reagent for condensing alcohols and acids, has been employed in the preparation of primary esters **12**.[13] Treatment of unprotected methyl α-D-glucopyranoside, 2-acetamido-2-deoxy-D-glucose, and maltose with triphenylphosphine, DEAD, and an equimolar amount of a carboxylic acid (*e.g.*benzoic, methacrylic or adamantoic acid) allowed regioselective 6-*O*-esterification (O-6′ for

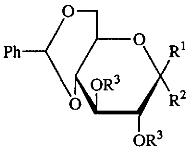


10 R = H
11 R = Ac



R = Bn, 4-NO$_2$-Bn, 4 MeO-Bn, Ph, 2,6-dichlorophenyl

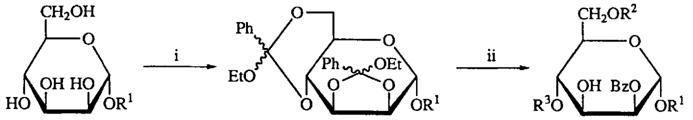
12



13 R^1 = , R^2 = OMe, R^3 = H
14 R^1 = SEt, R^2 = R^3 = H
15 R^1 = H, R^2 = OMe, R^3, R^3 = >=O

maltose) in moderate yields.[14] The conversion of a primary sulfate to an acetate is covered in Part 3 of this Chapter (Ref. 103).

Use of dibutyltin dimethoxide in place of dibutyltin oxide has been recommended for procedural simplicity and improved reproducibility in regioselective acylations, for example at O-3 of diol **13**.[15] Moderate selectivity has been observed in the benzylation of thioglucoside derivative **14** and related compounds with benzyl bromide under phase transfer conditions.[16] Opening of the known 2,3-carbonate **15** with ethanol or dodecanol gave the two expected 2- and 3-monoesters in nearly equal proportions.[17] A new method for the selective diprotection of α-D-mannopyranosides involved opening of diorthoesters **16** which were formed *in situ*, as shown in Scheme 1. As only the 2,3-orthoesters opened regioselectively, the 2,4- and 2,6-dibenzoates **17** and **18**, respectively, were obtained in approximately equal proportions.[18] The formation of deacetylation products **20, 21**, and **22** in 50, 3, and 34%, respectively, on treatment of the diacetate **19** with methanolic HCl is thought to be the first reported regioselective deacetylation of a 3,4-di-*O*-acetylglycopyranoside.[19] The 3,6-di-*O*-lauroyl, -myristoyl, -palmitoyl, and -stearoyl esters of methyl 2-amino-2-deoxy-D-glucopyranoside have been obtained by partial acylation of methyl 2-benzyloxycarbonylamino-2-deoxy-D-glucopyranoside, followed by *N*-deprotection, for use as positively charged components of liposomes.[20]



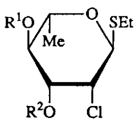
$R^1 = (CH_2)_n Me$
$n = 7$ or 13

16

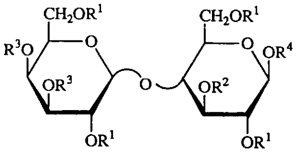
17 $R^2 = H, R^3 = Bz$
18 $R^2 = Bz, R^3 = H$

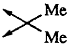
Reagents: i, $PhC(OEt)_3$, TFA, CH_3CN; ii, TFA, H_2O, CH_3CN

Scheme 1

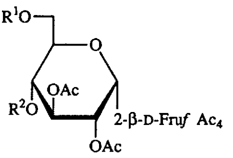


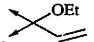
19 $R^1 = R^2 = Ac$
20 $R^1 = H, R^2 = Ac$
21 $R^1 = Ac, R^2 = H$
22 $R^1 = R^2 = H$



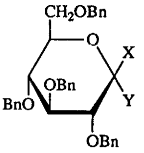
23 $R^1 = R^2 = Bn$ } $R^3 = H, R^4 = All$
24 $R^1 = R^2 = Bz$
25 $R^1 = R^2 = H$ } $R^3, R^3 =$  , R^4 = All, Bn, *etc.*
26 $R^1 = Bz, R^2 = H$

The benzyl protected allyl β-lactoside diol **23** afforded higher yields of 3′-*O*-substituted products than the corresponding pentabenzoate **24** in dibutyltin oxide-mediated esterifications.[21] Synthesis of monohydroxy β-lactoside derivatives **26** has been accomplished by use of 4.2 molar equivalents of benzoyl chloride on the pentaols **25** in pyridine at -45 °C.[22] Reaction conditions have been worked out for the regioselective acylation at C-2-OH in the glucose unit of sucrose. 2-*O*-Lauroylsucrose, for example, was produced in 70% yield when the unprotected sugar was treated with 2-*O*-lauroylthiazolidine-2-thione and catalytic quantities of sodium hydride in dry pyridine.[23] The 4-*O*- and 6-*O*-monoacryloyl derivatives **28** and **29**, respectively, of sucrose, which were formed on hydrolysis of the orthoester **27**, and their deacetylation products have been used in polymerization experiments.[24] The synthesis of 2,3- and 2,3′-di-*O*-palmitoyl- and -di-*O*-stearoyl-α,α-trehalose and of the 2-*O*-palmitoyl-3-*O*-stearoyl derivative has been achieved by tin-mediated acylation of the 4,6:4′,6′-di-*O*-benzylidene-protected disaccharide.[25]

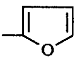


27 $R^1, R^2 =$


28 $R^1 = H, R^2 = COCH{=}CH_2$
29 $R^1 = COCH{=}CH_2, R^2 = H$

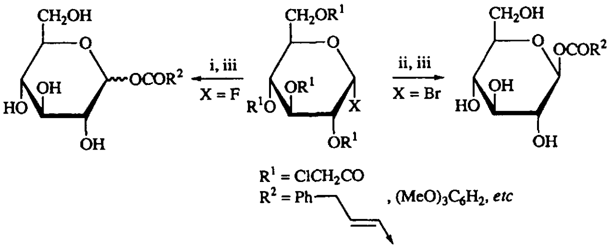


30 $X = H, Y = OH$
31 $X = OTms, Y = H$
32 $X = H, Y = O_2CPh,$

O_2CPr^i, O_2C—


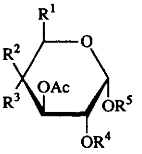
etc.

The anomeric acylation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**30**) with sterically undemanding acyl chlorides in dichloromethane in the presence of pyridine proceeded with good α-selectivity (*e.g.*, α/β 6:1 when using BzCl) which was diminished by catalytic DMAP. Sterically hindered reagents such as pivaloyl chloride or 2,4,6-trimethylbenzoyl chloride, however, gave mainly β-products (α/β *ca.* 1:6).[26] When pyridine was replaced by the stronger base triethylamine, the α/β ratios decreased as a consequence of faster mutarotation of **30** (*e.g.*, α/β 2:9 with BzCl).[27] α-Products, e.g. **32** were formed mainly and in some cases exclusively when the trimethylsilyl β-D-glucoside derivative **31** in dichloromethane was treated with carboxylic acids and boron trifluoride etherate.[28] Several peracetylated (2-trimethylsilyl)ethyl glycosides were transformed stereoselectively to 1-*O*-β-esters (*e.g.*, 1-*O*-β-pent-4-enoates) on exposure to acyl anhydrides and boron trifluoride etherate. The method is suitable for application to oligosaccharides and a convenient procedure for the preparation of the required anhydrides is given.[29]

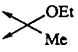


Reagents: i, R^2CO_2H, $BF_3{\cdot}OEt_2$; ii, R^2CO_2Ag; iii, 1-piperidinethiocarbamide
Scheme 2

1-*O*-Acyl-D-glucopyranoses have been prepared *via* chloroacetylated glycosyl halides; examples are given in Scheme 2.[30] An improved Koenigs-Knorr method (CaH_2, Ag_2CO_3, I_2) has been employed for the highly selective synthesis of 1-*O*-acyl-β-D-galactopyranose tetraacetates from glycosyl bromides and carboxylic acids.[31] Mild acid hydrolysis of *galacto*-configurated orthoacetates **33** gave exclusively the 1-*O*-α-esters **35**, whereas their *gluco*-analogues **34** furnished the 2-*O*-acetylated free sugars **36**. The importance of the conformation of the orthoacid intermediate for the course of the reaction and its dependence on the configuration at C-4 are discussed.[32]



R^1 = CH_2OAc or CO_2Me
33 R^2 = OAc, R^3 = H
34 R^2 = H, R^3 = OAc
} R^4, R^5 =

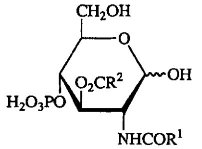


35 R^2 = OAc, R^3 = H, R^4 = H, R^5 = Ac
36 R^2 = H, R^3 = OAc, R^4 = Ac, R^5 = H

The specific anomeric deprotection of 2-aminosugar peracetates by silica gel in methanol has been reported.[33]

Some enzymic deprotecting group techniques for acylated peptides and carbohydrates using penicillin G. acylase and citrus acetylesterase to remove acetyl and phenylacetyl groups regioselectively have been described.[34] The use of acetic anhydride, succinic anhydride, aliphatic α,ω-alkanoic dicarboxylic acids (succinic, adipic, hexadecanedioic), and bis(2,2,2-trichloroethyl) esters of butyl α-D-glucopyranoside as acyl donors in the solvent-free esterification of sugars with an immobilized lipase has been explored. Selectivity for transfer to O-6 occurred in some cases, in others secondary sites were selectively substituted.[35] Accounts of the enzymatic hydrolysis of fully acetylated glucose, methyl glucopyranosides, and 2-acetamido-2-deoxy analogues[36] and of the enzymatic (subtilisin, lipase) preparation of partly acylated sucroses have been published.[37] Out of 96 enzymes tested for activity and selectivity in the hydrolysis of sucrose octaacetates, 16, 12, and 27 have been found to deacetylate at one, two, and three to five positions, respectively. In no case were acetyl groups removed from O-2, O-3, or O-3′.[38]

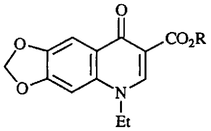
Pronase-mediated acetylation of glucose and other hexoses with *p*-nitrophenyl acetate in pyridine gave 6-*O*-acetates in good yields, while 6-deoxysugars gave product mixtures indicating poor selectivity with secondary hydroxyl groups.[39] Selective primary esterification of butyl α-D-glucopyranoside with long-chain fatty acids has been achieved under lipozyme catalysis in boiling hexane with azeotropic removal of water. The isolated 6-*O*-stearoyl and -lauroyl derivatives, on renewed exposure to the respective acids and lipozyme, gave the 2,6-diesters in yields of >95%.[40] Lipase OF (from *candida cylindracea)* caused deacylation of sucrose octaacetate in the glucose moiety, initially at O-6; subsequent 4→6 acetyl migration and renewed deacetylation at the primary site, followed by hydrolysis at the 3-position afforded 2,1′,3′,4′,6′-penta-*O*-acetylsucrose as the major product.[41] Lipases from a variety of sources have also been employed in the following selective acylations and deacylations: acetylation at O-4 of 1,6-anhydro-β-D-glucopyranose,[42] acetylation[43] as well as benzoylation, chloroacetylation and pivaloylation at O-3 of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and at O-2 of the α-anomer,[44,45] preferential hydrolysis of secondary before primary acetates in peracetylated methyl hexopyranosides,[46] removal of acetyl groups from the 4-position of 2,3,4-triacetylated alkyl β-D-xylopyranosides,[47] and of anomeric acetate from peracetylated disaccharides.[48]



37 $R^1 = R, R^2 = CH_2CH\begin{smallmatrix}(CH_2)_{10}Me \\ (CH_2)_{11}Me\end{smallmatrix}$

38 $R^1 = \underset{F}{C}H\underset{OH}{C}H(CH_2)_{10}Me, R^2 = R$

$R = CH_2CH(OH)(CH_2)_{10}Me$



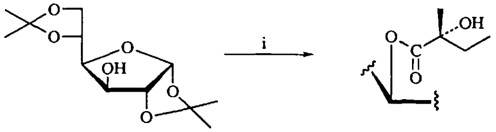
39 R = H

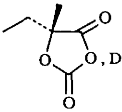
40 R = D-glucos-6-yl

In the presence of phenylboronic or butylboronic acid, lipase-catalysed esterifications of sugars can be carried out in hexane.[49] This method has been applied to the anomeric monoacetylation of fructose with stearic acid.[50]

The synthesis of several Lipid A subunit analogues with 2- or 3-alkyl-branched acyl groups at the 3-position, *e.g.* compound **37**[51], and of the two stereoisomeric fluorinated derivatives **38**[52] has been reported. Methyl 3-*O*-α-L-arabinofuranosyl-5′-*O*-feruloyl-β-D-xylofuranoside, the 5′-*O*-*p*-coumaroyl analogue and the two corresponding (1→2)-linked disaccharides have been obtained, following established synthetic strategies, for comparison with plant cell wall-derived materials.[53] The powerful antibiotic oxolinic acid (**39**) has been condensed with 1,2,3,4-tetra-*O*-benzyl-D-glucose to give derivative **40**, after debenzylation; the corresponding D-glucose 3-ester was prepared in a further attempt to improve the water-solubility, by use of 1,2:5,6-diacetoneglucose.[54]

A general method for the synthesis of α-amino-α-alkylalkanoates has been exemplified by reaction of 1,2-monoacetoneglucose with (*R*)-(+)-5-ethyl-5-methyl-1,3-dioxolane-2,4-dione as shown in Scheme 3.[55] Methyl α-D-gluco-, α-D-galacto-, and α-D-manno-pyranosides esterified at O-2, -3, and -4 with basic amino acids (lysine, ornithine, α,β-diaminopropionic acid) have been prepared, *via* 6-*O*-trityl intermediates, to investigate the relationship between chemical structure and taste.[56]

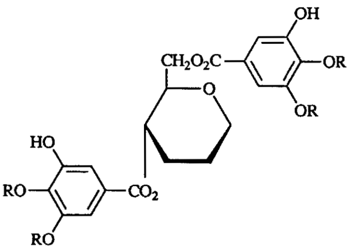


Reagents: i,  , DMAP, CH$_2$Cl$_2$

Scheme 3

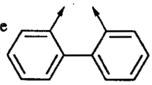
1.2 Isolation from Natural Sources.- 1,6-Di-*O*-isopentanoyl-β-D-glucopyranose has been isolated from *Centaurea aspera.*[57] 2,3-Di-*O*-(5-methylhexanoyl)-6′-*O*-acetylsucrose, its 2,3-di-*O*-(5-methylheptanoyl) analogue and the two corresponding 1′-*O*-acetyl tetraesters, isolated from *Nicotiana gossei*, have been shown to have insecticidal properties.[58] Several further sucrose polyesters from *Nicotiana* sp. are reported to have antibacterial activity.[59] 2,3,4,3′-Tetra-*O*-acylated sucroses have been characterized as constituents of an exudate from glandular trichomes of *hycopersicon typicum.*[60] A triacyltrehalose containing 2-methyl branched, unsaturated fatty acid groups has been isolated from *Mycobacterium fortuitum*,[61] and *Coryneacterium matruchotii* furnished a relatively simple glycolipid fraction from which trehalose 6-mono- and 6,6′-di-corynomycolate were obtained.[62]

A review on the classification of oligomeric hydrolyzable tannins and the specificity of their occurrence in plants has been published.[63] The biomimetic conversion of an elagitannin with a glucopyranose core into a C-glycosidic tannin has been brought about by heating for 2.5 h at 70 °C in phosphate buffer at pH 7.5.[64] Digalloyl ester **41** and several more hindered analogues, *e.g.* **42**, have been subjected to oxidation by lead tetraacetate in an attempt to mimic the oxidative coupling of glucose-derived digalloyl compounds which gives rise to ellagitannins.[65]

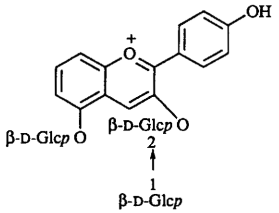


41 R = Me

42 R, R =



It has been demonstrated by examination of five anthocyanin pigments from red-purple *Pharbitis nil* cultivars, of basic structure **43**, that caffeoylation at the primary positions of the sophorosyl moiety reduces the rate and extent of hydration to colourless compounds.[66] Phenazoviridin, a new microbial free radical scavenger has been identified as the 6-deoxy-α-L-talopyranosyl ester **44**.[67] Characterization of the plant growth regulator Calonyctin A (see Vol. 26, Chapter 19) isolated from Chinese moonlight flowers as a mixture of two macrocyclic lactones containing L-rhamnose, quinovose, 3-hydroxy-2-methylbutanoic acid and either 11-hydroxytetra- or 11-hydroxyhexa-decanoic acid has been reported.[68]



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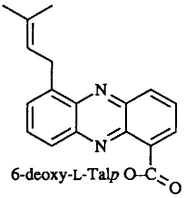
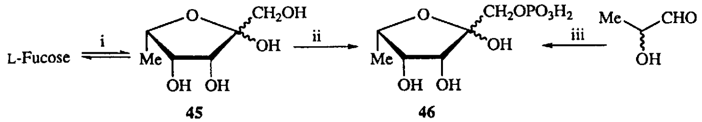


44

2.2 Phosphates and Related Esters

A review on the application of the phosphoramidite method to the synthesis of phosphorylated biomolecules covered, *inter alia*, mononucleotides, glycosyl phosphates, inositol phosphates and inositol phospholipids.[69] Dibenzyl *N,N*-diethyl phosphoramidite has been recommended as an efficient and convenient reagent for the preparation of dibenzyl glycosyl phosphites.[69a] Bicyclic phosphorylated carbohydrates have been reviewed (40 pp., 60 refs.) in Russian.[69b] The rearrangement of a sugar bicyclothiophosphate to a thiosugar bicyclophosphate is covered in Chapter 11.

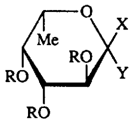


Reagents: i, Fucose isomerase; ii, rhamnulokinase, ATP; iii, DHAP, fuculose 1-phosphate aldolase

Scheme 4

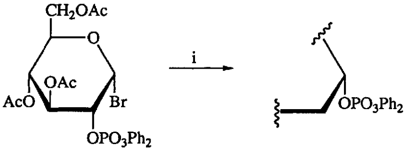
Rabbit muscle aldolase (RAMA) furnished ketose liphosphates with 3(*S*)/4(*R*) stereochemistry from dihydroxyacetone phosphate (DHAP) and simple aldehydes. When α-hydroxyaldehydes were used kinetic resolution occurred, provided there was a negative charge (*e.g.* COO^-) 4 or 5 atoms away from the aldehyde group.[70] Fructose 1,6-diphosphate aldolase from spinach leaves catalysed similar condensations between DHAP and aldehydes with a substrate specifity somewhat different from that of RAMA.[70a] A reinvestigation of the steric course of the hexulose phosphate synthetase-catalysed condensation between ribulose 5-phosphate and simple aldehydes is covered in Chapter 2.

Two protocols have been established for the large scale (up to 0.1 mmol) enzymic synthesis of 6-deoxyhexulose 1-phosphates. As shown in Scheme 4, 6-deoxy L-*lyxo*-hexulose 1-phosphate (L-fuculose 1-phosphate, **46**) was available either from L-fucose *via* fuculose (**45**) or, alternatively, by fuculose 1-phosphate aldolase-catalyzed condensation of racemic 3-hydroxypropanal and DHAP. The L-*arabino*-isomer of **46** was similarly obtained by use of the appropriate starting materials and enzymes; the enzyme-controlled aldol condensations proceeded stereospecifically and with complete kinetic resolution.[71] The previously reported expeditious one-pot multi-enzyme synthesis of D-tagatose 1,6-diphosphate from dihydroxyacetone and D-glyceraldehyde 3-phosphate (see Vol. 26, Chapter 7, Ref. 59) has been adapted to a 10 mmolar scale.[72] The preparation of D-[1-^{13}C]glucose 6-phosphate from D-ribose and ^{13}C-labelled methanol, utilizing methylotropic enzymes, has been reported.[73]



47 X = Br, Y = H, R = Bz
48 X = H, Y = OPO_3Bn_2, R = Bz
49 X = H, Y = OPO_3H_2, R = H
50 X, Y = H, OH, R^3 = Ac

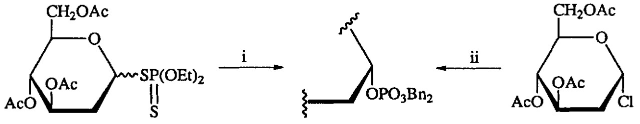
The phosphorylation of alditols, oligosaccharides, and glycoproteins by use of sodium phosphate in anhydrous media has been described,[74] and a paper on the direct esterification of a dialkyl phosphate with organic halides in the presence of silver oxide included a number of carbohydrate examples, such as the formation of peracetylated β-D-galactosyl phosphate from α-acetobromogalactose.[75] Chloro-*N*,*N*-diisopropylaminoalkoxyphosphines [ROP(Cl)N(i-Pr)$_2$] in pyridine have been introduced as convenient new reagents for the efficient formation of alkyl glycosyl phosphodiesters *via* phosphites.[76] In a practical gram-scale synthesis of β-L-fucopyranosyl phosphate (**49**), the precursor for GDP-fucose, α-bromide **47** reacted with silver carbonate and triethylammonium dibenzylphosphate under neighbouring group participation to give stereoselectively the β-dibenzylphospate **48**, which furnished **49**, as the dicyclohexylammonium salt, on hydrogenolysis followed by debenzoylation with methanolic cyclohexylamine.[77] Phosphate **49** has also been prepared from 2,3,4-tri-*O*-acetyl-L-fucose (**50**) by use of a trivalent phosphitylating reagent and subsequent oxidation and deprotection.[78]



Reagents: Bu_3SnH, $h\nu$

Scheme 5

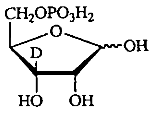
2-Deoxyhexopyranosyl 1-phosphates and analogous 2-deoxynucleoside derivatives have been generated by the nearly quantitative 2→1 radical migration illustrated in Scheme 5. The glycosyl phosphates were subsequently transformed to disaccharides by exposure to glycosyl acceptors and magnesium perchlorate. When a glycosyl acceptor was present during the irradiation reaction, the disaccharide was formed directly in good yield.[79,80] 2-Deoxyglycosyl phosphates have also been obtained from glycosyl halides or from *S*-(2-deoxyglycosyl) phosphorodithioates, as outlined in Scheme 6. The latter method was deemed superior.[81] 4-Deoxy-α-D-hexopyranosyl phosphates have been prepared by standard methods as potential enzyme substrates in a study of deoxysugar biosynthesis.[82]



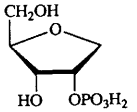
Reagents: i, $(BnO)_2PO_2H$, $I(\textit{sym}\text{-coll})_2ClO_4$; ii, $(BnO)_2PO_2Ag$

Scheme 6

The C-3 deuterated 5-phosphate **51** was an intermediate in the preparation of D-*erythro*-[3-^{2}H]imidazole glycerol phosphate from diacetoneglucose.[83] Several 2-*O*-phosphorylated 1,4-anhydropentitols, *e.g.* compound **52**,[84] 2′-*O*-methyl-adenosine 3′,5′-cyclic monophosphate,[85] 1,5-anhydroxylitol- and 1,5-anhydro-D-arabinitol-2,3,4-phosphate,[86] D-mannopyranose 1,4,6-triphosphate,[87] and a series of polyphosphorylated D-galactosides, such as compounds **53**,[88] have been synthesized by conventional procedures for use in biological studies.



51



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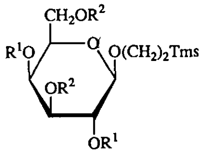
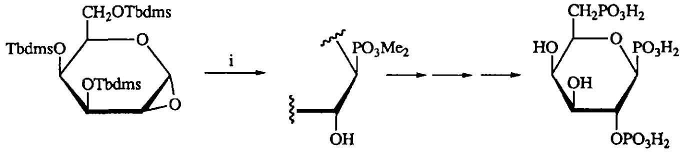


$R^1 = H, R^2 = PO_3Na_2$ or
$R^1 = R^2 = PO_3Na_2$

53

Two routes to 1,2-*trans*-configurated glycosyl phosphonates have been explored. The key-steps involved were the nucleophilic opening of the D-galactal-derived epoxide **54** with dimethyl(trimethylsilyl) phosphite, as shown in Scheme 7, and trimethylsilyl triflate-promoted displacement of anomeric acetate by trimethyl phosphite. Phosphonate **55** was further transformed, in eight steps and moderate overall yield, to the monophosphate-bisphosphonate **56**, an analogue of *myo*-inositol 2,4,5-triphosphate.[89]



54 **55** **56**

Reagents: i, $TmsP(OMe)_2$

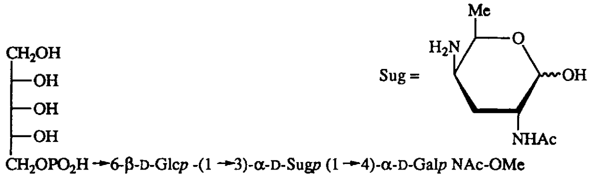
Scheme 7

The structures of the disugar phosphates agrocinopin C and D (see Vol. 26, Chapter 7, Ref. 79) have been revised on the basis of synthetic evidence.[90] The step by step syntheses of the β-D-xylopyranose 2-phosphate-containing oligosaccharides **57** and **58** found in the linkage region of heparan sulfate[91] and of a phosphorylated, KDO-containing trisaccharide related to Lipid A[92] have been described, as has the preparation of oligo(glycosyl phosphates) **59** and **60**, which are fragments of an extracellular phosphomannan and a capsular antigen, respectively.[93,94] UDP-2-Deoxy-D-galactose has been prepared chemically, in five moderately efficient steps involving coupling between uridine 5′-monophosphate morpholidate and the disodium salt of 2-deoxy-D-*lyxo*-hexopyranosyl phosphate.[95]

57 β-D-Glc*p*A-(1→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-β-D-Xyl*p*2P-OMe
58 β-D-Gal*p*-(1→3)-β-D-Gal*p*-(1→4)-β-D-Xyl*p*2P-OMe
59 [α-D-Man*p*-(1P→6)]$_4$-α-D-Man*p*-OMe
60 [α-D-Glc*p*NAc(1P→3)]$_3$-β-D-Glc*p*NAc-OC_6H_4*p*NO_2

Two routes to GDP-mannose have been explored: a non-enzymatic one using essentially Schmidt chemistry, and an enzymatic one involving a hexokinase, a phosphomannomutase, and a pyrophosphorylase. Overall, preference was given to the chemical approach, which was also applied to the synthesis of GDP-galactose, GDP-xylose, and GDP-2-acetamido-2-deoxy-D-glucose.[95a]

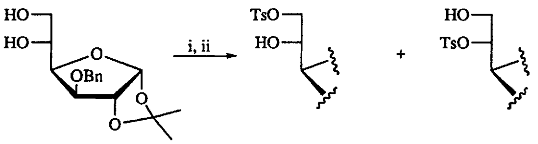
The trisaccharide ribitol phosphate repeating unit **61** of a cell wall associated complex polysaccharide from *Streptococcus pneumoniae* Type 1, which contains a rare amino-sugar, has been synthesized.[96]



61

3 Sulfonates

The regioselectivity in tin-mediated monotosylations of diols has been studied; use of dibutyltin oxide or hexamethylenetin oxide in the example shown in Scheme 8 gave the primary-**62** and secondary tosylate **63** in the ratios 3:7 and 20:1, respectively.[97] A report on the reactions of dimesylated methyl hexopyranosides and glucofuranoses with superoxide (KO_2) to give hydroxy products, either by direct hydrolysis, nucleophilic displacement, or *via* transient epoxides, has been published.[98] Amberlite IRA-410 (Cl^- form) resin in DMF has been recommended for the selective displacement by chlorine of the primary sulfonyloxy groups in 3,5-disulfonate derivatives of 1,2-*O*-cyclohexylidene-α-D-xylofuranose.[99]



62 **63**

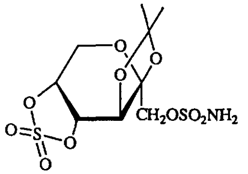
Reagents: i, Bu_2SnO or $(CH_2)_6SnO$, toluene; ii, TsCl

Scheme 8

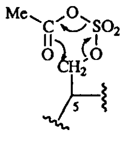
4 Other Esters

The cyclic sulfate **64** and the corresponding diastereomeric cyclic sulfites have been prepared from 1-*O*-benzyl-2,3-*O*-isopropylidene-β-D-fructopyranose as analogues of the anticonvulsant topiramate.[100] Methyl α-D-galactopyranoside 2,6-disulfate[101] and the three monosulfate derivatives of methyl α-L-fucopyranoside[102] have been synthesized by standard methods. Modified cyclodextrin sulfates and 3′-sulfated Lewis a are referred to in Chapter 4.

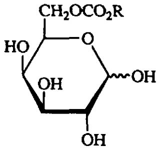
Boiling the potassium salt of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose 6-sulfate in acetic anhydride affords β-D-glucose pentaacetate very efficiently. The proposed mechanism involves unimolecular extrusion of SO_3 from the mixed anhydride **65**.[103]



64



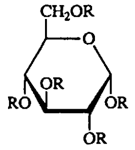
65



R = Me, All, Bn, *etc.*

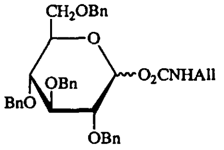
66

2-*O*-Sulfated D-glucuronic acid residues have been detected in rat liver heparan sulfate.[104] A chemically modified heparin furnished new, polysulfated, acidic oligosaccharides on degradation.[105] N.m.r. spectroscopic studies on unsaturated sulfated glycosaminoglycan disaccharides are referred to in Chapter 21. Helianthoside, the first asterosaponin containing a sulfated xylopyranose residue,[106] and several triterpenoids extracted from *Zygophyllum propinquum* containing 2-*O*-sulfo-β-D-quinovopyranosyl moieties have been reported.[107]



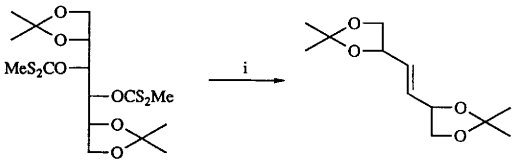
R = CONHR^1
R^1 = Ph, $(CH_2)_n$ Me, *etc.*
n = 2–7

67



68

The lipase-catalysed alkoxycarbonylation of D-glucose, D-galactose, D-mannose, D-ribose, and D- and L-arabinose using *O*-(alkoxycarbonyl)oximes (see Vol. 26, Chapter 7, Ref. 99) selectively furnished the primary products, *e.g.* carbonates **66**, whereas complex mixtures resulted from similar treatment of D-fructose, D-xylose, and D-lyxose.[108] 2-(4-Nitrophenyl)ethoxycarbonyl protection of nucleosides is referred to in Chapter 20. A high pressure technique for the synthesis of hexose pentacarbamates such as compounds **67**, involving treatment of unprotected sugars with a 20 molar excess of alkyl isocyanate in pyridine at 6 kbar, has been developed.[109] An anomeric mixture of the protected glycosyl *N*-allylcarbamates **68** has been obtained by treatment of 2,3,4,6-tetra-*O*-benzyl-D-glucose with allyl isocyanate in the presence of a base;[110] their use as glycosylating agents is referred to in Chapter 3. Dithiocarbonates are covered in Chapter 11.



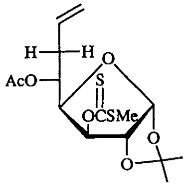
Reagents: i, H_3PO_2, Et_3N, AIBN, 1-dodecene

Scheme 9

A new strategy for converting *vic*-diols to alkenes, illustrated in Scheme 9, relies on reagents with P-H bonds, *e.g.* hypophosphorous acid or dialkyl phosphite, acting as radical reducing agents for thionoesters.[111] An unexpected radical isomerization led to the formation of dithiocarbonate **71** as by-product in the tributyltin hydride-promoted cyclization of the unsaturated thionoester **69** to carbocycle **70**.[112]

The involvment of a phenylboronate sugar adduct in the active transport of *p*-nitrophenyl β-D-glucopyranoside through a liquid organic membrane has been investigated.[113] The use of 1-naphthylboronic derivatives of carbohydrate diols in f.a.b.m.s. is covered in Chapter 22.

Cyclic orthoesters are referred to in Part 1 of this Chapter (Refs. 18, 24, 32).



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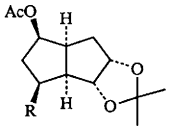

70 R = Me
71 R = $\mathrm{S\underset{\underset{O}{\|}}{C}SMe}$

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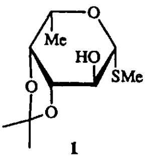
8

Halogeno-sugars

1 Fluoro-sugars

A review on the synthesis of chiral and bioactive organofluorine compounds has included a number of carbohydrate examples.[1] *Ab initio* calculations for the anomeric effect in glycopyranosyl fluorides have been made and the results compared with experimental evidence.[2] Glycosyl fluorides have been prepared from the corresponding glycosides, or 1,2-*O*-isopropylidene derivatives, using hydrogen fluoride in acetonitrile.[3,4] Peracetylated glycopyranosyl fluorides of di- and tri-saccharides have been obtained in good yields, and without cleavage of the inter-unit bonds, by treating the acetylated saccharides with pyridinium polyhydrogen fluoride.[5] Acetylated glycosyl bromides have been treated with triethylamine trishydrogen fluoride to afford the corresponding glycosyl fluorides with inversion of configuration.[6] Glycosyl azides can be converted into the corresponding glycosyl triazoles which on treatment with hydrogen fluoride-pyridine afford glycosyl fluorides (see vol. 25, p. 123).[7]

Treatment of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside with DAST afforded 2,3-*O*-isopropylidene-5-*O*-methyl-β-D-ribofuranosyl fluoride following 1→5 migration of the anomeric group.[8] Similar migrations have been observed with thioglycoside derivatives so that the fucoside **1** with DAST gave the 2-thiomethylglycosyl fluoride **2**, and the rhamnoside **3** gave the fucosyl fluoride **4** by a series of rearrangements,[9] while other thioglycosides have undergone analogous rearrangements.[10] The uloside **5** with DAST also afforded a rearrangement product **6**.[11] The preparation and reactions of some acylated and partially acylated glycosyl fluorides are mentioned in Chapters 5 and 7.



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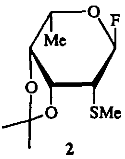

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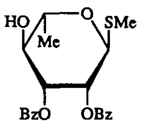

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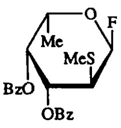

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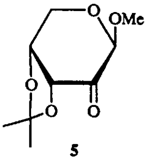

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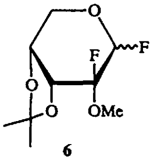

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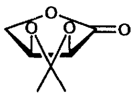

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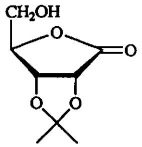

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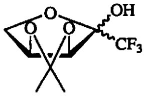
The preparation of 6-deoxy-6,6,6-trifluoro-D-mannose and -D-allose as well as 2,3,6-trideoxy-6,6,6-trifluorohexoses from some 2,2,2-trifluoroethyl-substituted furan derivatives has been described,[12,13] while treatment of lactones **7** and **8** with trimethylsilyltrifluoromethane gave the trifluoromethyl-substituted derivatives **9** and **10** respectively, from which 5-deoxy-5,5,5-trifluoro-L- and -D-lyxose were prepared - the latter following periodate cleavage of a diol. Similarly, from appropriate lactones 5-deoxy-5,5,5-trifluoro-D- and -L-ribose were prepared.[14]

The cycloaddition of the 2,4-dialkoxy-1,1-difluoro-buta-1,3-diene **11** to benzyloxyacetaldehyde has afforded the unsaturated pyranoside **12** from which the racemic 2,4-dideoxy-4,4-difluoropyranosides **13** were obtained.[15] The synthesis of 2-deoxy-2,2-difluoro-D-ribono-1,4-lactone has been achieved by application of the Reformatsky reaction of an ethyl difluoroacetate derivative with 2,3-*O*-cyclohexylidene-D-glyceraldehyde.[16] A study of the formation of 6-deoxy-6-fluorohexonolactones from 5,6-anhydro-hexonolactones and of 2-deoxy-2-fluoropentone-1,4-lactones from 2,3-anhydro-pentono-1,4-lactones has been reported,[17] and the synthesis of some 3-amino-2,3-dideoxy-2-fluoro-D-xylose derivatives has been reported.[18]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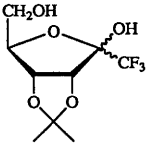
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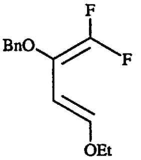
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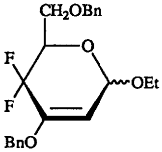
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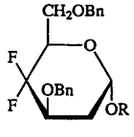
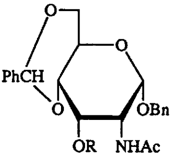
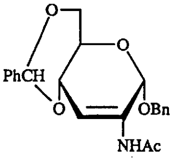

(±)

13 R = cyclohexyl
or pent-4-en-1-yl


14 R = H
15 R = Ms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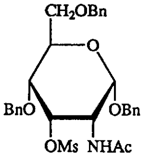
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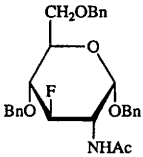
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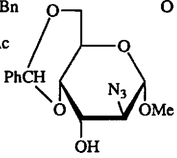
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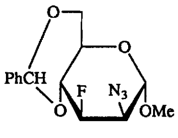
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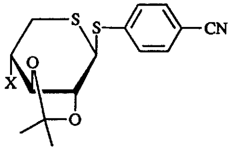
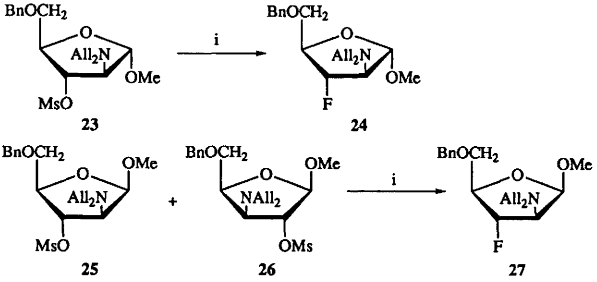

21 X = OH
22 X = F

In a search for synthetic routes to 2-acetamido-2,3-dideoxy-3-fluoro-D-gluco- and -mannopyranose, treatment of the alcohol **14** with DAST or its mesylate **15** with various sources of fluoride ion gave only the elimination product **16**. On the other hand, mesylate **17** suffered displacement by fluoride ion to give **18**, but in only 10% yield, whereas the alcohol **19** with DAST afforded only fluoro compound **20** in good yield.[19] Treatment of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-α-D-glucofuranose with tetrabutyl ammonium fluoride in DMF gave only the 4,5-unsaturated product as the E isomer whereas the C-5 epimer of the mesylate (the β-L-ido-compound) afforded only the 4,5-unsaturated Z isomer under the same conditions.[20] When exposed to DAST methyl 2,3-di-*O*-benzoyl-1-thio-β-L-fucopyranoside gave the corresponding 4-deoxy-4-fluoro- compound with inversion of configuration,[9] whereas the thio-glycoside **21**, under the same conditions, generated the product **22** with retention of configuration.[10] Methyl 2,3,6-tri-*O*-acetyl-α-D-glucopyranoside with DAST gave the corresponding 4-deoxy-4-fluorogalactopyranoside from which 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-galactopyranosyl bromide was prepared as a glycosyl donor.[21]

A full account of the synthesis of 3-deoxy-3-fluoro- and 2,3-dideoxy-2,3-difluoro-β-D-xylofuranosyl-containing nucleosides (see vol. 23, p. 213) has appeared,[22] and the synthesis of 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranosyl-containing nucleosides is covered in Chapter 20. Studies of fluorination of vicinal *trans*-(N,N-diallyl)amino mesylates have been extended to the furanose series. Mesylate **23** afforded the fluoride **24** (Scheme 1) , while the equilibrating mixture of β-anomers **25** and **26** gave **27** as the major product. Other analogous systems were examined in the same way.[23] Treatment of protected mono- and oligo-saccharide glycals with acetyl hypofluorite afforded 2-deoxy-2-fluoro-glycosyl acetates from which glycosides were prepared as potential glycosidase inhibitors. 2-Deoxy-2,2-difluoro-compounds were also prepared.[24]



Reagents: i, $Et_3N{\bullet}2HF$

Scheme 1

Deoxyfluoroglucose derivatives have been synthesized containing one or two long chain (C_{10} - C_{16}) ethers as ampiphilic compounds.[25] The three possible analogues of the disaccharide glycosyl transferase acceptor α-L-Fuc*p*-(1→2)-β-D-Gal*p*-*O*-$(CH_2)_7CH_3$ containing a deoxyfluorogalactosyl moiety have been prepared[26] and the same group have synthesized the 4″-deoxy-4″-fluoro analogue of trisaccharide β-D-GlcNAc*p*-(1→2)-α-D-Man*p*-(1→6)-β-D-Glc*p*-*O*-$(CH_2)_7CH_3$.[27] The ability of bovine galactosyl transferase to utilize 6-deoxy-6-fluoro-galactose is mentioned in Chapter 3, as is the conversion of 3′- and 4′-deoxyfluorolactoses into ceramide derivatives. The conformational analysis of 6-deoxy-6-fluoro-D-glucose by NMR spectroscopy is discussed in Chapter 21.

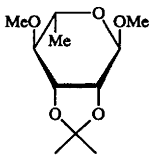
Further claims of improved procedures for the synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose have been published.[28-30]

2 Chloro-, Bromo-, and Iodo-sugars

Treatment of 1,2-*trans*-aldopyranosyl or -furanosyl peracetates with thionyl chloride and acetic acid has afforded high yields of the 1,2-*trans*-per-*O*-acetyl-glycosyl chlorides.[31] Better selectivity for the formation of α-1,2-*trans*-dibromides from glycals using $R_4N^+Br_3^-$ rather than bromine has been reported,[32] while glycoside **28** has afforded the 1,2-*cis*-dibromide **29** when treated with dibromomethyl methyl ether in the presence of zinc bromide.[33]

Iodination of the per-*O*-tributyltin ether of D-glucal with iodine has given 1,6-anhydro-2-deoxy-2-iodo-β-D-glucopyranose.[34] Selective cleavage of some fully methylated cyclodextrins at one glycosidic linkage followed by glycal formation and then NIS-promoted recyclization has given rise to cyclodextrins iodinated at one C-2 position.[35] Treatment of tri-*O*-acetyl-D-glucal with NIS and dibenzyl phosphate has afforded mainly the corresponding 2-deoxy-2-iodo-α-D-mannosyl phosphate.[36]

Some pentitols have been shown to produce mainly 1,5-dibromo-1,5-dideoxy derivatives on treatment with hydrogen bromide in acetic acid.[37] Methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside after acetylation and then hydrogenolysis (H_2, Pd/C) in the presence of added base (KOH) has afforded a high yield of methyl 6-chloro-4,6-dideoxy-α-D-*xylo*-hexopyranoside.[38] Di-*O*-acetyl-L-rhamnal in the presence of chlorine, silver acetate and methanol has generated a 30% yield of methyl 3,4-di-*O*-acetyl-2-chloro-2-deoxy-α-L-rhamnopyranoside which was one of the chlorinated derivatives used in the synthesis of chlorodeoxy analogues of α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-β-D-GlcNAc*p*-1-*O*-Me.[39]



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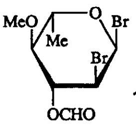

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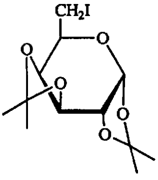

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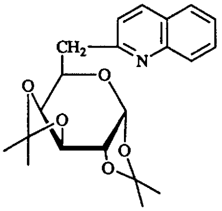

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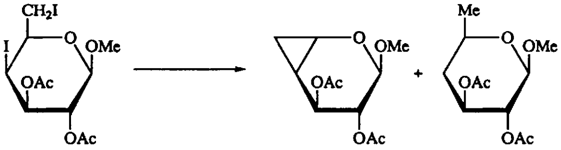

32 **33** **34**

Reduction of some 2-*O*-diphenylphosphorylglycosyl bromides with tributyltin hydride has afforded the corresponding 2-deoxyglycosyl diphenylphosphates,[40] and various acetylated methyl 2-deoxy-2-iodoglycosides have been reduced with tributyltin deuteride. It was found that the sizes and orientations of the ring substituents determined the stereochemistries of the products.[41] Dialkyl phosphites and hypophosphorous acid have been found to be alternative radical reducing agents for organic halides.[42] Substitution of iodide **30** by C-bonded quinoline in the presence of dibenzoyl peroxide to give the chain extended **31** is believed to proceed *via* a radical at C-6.[43] Hydrogenolysis of some 4,6-dideoxy-4,6-diiodo mono- and di-saccharide derivatives has afforded mixtures of the corresponding 4,6-dideoxy- and 4,6-cyclopropanyl-4,6-dideoxy- products. For example diiodide **32** gave a mixture of deoxy products **33** and **34**.[44]

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9
Amino-sugars

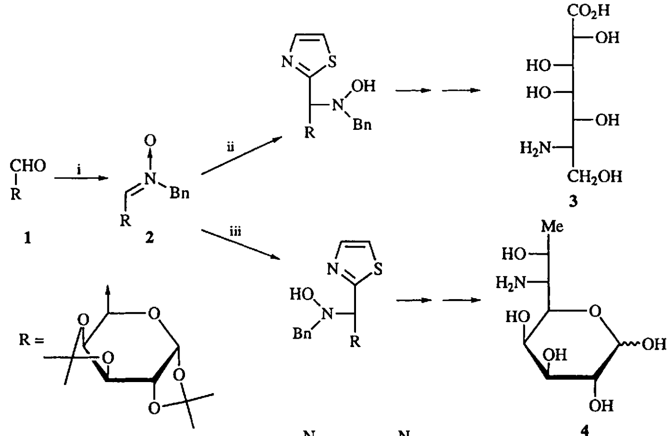
1 Natural Products

2-Acetamido-2-deoxy-β-D-glucopyranosyl residues are rare in plant derived natural products, but have been found in two oligoglycoside triterpenoid saponins from the legume *Calliandra anomala.*[1] D-Quinovosamine (2-amino-2,6-dideoxy-D-glucose) has been isolated from the cell walls of *Bacillus* sp. Y-25.[2]

2 Synthesis

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

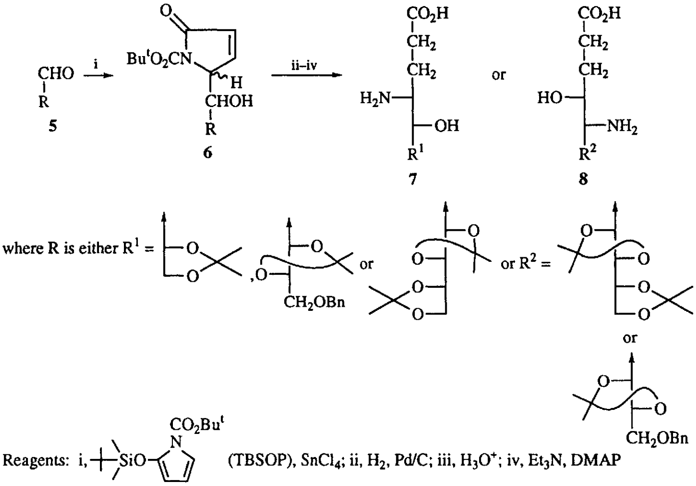
2.1 Chain Extension. - Aldolase-catalysed aldol condensation reactions used in the synthesis of sialic acids and aza-sugars have been reviewed (38 refs.).[3] Addition of 2-thiazolyl reagents to the nitrone **2**, available from the D-galacto-dialdose **1**, featured in syntheses of destomic acid **3** and



Reagents: i, $PhCH_2NHOH$; ii, $ZnBr_2$ then 2-thiazolyl-Li; iii, 2-thiazolyl-Li, Et_2AlCl

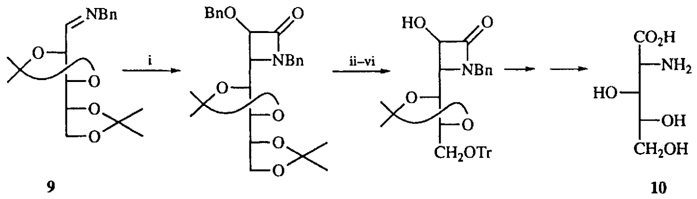
Scheme 1

lincosamine **4** (Scheme 1).[4] Condensation of aldehydo-sugars **5** with TBSOP (a silyloxypyrrole reagent) led to the synthesis of *C*-alditol-1-yl derivatives of γ-aminobutyric acid (GABA), i.e. the 4-amino-2,3,4-trideoxy-heptonic, -octonic and -nononic acids **7** and **8** (Scheme 2). The stereochemistry of each adduct **6** was *threo*; the D-*arabino*-adduct epimerized in base to the D-*ribo*-isomer.[5] (-)-Polyoxamic acid **10** has been synthesized from the D-arabinose imine derivative **9** (Scheme 3).[6] The Henry reaction (a nitroaldol condensation) of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdopyranose under modified conditions [$O_2NCH_2CH(OEt)_2$, Bu_4NF, Et_3N then TbdmsCl], gave mainly an L-*threo*-α-D-*galacto*-nitro-sugar adduct, from which amino-derivative **11** was obtained by reduction (H_2-Raney Ni), together with a lesser amount of an isomer.[7] Similarly, addition of the anions of various 2-aminoacetate esters ($Bn_2NCH_2CO_2Bu^t$, $Ph_2C{=}NCH_2CO_2Me$, and **12**) to pento- and hexo-dialdose derivatives gave mixtures of β-hydroxy-α-aminoacid derivatives; use of **12** gave the adduct **13** stereoselectively.[8]



Reagents: i, (TBSOP), $SnCl_4$; ii, H_2, Pd/C; iii, H_3O^+; iv, Et_3N, DMAP

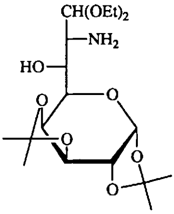
Scheme 2



Reagents: i, $BnOCH_2COCl$; ii, H_3O^+; iii, IO_4^-; iv, $NaBH_4$; v, H_2, Pd/C; vi, TrCl

Scheme 3

2.2 Epoxide Opening. - Ring-opening of epoxide **14** by azide was used in a new synthesis of methyl 3-amino-3,4-dideoxy-β-D-*xylo*-hexopyranoside **17** (Scheme 4), which was required for the preparation of nitrosourea derivatives. Intermediate azides **15** and **16** were obtained in a 3:2 ratio. An alternative route to epoxide **14** was also reported.[9] The D-*ribo*-aziridine **19** was obtained from the D-lyxo-epoxide **18** (Scheme 5) and used in the synthesis of epimino-nucleoside analogues (see Chapter 20).[10] Syntheses of methyl 2,3-*trans*-aminofluoropentofuranosides from 2,3-epoxides is covered in Chapter 8.



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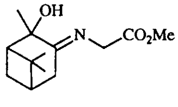

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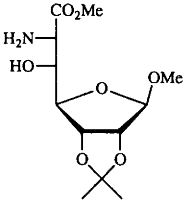

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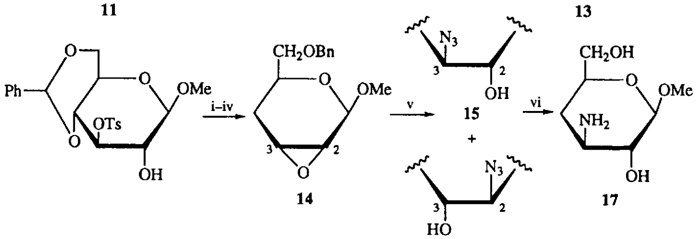
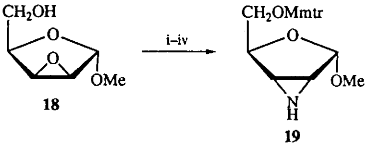


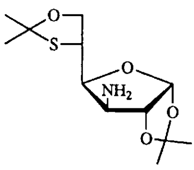
Reagents: i, NaBH$_3$CN, HCl; ii, SO$_2$Cl$_2$; iii, Bu$_3$SnH; iv, MeONa, MeOH; v, NaN$_3$, MeO⌒⌒OH, NH$_4$Cl; vi, H$_2$, Pd/C

Scheme 4



Reagents: i, NaN$_3$, EtOH, H$_2$O; ii, MmtrCl, Py; iii, MsCl, Py; iv, LiAlH$_4$

Scheme 5



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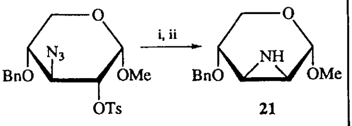
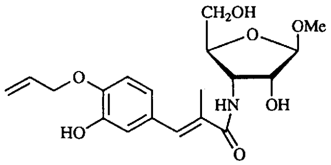
2.3 Nucleophilic Displacement. - Sulfonate ester displacement reactions continue to be widely applied in amino-sugar syntheses. The 3-amino-5-thioglucofuranose derivative **20** was obtained from the corresponding allofuranose 3-mesylate by displacement with azide ion and reduction (LiAlH$_4$) (see also section 2.6).[11] The 2,3-epimino-α-D-lyxopyranoside **21** was prepared in 11 steps from diacetoneglucose *via* 3-azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. Key steps were periodate C5/C6 cleavage, methanolysis, and a modestly selective 2-*O*-tosylation; the final steps are shown in Scheme 6.[12] The 3-amino-3-deoxy-D-ribofuranoside **22** was prepared as a potential antibiotic, incorporating features of the cyclitol antibiotic hygromycin A and nucleoside antibiotic A201A, from 1,2-*O*-isopropylidene-α-D-xylofuranose by a sequence involving azide ion displacement of a 3-triflate.[13]



Reagents: i, H_2, PtO_2; ii, NaOAc, DMF

Scheme 6



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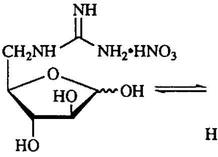
5-Guanidino-5-deoxy-D-arabinose, which exists as a mixture of ring isomers **23** and **24**, was synthesized by reaction of a 5-amino-derivative (derived from a 5-tosylate via a 5-azide) with 3,5-dimethylpyrazolylformamidinium nitrate. 5-Guanidino-5-deoxy-D-xylose and some diamino-sugar analogues (section 4) were also prepared.[14]

Benzoylation of α,α-trehalose afforded in 58% yield a heptabenzoate with a free 4′-hydroxy group, along with some octabenzoate and the hexabenzoate with the 4- and 4′-hydroxy groups free. From the heptabenzoate, the unsymmetrically substituted trehaloses **25** were synthesized by single or double inversions of triflate esters.[15]



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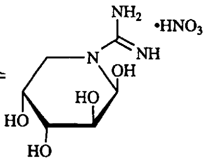

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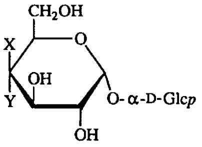
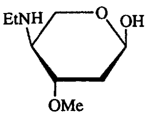


25 X,Y = H; N_3, NH_2 or NHAc



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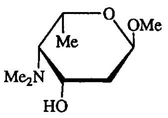

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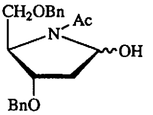
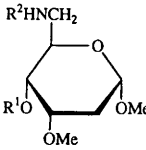


28

The 2,4-dideoxy-4-ethylamino-α-L-*threo*-pentopyranoside **26**, a component sugar of the calicheamicins,[16] and the 2,4,6-trideoxy-4-dimethylamino-α-L-*lyxo*-hexopyranoside **27**, the glycosidic residue of the antitumor antibiotic kedarcidin,[17] were synthesized by similar routes from methyl 2-deoxy-β-D-*erythro*-pentopyranoside and methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside, respectively. In each case, dibutylstannylidene complexes were utilized to effect selective benzylation, and azide was introduced by displacement of a tosyl group.

The 4-acetamido-pentofuranose **28** was synthesized by a route involving a double inversion at C-4 of the dibenzyl dithioacetal derivative of 2,3,5-tri-*O*-benzyl-2-deoxy-D-*erythro*-pentose, through sequential Mitsunobu and sulfonate displacement reactions; its conversion into nucleoside analogues is covered in Chapter 20.[18] The cyclophosphamide analogues **29-31** and the C-3 epimer of **31** were synthesized from the corresponding aminosugars. They were less active than cyclophosphamide itself as antileukemia agents. The aminosugar precursors of **29** and **30** were obtained by azide ion displacements of a 6-bromide and a 4-tosylate, respectively, and those of **31** and its C-3 epimer were prepared from tri-*O*-acetyl-D-glucal.[19] The syntheses of other sugar cyclophosphamide analogues are covered in Chapter 17. 6-Ammonio-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose derivatives were synthesized by reaction of the corresponding 6-iodo-sugar derivative with ammonia followed by quaternization (with either MeI or BnBr), and were tested as chiral phase-transfer catalysts in the reduction of ketones.[20]



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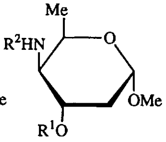

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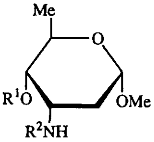

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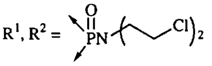
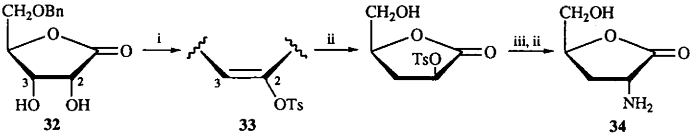
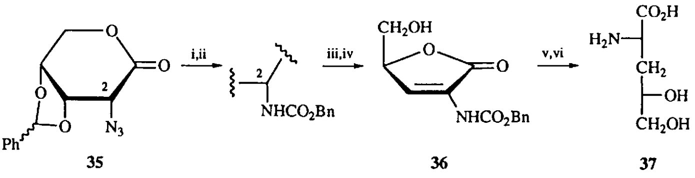


4,5-Dihydroxy-D-*erythro*-norvaline (as its lactone **34**) and its D-*threo*-isomer **37** were synthesized by stereospecific hydrogenation of butenolides **33** and **36**, available from D-ribono-1,4-lactone *via* the known derivates **32** and **35** (Schemes 7 and 8), respectively.[21]



Reagents: i, TsCl, Py; ii, H_2, Pd/C, EtOH, H_2O; iii, NaN_3, DMF

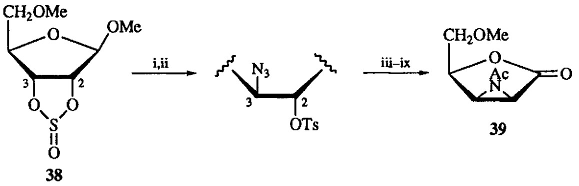
Scheme 7



Reagents: i, H_2,Pd/C, EtOAc; ii, BnO_2CCl, $NaHCO_3$; iii, NaH, THF; iv, H_3O^+; v, H_2, Raney Ni, EtOH; vi, H^+- form resin

Scheme 8

The D-ribose derived cyclic sulfite **38** was cleaved by azide ion attack, and the product was converted into the aziridine-2-carboxylate **39** (Scheme 9). The 2,3-epimer of **39** was similarly prepared from D-lyxose.[22]

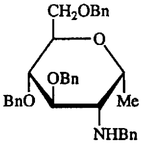


Reagents: i, NaN_3, DMF; ii, TsCl, Py; iii, H_3O^+; iv, TbdmsOTf, lutidine; v, Ph_3P; vi, NaOH, H_2O; vii, Ac_2O, Py; viii, Bu_4NF; ix, $Pr_4N{\bullet}RuO_4$

Scheme 9

2.4 From Glycosylamines. - α-*C*-Glycosides of 2-amino-2-deoxy-D-glucose, e.g. **40**, were stereoselectively obtained by vinylation (CH_2=CHMgBr) of a pentofuranosylamine derivative, followed by cyclization [i,Hg($O_2CCF_3)_2$; ii,$NaBH_4$].[23]

2.5 From Unsaturated Sugars. - Danishefsky and co-workers have utilized the allylic displacement shown in Scheme 10 to construct the core sugar of staurosporine (see also Chapters 13 and 24).[24] Hetero-Diels Alder reaction of persilylated lactal with bis(trichloroethyl) azodicarboxylate gave the oxadiazine adduct **41** which was used as a glycosyl donor in the Lewis acid catalysed synthesis of protected *N*-acetyl-lactosaminides.[25] Michael addition of L-phenylalanine methyl ester to the enone **42** (available from D-glucal) gave a major epimer which on reduction



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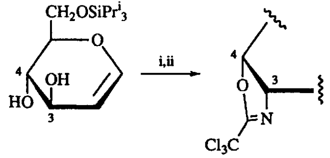
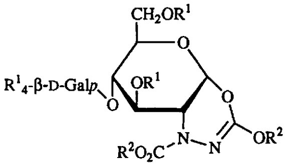
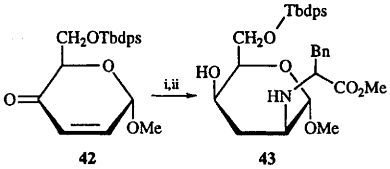


Reagents: i, NaH, Cl_3CCN; ii, $BF_3{\bullet}OEt_2$

Scheme 10



41 R^1 = Tbdms
R^2 = Cl_3CCH_2



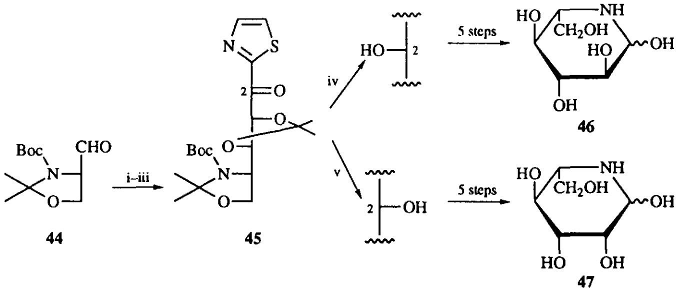
Reagents: i, PhCH(NH_2)CO_2Me, Et_3N; ii, $NaBH_4$

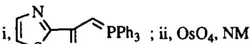
Scheme 11

yielded the D-*lyxo*-product **43** (Scheme 11). The β-anomer of **42** gave the D-*ribo*-isomer of **43**, epimeric at C-2 and C-4. These products are incorrectly drawn in the paper as phenylglycine adducts.[26]

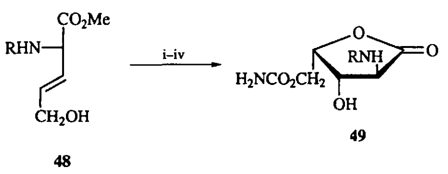
2.6 From Alduloses. - 3-Amino-3-deoxy-5-thioallose was synthesized from 1,2:5,6-di-*O,O*:*S,O*-isopropylidene-5-thio-α-D-*ribo*-hexofuranos-3-ulose by reduction ($LiAlH_4$) of its oxime derivative followed by hydrolysis (see also Section 2.3).[11] The conversion of a 2-deoxy-hexulopyranoside derivative into branched chain 3-nitro- and amino-sugars is covered in Chapter 14.

2.7 From Aminoacids. - Syntheses of aminosugars from serine and threonine have been reviewed.[27] Dondoni and co-workers used their thiazole chain extension methodology to prepare L-nojirimycin **46** and L-mannonojirimycin **47** from the L-serine derived aldehyde **44** (Scheme 12). As well, they reported alternative routes to **45**, **46** and **47** and an improved synthesis of the protected methyl glycosides of the 3-deoxy-analogues of **46** and **47** (cf. Vol.24, p.115), all from **44**.[28] They have also developed an improved method to convert various carbohydrate thiazole derivatives to the corresponding aldehydes (with i,MeOTf; ii,$NaBH_4$; and iii,$CuCl_2$-CuO) in yields of 70-85%.[29] The



Reagents: i,  ; ii, OsO_4, NMNO, Bu^tOH, H_2O; iii, $Me_2C(OMe)_2$, H^+;
iv, $NaBH_4$, MeOH, -60 °C; v, $NaAl(O{\sim}OMe)_2H_2$, PhMe, -78 °C

Scheme 12



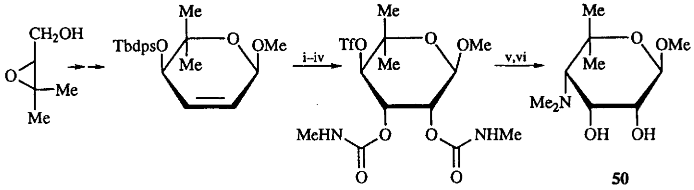
R = 9-phenylfluoren-9-yl

Reagents: i, 4-NO_2-C_6H_4OCOCl; ii, NH_3, H_2O; iii, $KMnO_4$, H_2O, EtOH; iv, Et_3N

Scheme 13

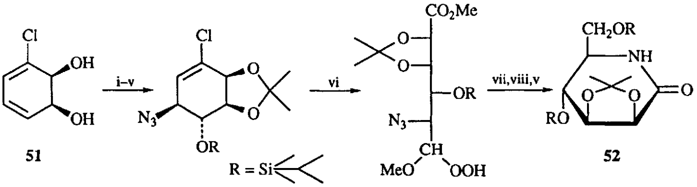
L-*xylo*-lactone **49**, a derivative of (+)-polyoxamic acid, and its D-*lyxo*-isomer were obtained as separable mixture by permanganate oxidation of alkene **48**, prepared in 5 steps from L-glutamic acid (Scheme 13).[30]

2.8 From Other Chiral Non-carbohydrates. - 3-Amino-2,3-dideoxy-2-fluoro-xylo-furanose and -pyranose derivatives have been synthesized from a D-glyceraldehyde derived β-lactam (see Chapter 8).[31] The amino-sugar residue of endiyne glycoside C-1027 was proved to be 4,6-dideoxy-4-dimethylamino-5-*C*-methyl-D-*ribo*-hexose by synthesis of the glycoside **50** of this sugar from a Sharpless asymmetric epoxidation product (Scheme 14). The intramolecular means of introducing the dimethylamino group is particularly noteworthy.[32] Hudlicky and co-workers have developed a route to mannojirimycin and related glycosidase inhibitors from the chlorobenzene microbial oxidation product **51**, as shown in Scheme 15 which leads to the mannonolactam **52**.[33]



Reagents: i, OsO_4, NMNO; ii, MeNCO, Et_3N; iii, Bu_4NF; iv, Tf_2O, Py; v, KH; vi, $LiAlH_4$

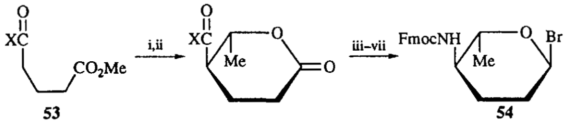
Scheme 14



Reagents: i, $Me_2C(OMe)_2$, H^+; ii, MCPBA; iii, LiCl; iv, NaN_3; v, RCl; vi, O_3, MeOH, H_2O, $NaHCO_3$; vii, $NaBH_4$, $CeCl_3$; viii, H_2, Pd/C

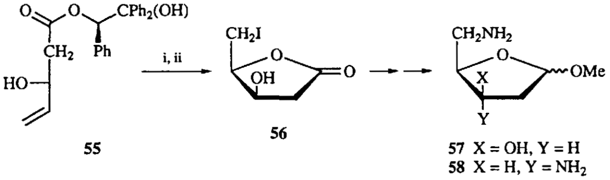
Scheme 15

Chiral auxiliaries feature in two aminodeoxysugar syntheses. The L-forosamine derivative **54** (Scheme 16) was prepared from the *N*-acylated oxazolidinone **53** derived from L-phenylalanine, and used in the total synthesis of the macrolide antibiotic lepicidin A. Key steps were asymmetric aldol condensation (step i) and Curtius reaction (acid to isocyanate with capture by fluorenylmethanol; step iv).[34] The 5-amino-2,5-dideoxy-D-*threo*-pentoside **57** and 3,5-diamino-2,3,5-trideoxy-D-*erythro*-pentoside **58** were synthesized by conventional triflate displacement reactions from iodolactone **56**, which was obtained in from the (R)-3-hydroxy-4-pentenoic acid ester **55** (Scheme 17). The chiral centre in the acid moiety of **55** was created in 84% ee by an asymmetric aldol reaction.[35]



Reagents: i, Bu_2BOTf, MeCHO; ii, Py•HOTs; iii, LiOOH; iv, Et_3N, $Ph_2P(O)N_3$, 9-fluorenylmethanol; v, $Bu^i{}_2AlH$; vi, Ac_2O, Py; vii, Me_3SiBr

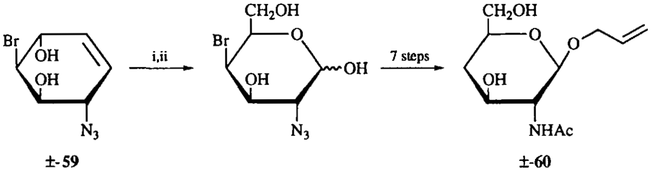
Scheme 16



Reagents: i, NaOH then HCl; ii, I_2, $NaHCO_3$

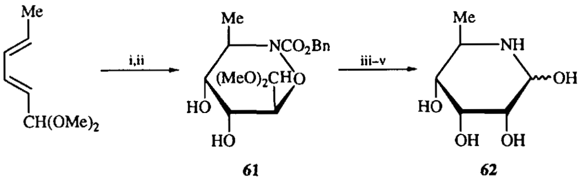
Scheme 17

2.9 From Achiral Non-carbohydrates. - 2-Acetamido-2,4-dideoxy-D- and L-*xylo*-hexopyranose were separately available following specific hydrolysis of the D-enantiomer in the racemic mixture of the allyl glycosides **60** by hexosaminidase. The racemate **60** was synthesized from *p*-benzoquinone *via* the known cyclohexene **59** (Scheme 18).[36] Racemic 5-amino-5,6-dideoxyallose **62** was synthesized from the hetero-Diels Alder adduct **61** (Scheme 19), and reduced (H_2, Pd/C) to



Reagents: i, O_3, MeOH then Me_2S; $NaBH_3CN$, HOAc, MeOH

Scheme 18



Reagents: i, $BnO_2CN{=}O$; ii, OsO_4, NMNO; iii, H_2, Pd/C; iv, SO_2; v, $Ba(OH)_2$

Scheme 19

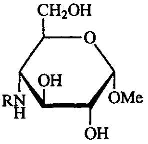
(±)-1,6-dideoxyallonojirimycin.[37]

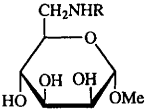
Amino-nucleosides are covered in Chapter 20.

3 Reactions

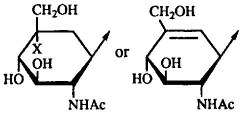
Syntheses of amino-sugar glycosides and disaccharides, including chromogenic substrates for *N*-acetyl-β-D-glucosaminidase, are covered in Chapter 3. Synthesis of protected 2-amino-2-deoxy-glycosyl azides is covered in Chapter 10. 2,3,6-Trideoxy-5-*O*-(4-nitrobenzoyl)-3-trifluoroacetamido-L-*ribo*-hexofuranosyl bromide, a furanoid ristosamine derivative, was synthesized from L-rhamnal *via* intermediates reported previously (Vol.25, p.253) to effect glycosylations.[38]

Full details on new methods for the synthesis of *N*-alkyl- and *N,N*-dialkyl-derivatives of 2-amino-2-deoxy-D-glucose (cf. Vol.26, Ch.9, ref.36) have been reported.[39] Four 1,4-imino-linked carbadisaccharides, e.g. **63**, were synthesized by reaction of methyl 4-amino-4-deoxy-α-D-glucoside with a cyclitol epimine.[40] The 1,6-linked di-*manno*-analogue **64** was obtained similarly by reaction of methyl 6-amino-6-deoxy-α-D-glucoside with a cyclitol epoxide, and was found to be an inhibitor of Jack bean α-D-mannosidase.[41]



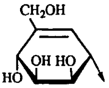


63 R = *e.g.*



X = H or OH

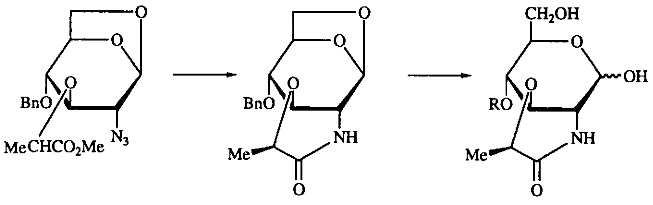
64 R =



The use of ethylenediamine (in BuOH at 90°C) has been proposed as a new general method of removing *N*-phthalimido protecting groups.[42]

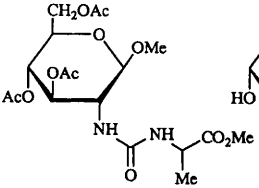
Muramic acid analogues, e.g. **67**, have been synthesized from the azide **65** *via* lactam **66** (Scheme 20).[43] Oxazolidine derivatives reported earlier (Vol.26, Ch.9, ref.37) have been converted into conformationally restricted muramoyl dipeptide analogues.[44]

O-Unprotected *N*-thioacylated derivates of 2-amino-2-deoxy-D-glucose and its 6-phosphate, and 2-amino-2-deoxy-D-mannose and -D-galactose have been synthesized for the first time and in high yield from the aminosugar hydrochlorides [by reaction with HC(S)OEt, $MeCS_2Me$ or $EtCS_2Me$ in $MeOH,H_2O,Et_3N$].[45] Fourteen aminoacid ester containing ureido-sugars, e.g. **68**, were synthesized by methodology reported earlier (Vol.24, p.118, Scheme 21).[46] The formation and cyclization of



65 **66** **67** R = β-D-GlcNAc

Scheme 20



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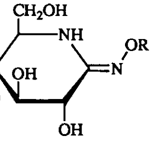
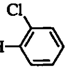
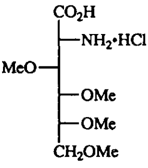


69 R = H

70 R = CONH–





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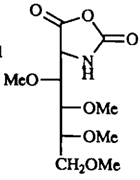


72

2-deoxy-2-ureido-aldoses to 1,2-cyclic carbamate is covered in Chapter 10.

Conventional protecting group manipulations have been used to produce analogues of lipid A containing a 2-amino-2-deoxy--D-galactose 4-phosphate residue,[47] and *N*,*O*-acylated 2-amino-2-deoxy-D-glucose 4-phosphate moieties *O*-glycosidically linked to L-serine,[48] and analogues of lipid X containing fatty alkyl phosphonate moieties.[49] Carbocyclic analogues of lipid X are covered in Chapter 18.

A full account has been published of earlier work (Vol.24, p.120; Vol.25, p.117), with some additions, on the preparation of amidine, amidrazone and amidoxime derivatives of aldonolactams as potential glycosidase inhibitors.[50] The D-gluconohydroximino-1,5-lactam **69**, and from it *O*-carbamoylated analogues such as **70**, have been synthesized from the corresponding D-glucono-1,5-lactam tetra-*O*-benzyl ether (by reaction with i, $Et_3O.BF_4$; ii, NH_2OH), and shown to be β-glucosidase inhibitors.[51]

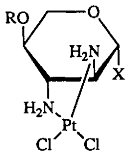
The 2-amino-2-deoxy-D-gluconic acid derivative **71** has been synthesized from 2-acetamido-2-deoxy-D-glucose, converted to the *N*-carboxy-anhydride **72** by reaction with trichloromethyl chloroformate, and polymerized to polyamides of molecular weight about 10,000 daltons.[52]

Efficient, conventional syntheses of the 3-, 4- and 6-*O*-methyl ether derivatives of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside have been detailed.[53] 3,6-Di-*O*-fatty acyl derivatives of methyl 2-amino-2-deoxy-D-glucopyranoside have been prepared for use as positively charged components of liposomes.[54] Methods for determining the absolute configurations of sugars, including aminosugars, by *in situ* formation of trinuclear metal complexes, is covered in Chapter 22.

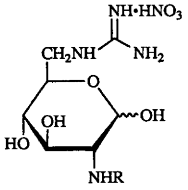
4 Diamino-sugars

A branched-chain diamino-sugar constituent of an antibiotic is covered in Chapter 19.

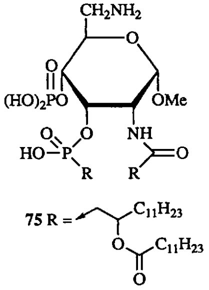
The cisplatin analogues **73** were synthesized from L-arabinose in a multi-step procedure via epoxide and epimine intermediates.[55] The potent serine protease inhibitors, 2-amino-2,6-dideoxy-6-guanidino-D-glucose and its 2-*N*-acetyl derivative **74**, were synthesized by reaction of benzyl 2-*N*-protected-2,6-diamino-2,6-dideoxy-α-D-glucopyranoside with 3,5-dimethylpyrazolylformamidinium nitrate followed by hydrogenolysis.[14]



73 X = OMe, R = H or Me
or X = H, R = H



74 R = H or Ac



75 R =

A 2-acetamido-4-amino-2,4-dideoxy-β-D-glucopyranosyl residue was synthesized and incorporated as the terminal residue of a trisaccharide glycoside, in connection with studies of the acceptor requirements of *N*-acetylglucosaminyl transferase V.[42] A 2-acetamido-4-amino-2,3,4,6-tetradeoxy-α-D-*xylo*-hexopyranosyl residue was incorporated into a trisaccharide-ribitol-phosphate, the repeat unit of a *Streptococcus pneumoniae* polysaccharide.[56] The synthesis of diamino-sugar **58** is covered in Section 2.8.

The diamino-sugar 3-*O*-alkylphosphonate **75**, an analogue of lipid X, has been synthesized via a 2-amino-6-azido-sugar derivative, the azide being introduced by sulfonate displacement.[49]

The synthesis of unsaturated 4-azido-sialic acid derivatives is covered in Chapter 10, and the synthesis of 2-acetamido-1,2-dideoxynojirimycin in Chapter 18.

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10

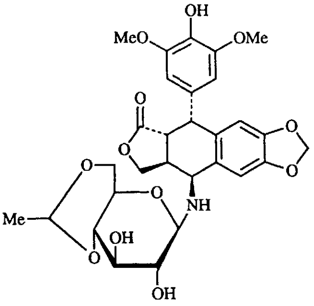
Miscellaneous Nitrogen Derivatives

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

1.1 Glycosylamines. - The unambiguous assignment of anomeric configuration of glycosylamines and diglycosylamines by ^{1}H-n.m.r. spectroscopy (cf. Vol.21, p.100, ref.6) has been extended to those containing α-D-Ara*p*-, β-D-Man*p*- and β-L-Rha*p*- residues.[1]

Kochetkov's method for preparing glycosylamines from free sugars by reaction with aqueous ammonium carbonate (Vol.20, p.106) has been optimized for use with cellobiose, maltose, lactose and melibiose on a gram scale,[2] and applied to a di- and hepta-saccharide;[3] the conversion of the glycosylamines into *N*-glycopeptides is covered in Section 1.5.

N-[2-(Perfluoroalkyl)ethyl]-lactosylamines were synthesized as non-ionic surfactants by aza-Wittig reaction of lactose (with $RCH_2CH_2N_3$ and Ph_3P, where R = C_6F_{13}, C_8F_{17} or $C_{10}F_{21}$).[4] The rates of reactions between sugars and primary aromatic amines, determined by h.p.l.c. on an amino-bonded column, correlated well with hydrogen bonding energies estimated by molecular mechanics calculations.[5] *N*-(3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl) derivatives of a range of



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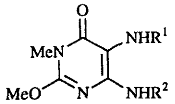
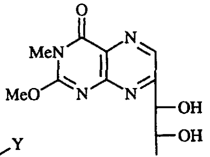


2 R^1 = α, β-Rib*p*, R^2 = H
3 R^1 = R^2 = α-Xyl*p*



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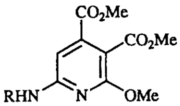
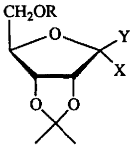
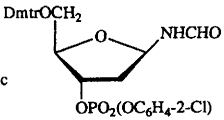


5 R = *e.g.* β-D-Xyl*p*-Ac$_3$



6 X = NHCHO, Y = H, R = Ac
7 X = NC, Y = H, R = Ac
8 X = R = H, Y = N=CHNMe$_2$
9 X = R = H, Y = NHCHO



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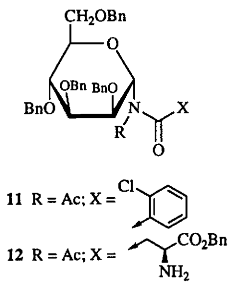
primary and secondary amines were obtained with high stereoselectivity by use of a *O,O*-dialkyl-*S*-α-D-glycosyl-phosphorodithioate as a glycosyl donor.[6] The glucosylamine analogue **1** of the antitumor *O*-glycoside etoposide was synthesized by *N*-alkylation of 4,6-*O*-ethylidene-2,3-bis-*O*-(trimethylsilyl)-β-D-glucosylamine, which was itself synthesized from acetobromoglucose *via* D-glucosyl azide.[7] 5-Mono- and 5,6-diglycosyl-aminopyrimidines, e.g. **2** and **3**, were obtained by reaction of ribose or xylose with 5,6-diamino-2-methoxy-3-methylpyrimidin-4(3H)-one in alcohol solution, whereas in the presence of acetic acid, 7-polyhydroxyalkylpteridines, e.g. **4**, resulted.[8] 2-(Glycosylamino)pyridines **5** were synthesized from 6-(glycosylamino)-2-methoxypyrimidin-4(3H)-ones by Diels Alder/retro-Diels Alder reactions with dimethyl acetylenedicarboxylate.[9]

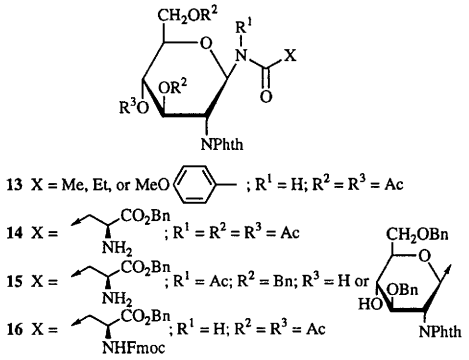
1.2 Glycosylammonium Salts. - Koenigs-Knorr syntheses of the *N*-glucuronides of (S)-(-)-nicotine,[10] cotinine and *cis*- and *trans*-3-hydroxycotinine[11] have been reported. The conformational analysis of the glycosylnitrilium ions that are intermediates in glycosylation reactions in acetonitrile, is covered in Chapter 21.

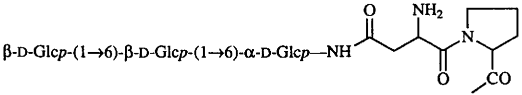
1.3 Glycosylamides Including *N*-Glycopeptides. - Reaction of 2,3-*O*-isopropylidene-D-ribofuranosylamine with formic-acetic anhydride gave the *N*-formyl-α-D-ribosylamine **6** specifically, and thence the α-ribosylisocyanide **7** (on reaction with $POCl_3$-Pr^i_2NH). Alternatively, reaction with dimethylformamide dimethyl acetal gave the β-amidine **8** selectively, and on hydrolysis the *N*-formyl-β-D-ribosylamine **9**.[12] Synthesis of the protected 2′-deoxyribosylformamide **10** and its inclusion into an oligo-DNA has also been reported.[13]

N-(Bromoacetyl)-β-D-glucosylamine and β-cellobiosylamine derivatives were synthesized directly from the glycosylamines, as affinity labels for a β-glucosidase and a cellulase, which enzymes were inactivated by first order kinetics.[14] Twenty seven di- to oligo-saccharides were immobilized by glycosylamine formation through reaction with the primary amine function of a Fractogel resin, and stabilization of the linkage by *N*-acylation (with Ac_2O). The affinity properties of the resulting matrices were evaluated with 4 monoclonal antibodies and 10 lectins.[15]

The α-D-mannosylamides **11** and **12** were formed by reaction of the corresponding 4-pentenyl α-mannoside with *N*-bromosuccinimide and respectively *o*-chlorobenzoic acid and an aspartic acid derivative in acetonitrile, in a fashion entirely analogous to that found for the D-*gluco*-system (Vol.24, p.124). The products can be *N*-deacetylated by treatment with sodium methoxide. Compound **11** adopts a conformation that is between a boat ($B_{2,5}$) and a twist boat ($^1S_5$).[16] β-Linked 2-deoxy-2-phthalimido-D-glucosylamides **13** were obtained when the corresponding 4-pentenyl glycoside was induced to react with simple nitriles (in the presence of NIS, Et_3SiOTf and 1 mol. equiv. of H_2O), but the reaction failed with β-branched nitriles [e.g. $BnO_2CNH(BnO_2C)CHCH_2CN$







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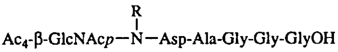
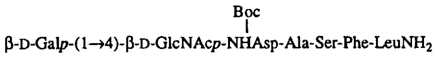


$$\mathrm{Ac_4\text{-}\beta\text{-}GlcNAc}p\mathrm{-}\overset{\displaystyle R}{\overset{|}{N}}\mathrm{-Asp\text{-}Ala\text{-}Gly\text{-}Gly\text{-}GlyOH}$$

18 R = maleyl



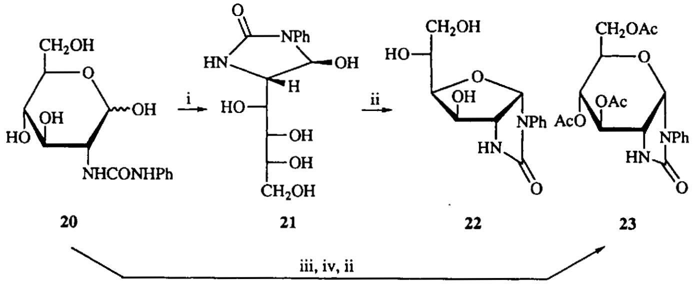
$$\mathrm{\beta\text{-}D\text{-}Gal}p\mathrm{\text{-}(1\to4)\text{-}\beta\text{-}D\text{-}GlcNAc}p\mathrm{\text{-}NH\overset{\displaystyle Boc}{\overset{|}{A}}sp\text{-}Ala\text{-}Ser\text{-}Phe\text{-}LeuNH_2}$$

19

or Me_2CHCH_2CN]. The desired β-linked *N*-(2-amino-2-deoxy-D-glucosyl)- and *N*-chitobiosyl-asparagine derivatives **14** and **15** could be obtained, however, by the reaction of the corresponding *N*,*O*-protected 4-pentenyl β-glycosides with *N*-bromosuccinimide and an aspartic acid derivative in acetonitrile, as above.[17] The *N*,*O*-protected 4-*N*-(2-amino-2-deoxy-D-glucosyl)-asparagine **16**, useful for *N*-glycopeptide construction, was obtained by reaction of the corresponding β-glycosyl azide with an aspartic acid derivative and triethylphosphine. Yields were poorer with glycosyl components bearing a 2-OAc rather than a 2-NHAc group.[18] Nephritogenoside **17** and its β-anomer[19] and many simple *O*- and *N*-glycopeptides, e.g. **18**,[20] were synthesized by chemical and enzymatic methods of peptide chain elongation from smaller glycopeptide precursors. The sequential use of a glycosyltransferase and a protease was also demonstrated, e.g. in the synthesis of **19** from a *N*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-tripeptide.[18] β-Glycosylamines of D-GlcNAc*p*, α-D-Fuc*p*-(1→6)-D-GlcNAc*p*, *N*,*N*-diacetyl-chitobiose and a pentamannosyl-*N*,*N*-diacetyl-chitobiose were coupled to a range of synthetic peptides including a pentapeptide which corresponds to residues 291-295 of ovalbumin.[3]

Under alkaline conditions, 1-(di-*N*-benzoyl)amino-1-deoxy-D-glucitol has been reported to form *N*-benzoyl-β-D-glucopyranosylamine and two other isomeric products, that were assigned somewhat unusual 1,2-*N*,*O*-(α-hydroxybenzylidene)-glucosylamine structures.[21]

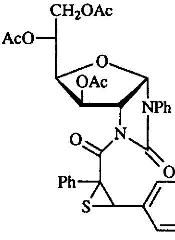
1.4 *N*-Glycosyl-ureas, -carbamates and Related Compounds. - Kinetic studies of the acid- and base-catalysed anomerization of *N*-mono- and *N*,*N'*-bis-(D-glucopyranosyl)urea indicate that the key step is the formation of an acyclic imine as the intermediate.[22] Reaction of 2-amino-2-deoxy-D-glucose, -galactose or -mannose with aryl isocyanates at pH 7 gave 2-ureido-2-deoxypyranoses (e.g. **20**) that are converted to 5-hydroxyimidazolidin-2-one derivatives (e.g. **21**), slowly in neutral medium but rapidly at pH >7 (Scheme 1). At pH >10, **21** epimerizes at C-2. At acidic pH, both **20** and **21** are further converted into furanosyl derivatives **22**. The pyranosyl derivative **23** was synthesized from **20** by per-*O*-acetylation, 1-*O*-deacetylation and cyclization in mild acid.[23] Analogous reactions were reported for 2-amino-2-deoxy-D-*glycero*-L-*gluco*-heptose and its *N*-ethyl-analogue (cf. Vol.23, p.110, ref.19).[24] The fused urea derivative **24** was obtained by reaction of a sugar-fused imidazo[2,1-*b*]thiazolium-3-olate zwitterion (Vol.25, p.132, compound **100**) with 4-dimethylaminobenzaldehyde.[25]



Reagents: i, H_2O, pH<10; ii, HOAc, H_2O; iii, Ac_2O, Py; iv, MeOH, SiO_2

Scheme 1

N-Protection of glycosylamines was achieved by reaction with diethyl ethoxymethylenemalonate, to yield *N*-(2,2-diethoxycarbonylvinyl) derivatives of both mono- and di-saccharides, e.g. the β-L-rhamnosyl derivative **25**. *O*-Protected glycosylamines were obtained from these by *O*-acylation (Ac_2O,Py or BzCl,Py) and *N*-deprotection (Cl_2, CH_2Cl_2), and were converted into glycosyl isothiocyanates (Cl_2CS, $CaCO_3$, H_2O) then *N*-glycosyl-thioureas (with NH_3 or $PhCOCH_2NH_2$).[2,26] Partial *O*-benzylation of **25** revealed the reactivity of its hydroxy-groups to be 3-OH > 4-OH ≈ 2-OH.[26]



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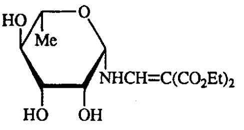

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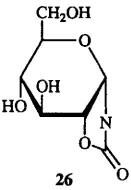

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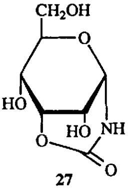

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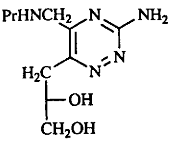
2,3,4,6-Tetra-*O*-acetyl- and benzoyl-β-D-glucopyranosyl isothiocyanate continue to find use as derivatization reagents in h.p.l.c. methods for resolving enantiomeric amines as their diastereomeric glycosylthiourea derivatives.[27,28] Terminal epoxides could be similarly resolved when reacted with butylamine prior to derivatization.[29]

Treatment of α-D-glucopyranosyl azide with triphenylphosphine in the presence of carbon dioxide afforded carbamates **26** and **27**, in which the configuration at C-3 is retained and inverted, respectively, as well as their α-D-furanose isomers. Similar results were observed for α-D-xylopyranosyl azide, and a mechanism involving intramolecular displacement at C-3 was invoked to explain the inverted products.[30]

1.5 Amadori and Maillard Reactions. - The mechanism by which aminoguanidine inhibits biological "advanced glycosylation", the further reaction of Amadori products, has been investigated. Its reaction with 1-deoxy-1-propylamino-D-fructose, led to the triazines **28** and **29**.[31] Treatment of Amadori compounds derived from aldoses and aromatic amines with bakers' yeast led to a reversal of the Amadori rearrangement and recovery of the amines in quantitative yield; the proposed mechanism involves isomerase activity.[32] The influence of reaction conditions, especially pH, on the five main u.v.-absorbing products of the glucose/propylamine reaction was investigated by h.p.l.c., oxyheterocycles predominating under neutral conditions, pyrroles dominating at pH 5.[33] Aroma compounds produced from cysteine and rhamnose under roasting conditions (200-220°C) were fractionated and identified by adsorption chromatography on silica gel then g.l.c.-m.s. Of the



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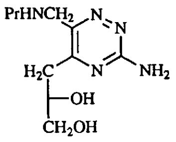

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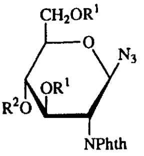
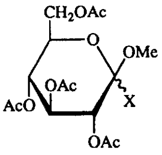


30 $R^1 = R^2 = Ac$
31 $R^1 = Bn, R^2 = H$



32 $X = N_3$
33 $X = OMe$

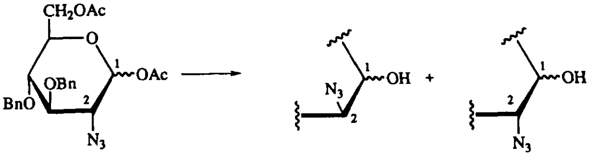
180 compounds detected, 125 were identified, and these were mostly furan, pyrrole and thiophene derivatives.[34] The reaction of taurine with glucose, and the antioxidant properties of the product were briefly investigated.[35]

2 Azido- and Diazirino-sugars

Work on the synthesis, structure and reactions of glycosyl azides from 1961 has been reviewed (24 pages, 129 refs).[36] Acetylated β-glycosyl azides were synthesized effectively quantitatively by reaction of the corresponding glycosyl halides with 1,1,3,3-tetra-*N*-methylguanidinium azide in dichloromethane. The same reagent was effective in conversion of a primary triflate to azide.[37] Phase-transfer catalysis was used in the synthesis of peracetylated 2-amino-2-deoxy-β-D-glucopyranosyl azide from the corresponding α-chloride and sodium azide. The *N*-phthalimido-protected azide **30** was obtained from the corresponding glycosyl fluoride (with Me_3SiN_3, $BF_3.OEt_2$).[38] Several examples of the utility of the azido-group as protection for the anomeric position have been reported; it remains intact during the following operations elsewhere on the molecule: removal of ester-groups, introduction of ether-type protection, glycosylation of hydroxy-groups and reductive opening ($NaBH_3CN$) of acetal groups. The conversion of **30** to **31** is one such example. These glycosyl azides can be converted to tetrazoles by reaction with di-*tert*-butyl acetylenedicarboxylate (Vol.25, p.123) and then to glycosyl fluorides with hydrogen fluoride - pyridine, for use as glycosyl donors.[39] The anomeric configuration in glycosyl azides, e.g. 2,3-*O*-isopropylidene-α- and β-D-ribofuranosyl azide, could be distinguished using m.s. methods, particularly from the decomposition pattern of the $[M\text{-}CH_3]^+$ ion in the MIKE spectra recorded under c.i. conditions.[40]

Separable mixtures of the anomeric methyl (or ethyl) 1-azido-D-glucosides **32** were synthesized from the anomeric orthoester **33** (with Me_3SiN_3, $BF_3.OEt_2$).[41]

The 2-azido-D-glucosyl acetate **34** was converted into a mixture (1:7 to 1:30 depending upon reaction conditions) of the 2-azido-D-mannose **35** and its D-*gluco*-isomer **36**, respectively, on reaction with piperidine in tetrahydrofuran (Scheme 2). Compound **35** was converted to its 1-*O*-

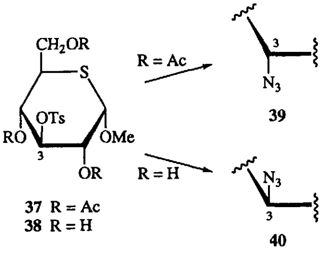


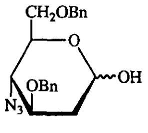
34 **35** **36**

Scheme 2

trichloroacetimidate and used for the synthesis of oligosaccharides (see Chapter 2 and 3).[42] Benzeneselenol has been used to reduce 2-azido-groups to 2-amino-groups.[43]

Reaction of the acetylated 5-thio-3-tosylate **37** with sodium azide in dimethylformamide gave D-*allo*-azide **39** in only 10% yield, along with greater amounts of the products of elimination of tosic acid. The triol **38**, however, gave the D-*gluco*-azide **40**, isolated in 36% yield after acetylation, presumably by way of apparent diequatorial ring opening of epoxide intermediate(s).[44] The 4-azido-2,4-dideoxy-D-*arabino*-hexose **41** was synthesized from methyl β-D-galactopyranoside and used in the synthesis of a potential precursor to the alkaloid retronecine (see also Chapter 24).[45] The 4-azido-2,3,4-trideoxy-D-*threo*-hexoside **42** was synthesized from ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside and used in the synthesis of acyclonucleosides.[46] The azido-groups of **41** and **42** were introduced by displacements of mesylates with azide ion.





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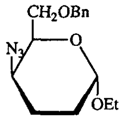

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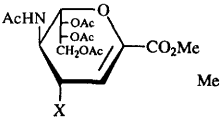
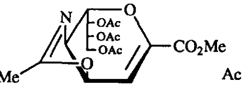
The 4-azido- and 4-thio-sialic acid derivatives **43** were obtained by ring opening the oxazoline **45** (with LiN_3, Me_3SiN_3 or AcSH). Oxazoline **45** was formed by treatment of the 4-acetate **44** with boron trifluoride diethyl etherate.[47] Azido-phenylselenation of *O*-acetyl- and benzyl-protected glycals has been effected [with PhSeSePh, NaN_3, $(AcO)_2IPh$]. Tri-*O*-acetyl-D-glucal gave the 2-azido-α-D-gluco- and α-D-mannosides **46** in similar amounts, whereas tri-*O*-acetyl-D-galactal gave the 2-azido-α-D-galactoside **47** in 70% yield.[48,49] The reaction probably involves addition of an electrophilic radical at C-2. The use of 2-azido-glycosyl donors in the synthesis of glycosides is covered in Chapter 3.



43 X = N_3 or SAc
44 X = OAc



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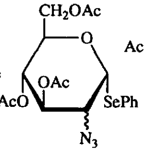

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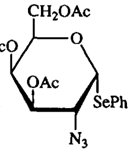
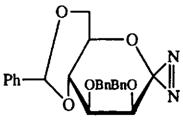


47

Spiro-diazirines of protected glucose, mannose and 2-acetamido-2-deoxy-glucose, e.g. **48**, have been prepared and shown to yield methyl glycosides on thermolysis in methanol.[50] On photolysis in the presence of ketones, they formed spiro-oxiranes, e.g. **49** from the corresponding glucosylidene diazirine and cyclohexanone.[51] The synthesis and photolysis of the diazirines **50-52** have been reported. While **50** in water gave only **53** (or its 2-^{2}H analogue **54** in D$_2$O), **51** gave **55** and **56**, while **52** did not give a major product.[52]



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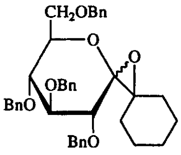

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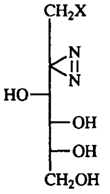
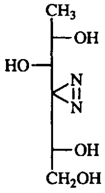


50 X = OH
51 X = H



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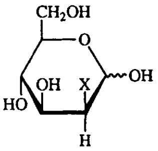
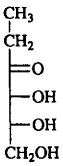


53 X = H
54 X = D



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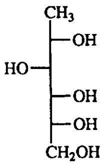

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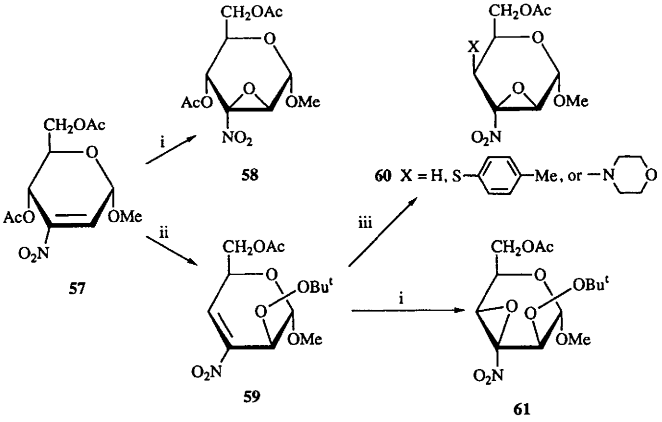


Reagents: i, MCPBA; ii, Bu^{t}O$_2$H; iii, NaBH$_4$, 4-MeC$_6$H$_4$SH, or 

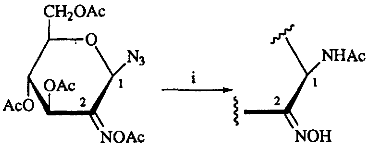
Scheme 3

3 Nitro-sugars

The unsaturated nitro-sugar **57** could be epoxidized to **58**, or converted into the relatively stable peroxide **59** and then into the epoxides **60** or **61** (Scheme 3).[53] Oxidation of an amino-sugar to a nitro-sugar is covered in the next section. Reference is made to branched-chain nitro-sugars in Chapter 14.

4 Oximes, Hydroxylamines and Amidines

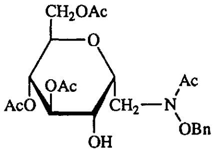
The 2-acetoxyimino-2-deoxy-β-glycosyl azide **62** was obtained from the corresponding α-chloride (by reaction with NaN_3, CH_3CN), and converted into the *N*-(2-deoxy-2-oximino-β-glycosyl)-acetamide **63** in low yield on hydrogenation (Scheme 4).[54] *O*→*N* Acetyl migration was a component of the formation of the *C*-glycoside **64** on reaction of acetobromoglucose with formaldehyde *O*-benzyl-oxime in the presence of a thermal source of tributyltin radicals [i.e. bis(tributylstannyl)benzopinacolate].[55] The 4-hydroxyamino-sugar residue **68**, present in the calicheamicins, was synthesized from D-galactose *via* the bromide **65** and amine **66** (Scheme 5). The formation of nitro-sugar **67** from **66** on reaction with ozone is the first example of an oxidation



62 **63**

Reagent : i, H_2, Pd/C

Scheme 4



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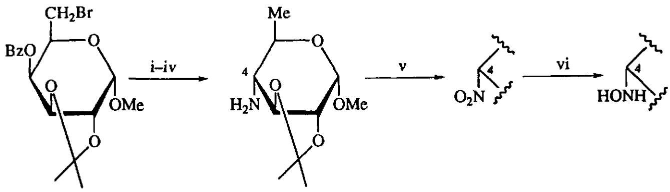


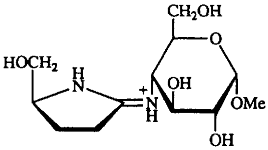
65 **66** **67** **68**

Reagents: i, $LiAlH_4$; ii, MsCl, Py; iii, NaN_3, DMF; iv, $NaBH_4$, DMF, MeOH; v, O_3; vi, Zn, NH_4Cl, THF

Scheme 5

of a primary amine attached to an unbranched carbon atom. Oxidation of **66** with *m*-chloroperbenzoic acid yielded an unwanted 4-oxime.[56] Full details of the synthesis of 1,2-*O*-cyclohexylidene-3-deoxy-3-hydroxyamino-5-*O*-toluoyl-α-D-ribofuranose (Vol.26, Ch.10, ref.49) have been published. This compound was converted to the corresponding *N*-arylmethyl-analogues (i,ArCHO; ii, $NaBH_4$), and their spontaneous oxidation in air to nitroxide radicals was examined.[57] Various *N*-alkyl-hydroxyamino-sugar derivatives have been synthesized as potential surfactants for solubilization of membrane proteins; *N*-(D-galactos-6-yl)-*N*-lauryl-hydroxylamine was the only deprotected material characterized.[58]

Amidine pseudodisaccharides, e.g. **69**, were prepared as potential glycosidase inhibitors by condensation, e.g. of an *N*,*O*-benzyl-protected lactam (activated by reaction with MeOTf) with an *O*-benzyl protected amino-sugar, followed by deprotection (H_2, Pd/C).[59]



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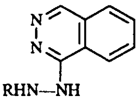
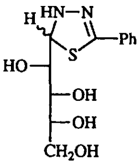


70 R = β-D-Gal*p* (1→4)-β-D-Gal*p* -
71 R = H



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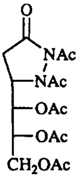

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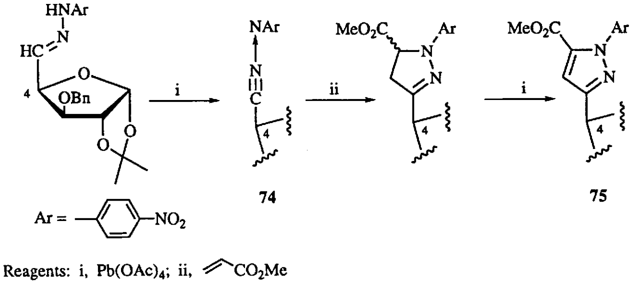
5 Hydrazones and Related Heterocycles

The synthesis and anti-mycobacterial activity of D-xylose isonicotinoylhydrazone has been reported.[60] The lactosyl hydrazine derivative **70**, identified by h.p.l.c.-m.s. methods, is formed apparently by reaction of lactose with hydralazine **71** in a pharmaceutical tablet.[61] The equilibrium formed between the acyclic and cyclic forms of D-glucose thiobenzoylhydrazone, including the 1,3,4-thiadiazol-2-ine isomer **72** (~45% of the mixture), has been investigated.[62]

Pyrazolidin-3-ones, e.g. **73**, were formed by reaction of hydrazine with 2,3-dideoxy-hex-2-enono-1,5-lactone derivatives, followed by acetylation. The stereochemistry at C-3 in these products results from *trans*-addition of hydrazine with respect to the C-5 substituent of the lactone.[63]

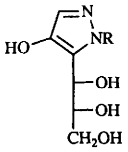
Pyrazole *C*-glycoside analogues, e.g. **75**, were obtained by 1,3-dipolar cycloaddition of alkenes to nitrilimines, e.g. **74**, formed from aldehydo-sugar hydrazones (Scheme 6).[64] Mixtures of the 4-pyrazolol derivatives **76** and **77** (R = Me or Ph) were synthesized by condensation of 3-ketoglucose with methyl- or phenyl-hydrazines; with hydrazine itself, however, 4-pyrazolol **77** (R = H) was the sole product.[65]



74 **75**

Reagents: i, $Pb(OAc)_4$; ii, CO_2Me

Scheme 6



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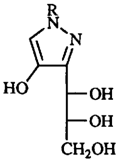

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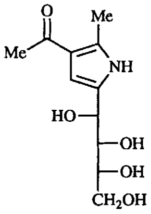
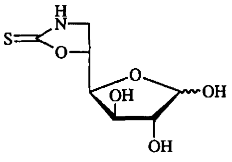


78

6 Other Heterocycles

The further reactions of 2-methyl-5-(D-*arabino*-tetritol-1-yl)furoyl hydrazone derivatives have been reported.[66] The pyrrole derivative **78** was obtained by reaction of D-fructose with acetylacetone and ammonium carbonate in DMSO (in 47% yield), or of 2-amino-2-deoxy-D-glucose with acetylacetone and sodium carbonate in DMSO (in 78% yield).[67]

The intramolecular cyclization of 6-deoxy-6-isothiocyanato-sugar derivatives into 2-thiono-1,3-oxaza-heterocycles, e.g. **79** and **80**, has been reported.[68] The mannofuranose-sprirohydantoin **83** and its C-2 epimer were synthesized from azide **81**, which was converted into the amine **82** (major) and its C-2 epimer by formation and ring contraction of a 3-imino-derivative (Scheme 7).[69] The conversion of alditols to cyclic urea and thiourea derivatives is covered in Chapter 18.



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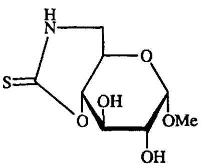

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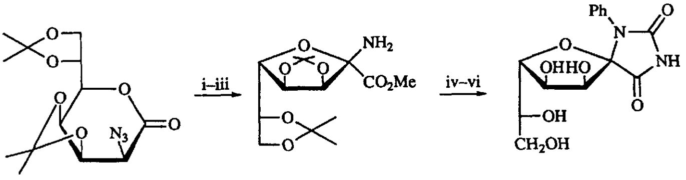
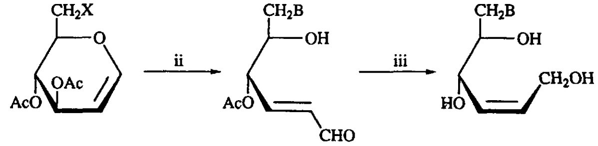


81 **82** **83**

Reagents: i, H_2, Pd/C, EtOAc; ii, Br_2, MeOH, NaOAc; iii, Et_3N; iv, PhNCO; v, MeOH; vi, H_3O^+

Scheme 7

N-Alditol-1-yl bases, e.g. the thymine derivative **86**, were synthesized from the 6-*O*-tosyl-D-glucal derivative **84** (Scheme 8). The *cis*-double bond in **86** results from a Michael addition and elimination of methanol prior to reduction of the *trans*-enal **85**.[70] Reductive ring-opening of nucleosides to *N*-(1-deoxy-D-*ribo*-pentitol-1-yl)purines is covered in Chapter 20.



i **84** X = OTs → X = B

85 B = thymin-1-yl

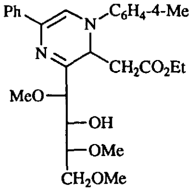
86

Reagents: i, NaH–BH; ii, $HgSO_4$, H_3O^+; iii, $NaBH_4$, MeOH

Scheme 8

The dihydropyrazine **87**, a possible food flavour intermediate, was obtained from 3,5,6-tri-*O*-methyl-D-glucose by sequential treatment with *p*-toluidine, phenacyl bromide and glycine ethyl ester.[71] Sequential reaction of *o*-phenylenediamine and *m*-fluorophenylhydrazine with dehydroisoascorbic acid gave products analogous to those obtained previously from dehydroascorbic acid (Vol.22, p.116-7).[72]

Mannojiritetrazole **88** has been synthesized from 2,3,4,6-tetra-*O*-benzyl-D-mannose by a route similar to that reported for the *gluco*-isomer (Vol.25, p.131) but using an oxidation-reduction-sulfonate displacement sequence to obtain the desired stereochemistry at C-5; both **88** and its *gluco*-isomer are transition state analogue inhibitors that are highly selective for mannosidase and glucosidase enzymes, respectively.[73] Thermolysis of the 1,1-diazide **89** gave the tetrazole **90** (82% yield) whereas photolysis resulted in partial formation of its C-2 epimer (sugar numbering). Analogous results were obtained for the *galacto*-isomers.[74]



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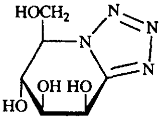

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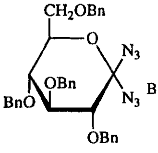

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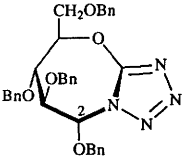

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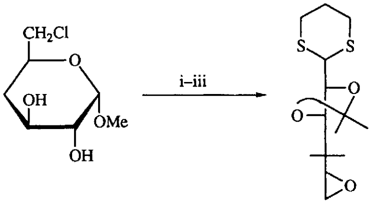
11

Thio- and Seleno-sugars

The dithiane **2**, a key intermediate in the synthesis of milbemycins, has been obtained from chlorodeoxy-sugar **1** (see Chapter 8) as shown in Scheme 1.[1] 3,4-*O*-Isopropylidene-α-L-rhamnose dithioacetal is referred to in Chapter 6.

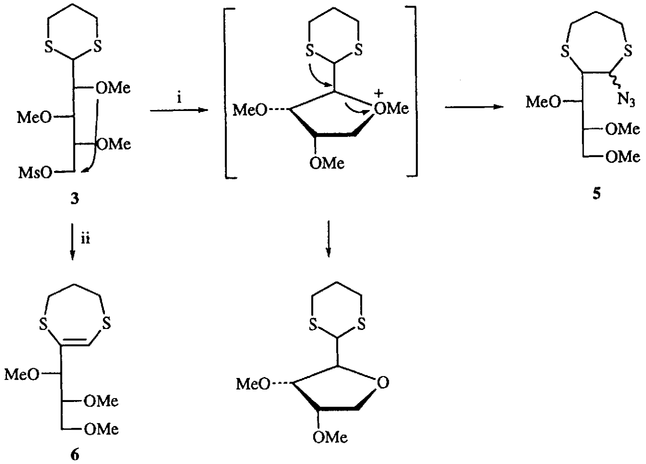


1 **2**

Reagents: i, $HS(CH_2)_3SH$, HCl; ii, acetone, $CuSO_4$, TsOH; iii, NaOH

Scheme 1

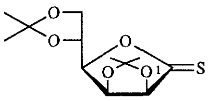
A novel reaction of carbohydrate dithianes bearing a mesyloxy group at the 5-position has been discovered on attempted substitution of the mesylate in compounds **3** by azide. As illustrated in Scheme 2, participation, first by O-2 and then by sulfur, led to the formation of rearranged products **4** and **5** with little direct displacement. Pyrolysis of **3** in the absence of lithium azide gave the unsaturated product **6** in high yields.[2] The reduction of dithioacetal mono-*S*-oxides to dithioacetals by use of lithium aluminium hydride has been reported.[3]



Reagents: i, LiN_3, DMF, 100 °C; ii, pyrolysis

Scheme 2

The potential and limitations of ethyl 1,2-*trans*-disposed 2-*O*-phenoxythiocarbonyl-1-thioglycosides as glycosyl donors (see Vol. 26, Chapter 11, Scheme 6) have been further investigated.[4] Cycloaddition reactions of glyconothio-1,4-*O*-lactone **7** with 1,3-dienes, diazomethane, and ethyl diazoacetate furnished adducts such as **8**, dihydrothiazoles **9** and **10**, and alkene **11** (formed *via* a spirothiirane), respectively. Similar results were obtained with 2,3-*O*-isopropylidene-1-thiono-5-*O*-trityl-D-ribono-1,4-*O*-lactone.[5]



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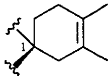

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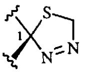

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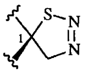

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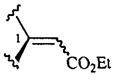
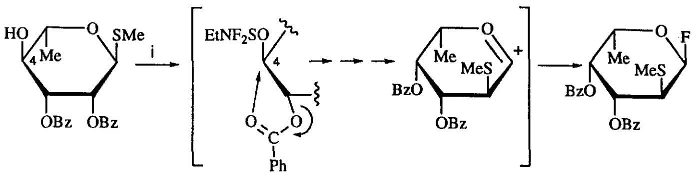


11

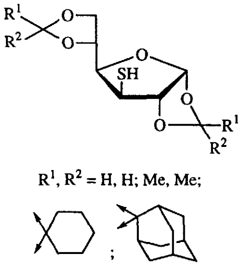
A review on the synthesis, chemical transformations and biological properties of thio- and seleno-sugar nucleosides, with S or Se at 2′, 3′, 5′, or as the ring hetero atoms, and including sections on *C*-sulfonate nucleosides and oligonucleotides with sulfur-containing linkages has been published.[6] Treatment of several 6-deoxy-1-thiohexopyranosides with DAST furnished unexpected products. The sulfoxo intermediate **13**, formed initially from L-rhamnose derivative **12**, for example, underwent successive intramolecular rearrangements of the benzoyl- and *S*-methyl-groups to give carbonium ion **14** (Scheme 3), which on attack by fluoride from above the ring gave the 2-*S*-methylthio-α-L-fucopyranosyl fluoride dibenzoate **15** in 42% yield.[7] A series of acetal protected 3-thio-α-D-glucofuranoses **16** and related 3-thio-α-D-*ribo*-furanose derivatives have been generated as ligands



12 **13** **14** **15**

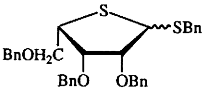
Reagents: i, DAST, CH_2Cl_2

Scheme 3



R^1, R^2 = H, H; Me, Me;

16



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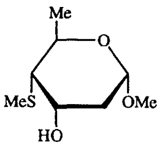
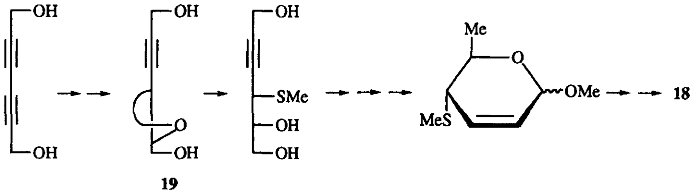


18

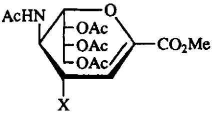
for metal-catalysed asymmetric synthesis.[8] The preparation of 2′,3′-dideoxynucleosides from 2-deoxy-D-ribose *via* 3-alkylthio intermediates is covered in Chapter 20.

The tribenzyl ether **17** of benzyl 1,4-dithio-L-lyxofuranoside has been obtained from D-ribose by a known procedure (see Vol. 26, Chapter 11, Ref.7 and Vol. 25, Chapter 11, Scheme 4).[9] Two new multi-step syntheses of methyl 2,6-dideoxy-4-methylthio-α-D-*ribo*-hexopyranoside [methyl 4-methylthiodigitoxoside (**18**)], a constituent of calicheamycins and esperamycins, used D-galactose[10] and D-fucal,[11] respectively, as starting materials, which allowed introduction of the sulfur substituent by nucleophilic displacement of a 4-*O*-sulfonate group by thiobenzoate. Alternatively, glycoside **18** has been obtained by asymmetric synthesis from propargylic alcohol dimer, with formation of epoxide **19** by Sharpless oxidation and its regioselective opening with sodium methanethiolate as key-steps, as indicated in Scheme 4.[11]

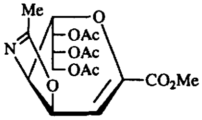


Scheme 4

The *S*-acetylthio group has been introduced at C-4 of unsaturated sialic acid derivatives, such as **20**, with retention of configuration by treatment with BF_3-etherate to form the oxazoline **22** which was opened by thioacetic acid to afford **21**.[12] The known unsaturated thiolactone dimethyl ether **23** has been converted, after a change of protecting groups, to the thioascorbic acid derivatives **24** (*threo*/*erythro* = 6:1) by aldol-like chain extension using 2-*t*-butyl dimethylsilyloxyacetaldehyde and butyl lithium.[13]



20 X = OAc
21 X = SAc



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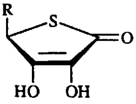
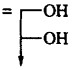
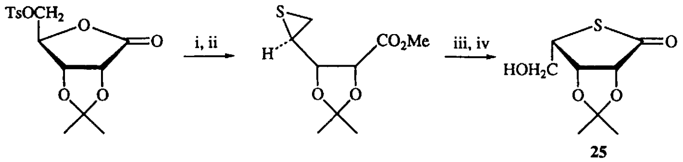


23 R = H
24 R =



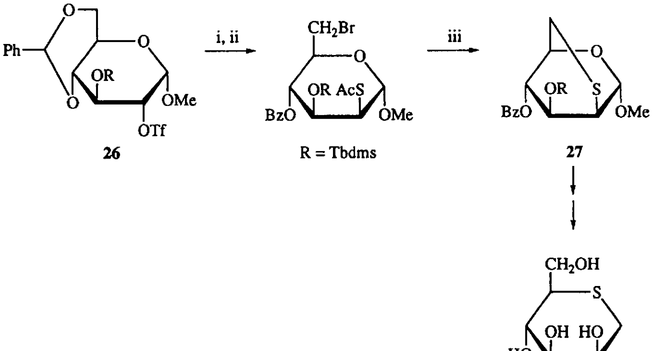
The first reported synthesis of aldopentono-1,4-thiolactone **25** is shown in Scheme 5. The D-*ribo*-isomer of **25** was similarly made from D-gulono-1,4-lactone.[14] The synthesis of 1-(5-thio-β-D-xylopyranosyl)-pyrimidine and-lumazine nucleosides is referred to in Chapter 20.



Reagents: i, NaOMe; ii, $(NH_2)_2CS$, MeOH; iii, KOAc, HOAc, DMF; iv, H_3O^+

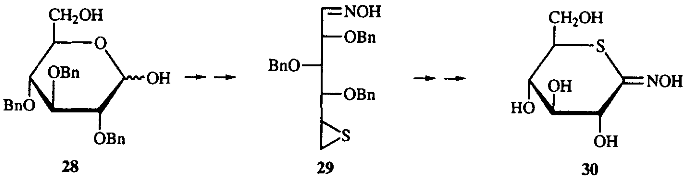
Scheme 5

The synthesis of thio-anhydroalditol **27**, an analogue of deoxymannojirimycin, from D-glucose derivative **26**, outlined in Scheme 6, involved displacement of sulfonate by a sulfur nucleophile with inversion of configuration at C-2 followed by intramolecular displacement of bromide by the sulfur at C-6 which then became C-1 of the end product **27**.[15] 5-Thio-D-gluconohydroximo-1,5-lactone **30** via acyclic intermediates, *e.g.*, thiirane oxime **29** (Scheme 7), for evaluation as β-glycosidase inhibitor.[16] A range of *O*-protected 5-thio-D-hexopyranoses with a variety of substituents at the anomeric centre, obtained by standard methods, have been oxidized with MCPBA or BSNPO [2-benzenesulfonyl-3-*m*-nitrophenyloxaziridine] to the corresponding sulfoxides to examine the influence of the anomeric substituent on the axial/equatorial product ratio (see Vol. 24, Chapter 11, Ref. 23).[17] 5-Thio-α-D-*ribo*-hexofuranos-3-ulose 1,2:5,6-diacetonide **31** has been transformed to 3-amino-3-deoxy-5-thio-D-allose hydrochloride (**33**) *via* oxime **32**.[18] A full paper on the formation of



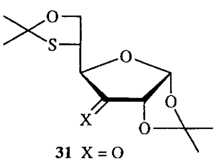
Reagents: i, KSAc, DMF; ii, DBS, CCl_4; iii, NaOMe

Scheme 6

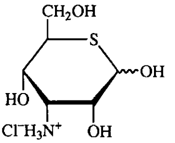


Scheme 7

hexahydrothiophene derivatives, *e.g.*, **34**, by treatment of D-mannitol 2,5-bis-dithiocarbonate diacetals with tributyltin hydride has been published (see Vol. 22, Chapter 11, Ref. 8).[19] The reaction of methyl 5-thio-3-*O*-tosyl-α-D-glucopyranose and its triacetate with sodium azide is covered in Chapter 9.



31 X = O
32 X = NOH



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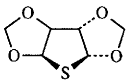
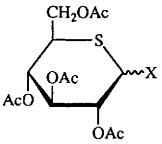
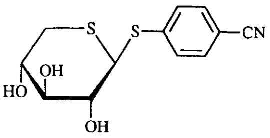


34

A short synthesis of 1,5-dithio-β-D-glucopyranose tetraacetate (**36**) involved exposure of the known bromide **35** to thiourea in butan-2-one. Compound **36** was converted to a number of biologically interesting thioglycosides, *e.g.*, 5-thio-analogues of glucosinolates.[20] The 2- and 4-monomethyl ethers and the 4-deoxy-4-fluoro derivative of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside (**37**) (see *Chem. Abstr.* 1991, **114**, 122 964) have been prepared in a quest for orally active antithrombotic agents.[21]



35 X = Br
36 X = β-SH



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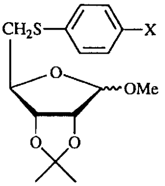
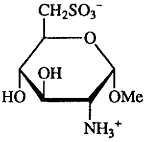


X = F, Cl, Br, or I
38

Substituted phenylsulfides **38**[22] and sulfonate **39**[23] have been obtained from the corresponding primary tosylates by displacement with sulfur nucleophiles followed, in the latter case, by oxidation and deprotection, and the 6-thiocyanate **40**, a new compound, has been prepared from the corresponding bromide during a search for a glucose derivative with fully resolved ^{2}H-n.m.r. spectrum.[24] Thiofunctionalization by use of the Mitsunobu method has been reported. The reaction proceeded readily at the primary position of several methyl glycosides, but attempts to introduce a secondary thio-group failed in all cases except in the preparation of the 3,6-dithio-sugar **41** from



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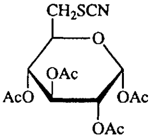

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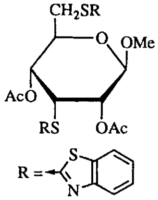
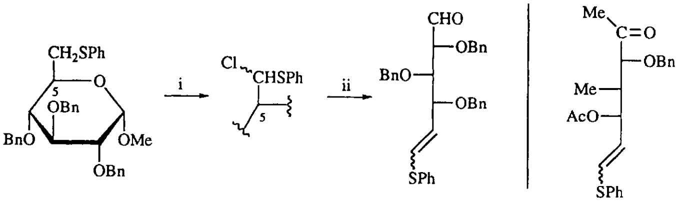


41

methyl β-D-glucopyranoside. Conversion of the thio-sugars thus prepared to deoxy-sugars is covered in Chapter 12.[25]

The fragmentation of α-chlorothioethers has been studied by use of the model reaction shown in Scheme 8, before application to the synthesis of vinyl thioether **42**, a segment of trienomycin and mycotrienin macrolide antibiotics.[26]

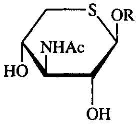


42

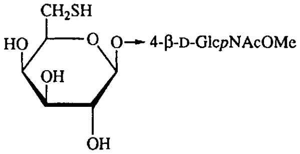
Reagents: i, NCS, CCl_4; ii, Zn/Ag–graphite, THF

Scheme 8

The galactosyl transferase-catalysed synthesis of disaccharide **44** from 5-thiosugar **43** and UDP-galactose in 40% yield has been reported.[27] A nitrosugar route to 2-thiosophorose and its calcium ion promoted epimerization to 2-thioepisophorose are covered in Chapter 3. The acceptor-analogue inhibitor **45** of (2→6)-α-D-sialyltransferase has been prepared from methyl 2-acetamido-2-deoxy-α-lactoside by a sequence of standard reactions.[28] Good yields and high selectivity have been achieved in the formation of 1,2-*cis*-configurated glycosides of 5-thioaldopyranoses, such as disaccharide **46**, by use of the trichloroacetimidate method.[29] The synthesis of sulfur-linked disaccharides with fucosyl non-reducing end groups is covered in Chapter 3.



43 R = H
44 R = β-D-Gal*p*



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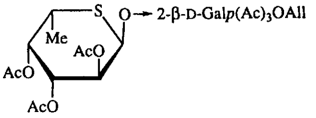

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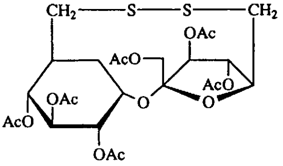
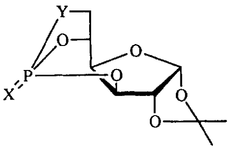


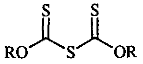
47

6,6′-Dithiosucrose, available by adaptation of a known synthetic method (see Vol.22, Chapter 11, Ref.12), has been converted to the cyclic disulfide **47** by atmospheric oxidation (in the presence of sodium carbonate) and subsequent acetylation. The redox reaction, dithiol ⇌ disulfide, was studied in order to examine the conformations of disaccharides in solution.[30]

The rearrangement of the glucofuranose bicyclothiophosphate derivative **48** to the 6-thioglucose bicyclophosphate **49** on exposure to lithium bromide in dioxane has been reported.[31] Irradiation with visible light caused the transformation of xanthic anhydrides **50** to xanthates **51** in 70-80% yield by a radical chain reaction.[32]



48 X = S, Y = O
49 X = O, Y = S



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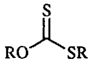
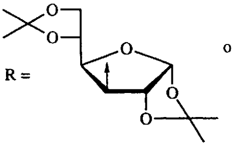


51

R =



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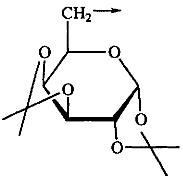

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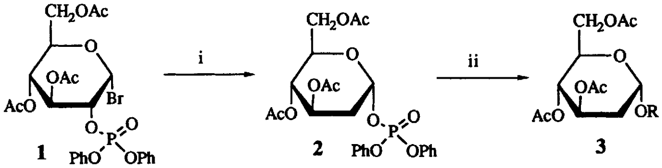
12

Deoxy-sugars

Barton's group have given full accounts of earlier brief reports (see Vols. 25 and 26) on the use of phenylsilane, triphenylsilane and triethylsilane,[1] and of diphenylsilane[2] as hydrogen sources in free radical deoxygenations of thionocarbonates, with particular emphasis on the applications of these methods for the preparation of deoxysugars.

In an interesting approach to glycosides of 2-deoxysugars, Giese and coworkers have reported that treatment of the 2-*O*-phosphoryl glycosyl bromide **1** (Scheme 1) with Bu_3SnH under conditions of photochemical initiation gives the product **2** of free radical rearrangement, in the same way as was reported earlier from the same laboratory for 2-*O*-acyl glycosyl bromides (Vol. 22, p. 129). The anomeric phosphate **2** could be used, with various partially-protected sugars ROH, to give disaccharides **3** in good yield and with moderate α-selectivity.[3] It has been shown that addition of methanol to tri-*O*-acetyl-D-glucal using triphenylphosphonium bromide as catalyst can give **3** (R = Me) in up to 82% yield and with high α-selectivity, and this reaction was used in a large scale route to the lactone unit of the mevinic acids.[4] A full account has appeared of an earlier report (Vol. 25, p. 8) describing the *threo*-selective reaction of free sugars with allyl bromide and tin metal in aqueous media, and the subsequent ozonolysis of the allyl adducts to give 2-deoxyaldoses.[5] The stereochemistry of reduction of various 2-deoxy-2-haloglycopyranoses with Bu_3SnD has been investigated in terms of the influence of steric and conformational effects; both the sizes and orientations of the ring substituents were important in determining the stereochemical outcomes of the reactions.[6]

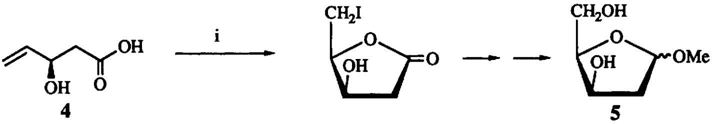


Reagents: i, Bu_3SnH, hν; ii, ROH, $Mg(ClO_4)_2$, ether

Scheme 1

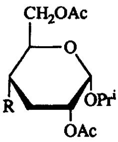
The hydroxyacid **4** (Scheme 2) can be prepared by an asymmetric aldol condensation; an efficient iodolactonization can then be used to make the 2-deoxy-D-pentofuranosides **5**.[7]

The 3-deoxyglycoside **6** has been obtained by reduction of the corresponding 2,3-unsaturated compound, and the 3,4-dideoxy-compound **7** by reduction of the known 3,4-ene-2-one.[8] The 3-deoxyglycoside **8** and 4-deoxycompound **9** have both been prepared from *n*-octyl β-D-galactopyranoside by sequences involving respectively regioselective allylation and benzylation of the stannylene derivative at O-3. Fucosylation of both of these compounds at O-2 gave deoxy-analogues of α-L-Fuc-(1→2)-β-D-Gal-O-*n*-Oct, and the analogue deoxygenated at C-6 of the galactose unit was also prepared.[9] Two simple synthetic routes to 4-deoxy-D-*lyxo*-hexose have been developed, starting from levoglucosenone.[10] Both 2-acetamido-2,4-dideoxy-D-*xylo*-hexopyranose (**10**) and its L-enantiomer, have been prepared, ultimately from *p*-benzoquinone, via racemic intermediates, resolution being effected by treatment of the allyl β-glycosides with hexosaminidase, which hydrolysed only the β-D-glycoside to give **10**.[11] The preparation of some 4-deoxy-D-hexopyranosyl 1-phosphates is discussed in Chapter 7, and a new route to methyl 3-amino-3,4-dideoxy-β-D-*xylo*-hexopyranoside is mentioned in Chapter 9.

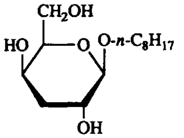


Reagents: i, I_2, $NaHCO_3$, THF

Scheme 2



6, R = OAc
7, R = H



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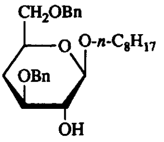

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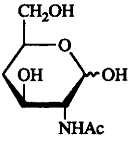

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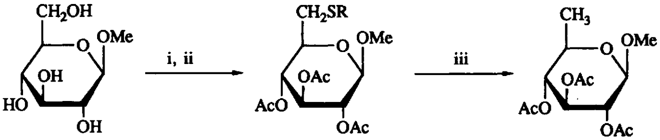
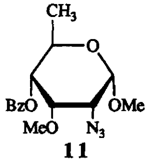


Reagents: i, Ph_3P, DEAD, 2-mercaptobenzothiazole, Py; ii, Ac_2O; iii, Ra Ni or Bu_3SnH, AIBN, C_6H_6

Scheme 3

A new general route to 6-deoxyglycopyranosides, involving the introduction of a sulfur-containing group by Mitsunobu chemistry, is illustrated by the example in Scheme 3 (R = benzothiazol-2-yl). In this particular case, use of 2 equivalents of each reagent led to an additional substitution (with inversion) at C-3, and, after desulfurization, to the 3,6-dideoxysugar, but in other cases examined, including some disaccharides, substitution only proved possible at the primary positions.[12] A new synthesis of 1,2,3,4-tetra-*O*-acetyl-α-D-fucopyranose involves reduction of the tosylate of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose using $NaBH_4$ in DMSO, and subsequent acetolysis.[13] Methyl 6-deoxy-α-D-glucopyranoside has been made with a single deuterium label at C-6 by treatment of the 6-bromo-compound with $NaBD_4$ in D_2O in the presence of $PdCl_2$,[14] and the 2-azido-2,6-dideoxycompound **11** has been prepared by reduction of the 6-

bromo-precursor with sodium cyanoborohydride in HMPA, in the presence of NaI.[15] For a route to the hydroxyamino sugar of the calicheamycins involving reduction of a 6-bromo function, see Chapter 10.



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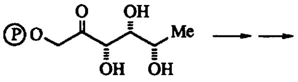

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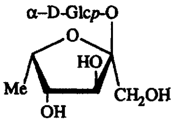
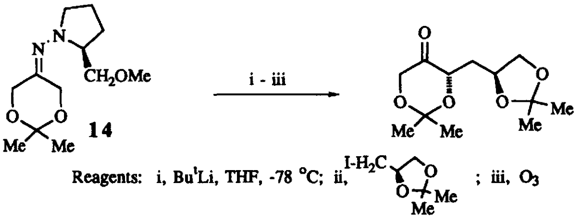


13

Condensation of (*S*)-lactaldehyde with dihydroxyacetone phosphate in the presence of fructose diphosphate aldolase gave the 6-deoxyketose phosphate **12**, and this, on treatment with acid phosphatase and then with sucrose synthase in the presence of UDPG, was converted into the 6-deoxy-L-sorbose disaccharide **13**.[16]

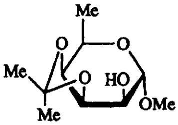
Enders' group have used their SAMP/RAMP methodology in an interesting *de novo* synthesis of deoxyketoses. An example of this approach is outlined in Scheme 4, and two successive alkylations can be carried out to give α,α'-disubstituted derivatives of the hydrazone **14** (or its enantiomer).[17]



Reagents: i, $\mathrm{Bu^tLi}$, THF, -78 °C; ii, ; iii, O_3

Scheme 4

There have been several reports concerning the synthesis of 2,6-dideoxyhexoses. New routes to methyl 2,6-dideoxy-α-D-*arabino*- and α-D-*lyxo*-hexopyranosides have been described, involving selective deoxygenation at C-2 in 6-deoxy precursors. In the D-*lyxo*-series, the high-yielding formation of acetal **15** by rearrangement of the 2,3-*O*-isopropylidene derivative was particularly useful in gaining access to a suitable material for deoxygenation.[18] In a novel approach to the total synthesis of racemic 2,6-dideoxysugars, the enone **16** was prepared by cycloaddition of butyl vinyl ether to acetyl ketene, generated *in situ*; stereoselective DIBAL reduction and hydroboration then gave the DL-olivoside **17**, and other configurations were accessible by inversion as



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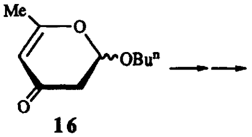

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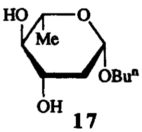
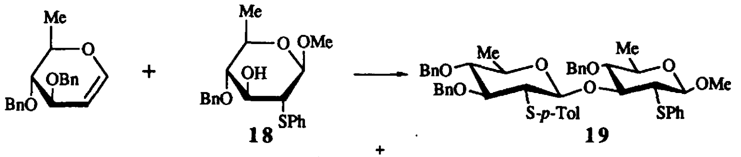


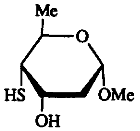
17

appropriate at C-3, at C-4, or at both centres.[19] A key step in a stereoselective approach to the C', D'-disaccharide of aureolic acid is shown in Scheme 5, the coupled product **19** being desulfurized with Raney nickel. The precursor **18** was itself made from a glycal in a similar fashion.[20]



Reagent: i, $p\text{-Tol-}\overset{+}{\mathrm{S}}(\mathrm{S}\text{-}p\text{-Tol})_2\ \mathrm{SbCl_6^-}$

Scheme 5



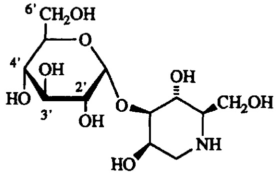
20

In a route to the calicheamicin constituent **20** from D-galactose, C-6 was deoxygenated by hydride reduction of a tosylate, and C-2 by reductive opening of an epoxide.[21]

The trisaccharide component of the antibiotic gonefromycin has been shown to consist of two molecules of 2,6-dideoxy-3-*O*-methyl-L-*lyxo*-hexose, separated by one of the L-*ribo*-isomer.[22]

A series of communications have reported details of the biosynthesis of ascarylose (3,6-dideoxy-L-*arabino*-hexopyranose), as its cytidine diphosphate conjugate, in *Yersinia pseudotuberculosis*, where ascarylose occurs in the *O*-antigen.[23-26]

3-*O*-(α-D-Glucopyranosyl)-deoxymannojirimycin (**21**) is a good inhibitor of the Golgi membrane endomannosidase which releases the disaccharide α-D-Glc-(1→3)-D-Man from immature *N*-glycoproteins. All analogues of **21** monodeoxygenated in the glucose unit have now been prepared, and it was found that the 3'- and 4'-hydroxy groups were more essential to maintain inhibitory potency than were those at the 2'-and 6'-positions.[27]



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The 6'-deoxyanalogue of β-D-Gal-(1→4)-β-D-GlcNAc has been prepared and found to inhibit the enzymic transfer of sialic acid to the disaccharide.[28] There has been a report on specifically deoxygenated derivatives of 2-(trimethylsilyl)ethyl β-lactoside (see Vol. 26 for similar derivatives of methyl β-lactoside).[29] Bundle's laboratory has reported the synthesis of the 4-, 6-, and 4'-deoxy-derivatives of the disaccharide α-L-Rha-(1→3)-β-D-GlcNAc-OMe, a component of the *Shigella flexneri* Y polysaccharide antigen,[30] and this work was extended to the trisaccharide level by the preparation of the 4-, 6-, 4'-, 3"- and 4"-deoxy-derivatives, and the 4',4"- and 3",4'-dideoxy-derivatives, of α-L-Rha-(1→3)-α-L-Rha-(1→3)-β-D-GlcNAc-OMe.[31]

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13
Unsaturated Derivatives

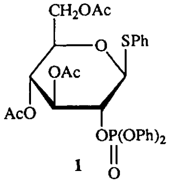
1 Glycals

A paper on the use of polarized π frontier orbital theory for correctly predicting the selectivities of protonation and sulfenylation of pyranoid and furanoid glycals has appeared.[1] The cycloaddition adducts formed by the high pressure addition of tosyl isocyanate to glycal acetates (see Chmielewski *et al.*, Vol. 19, p. 131) have been shown to revert on heating to 60°-70°.[2] The rate of retro-addition increases with rising temperatures and increasing solvent polarity.

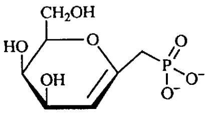
An alternative high yielding route to acylated pyranoid glycals involves reductive elimination of acylated glycosyl bromides with zinc in ethyl acetate containing 1-methylimidazole (aprotic conditions).[3] The treatment of sugars protected other than at C-1 with ArSSAr and trialkylphosphanes affords the corresponding aryl thioglycosides which on further treatment with potassium graphite laminate afford good yields of glycals.[4] The process is applicable to both furanoid and pyranoid sugars.

In an attempt to convert the 2-*O*-diphenylphosphoryl-1-thiopyranoside **1** into the corresponding 2-deoxy-1-*O*-diphenylphosphoryl compound by way of a β-(phosphonooxy) alkyl radical rearrangement, induced by treating **1** with tributyltin hydride and AIBN, the only product obtained was tri-*O*-acetyl-D-glucal.[5] However, see Chapter 12, ref 3 for a successful approach utilizing a light-induced reaction on a glycosyl bromide.

The preparation of phosphonate derivatives **2** and **3**, made as transition state analogues for reactions of β-galactosyl transferase of bovine milk, have been reported using tri-*O*-acetyl-1-*C*-formyl-D-galactal as the key intermediate.[6]



1



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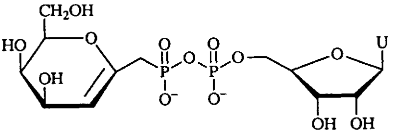


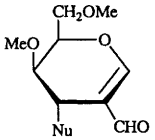
3

The displacement of an allylic methoxy group from 1,5-anhydro-2-deoxy-2-formyl-3,4,6-tri-*O*-methyl-D-*lyxo*-hex-1-enitol with various nucleophiles in the presence of boron trifluoride etherate to afford D-*xylo* derivative **4** has been described.[7] (See Vol. 25, p. 151, ref. 5 and Vol. 26, p. 148, ref. 8). Similar reactions using 1,5-*arabino*-hex-1-enitol analogues afford both *ribo*- and *arabino*-products.

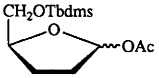
The preparation of 1,5-anhydro-2-deoxy-3-*O*-(α-D-glucopyranosyl)-D-*arabino*-hex-1-enitol as an inhibitor of golgi membrane *endo*-α-D-mannosidase which releases α-D-Glc(1→3)-D-Man has been reported.[8]

The synthesis of tributylstannylglycals by treating glycals with *t*-butyllithium then tributyltin chloride is successful when the O-3 is unsubstituted; otherwise furans are formed. However, Scheme 1 shows how glycal phenyl sulfones with O-3 substituents can be converted to the *C*-stannyl analogues, useful for preparing 1-*C*-arylglycals.[9]

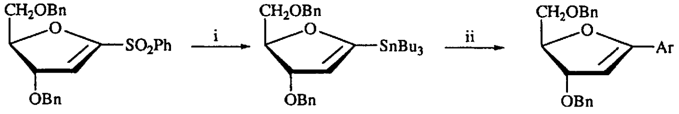
Flash vacuum pyrolysis of the glycosyl acetate **5** affords a high yield of the corresponding glycal.[10]



4 Nu = OMe, OEt, OBn, or SPh



5

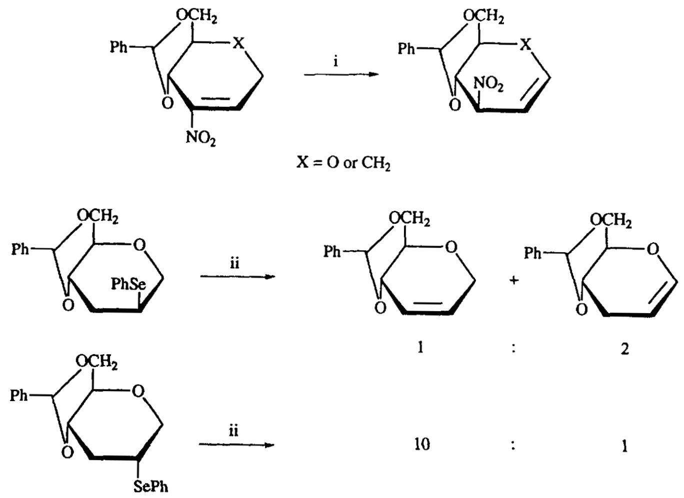


Reagents: i, Bu$_3$SnH, AIBN; ii, ArI, Pd(OAc)$_2$, AsPh$_3$

Scheme 1

Tri-*O*-acetyl-D-glucal has been transformed into the novel (2Z,4E)-1,3,6-triacetoxyhexa-2,4-diene as a useful Diels-Alder diene by initial Perlin transformation (*Carbohydr. Res.*, 1975, **42**, 267) and successive treatment with DBU, sodium borohydride and acetic anhydride in pyridine.[11]

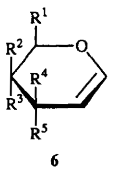
Rearrangement and elimination reactions on nitro-olefins and phenylseleno sugars have been performed to study the effects of substituted *O*-atoms on the rates and acidities of various hydrogen atoms (Scheme 2).[12] (See Vol. 25, p. 153, ref. 11 for related work). Thus, as shown in the scheme, the double bond migration from C2→C1 in the nitro-olefin was found to be faster when X = O than when X = CH$_2$. The authors concluded from their experiments that the orientation of the nonbonding electrons on O can suppress or enhance the hydrogen acidities and therefore play a vital role.



Reagents: i, Et_3N; ii, H_2O_2

Scheme 2

Various glycals, **6** can be transformed by oxidative double bond cleavage into aldehydo formates **7** with ozone which are useful precursors of β-lactam antibiotics.[13] (See also Chapter 16 for a similar process to produce ester formates.)



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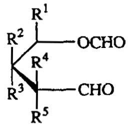
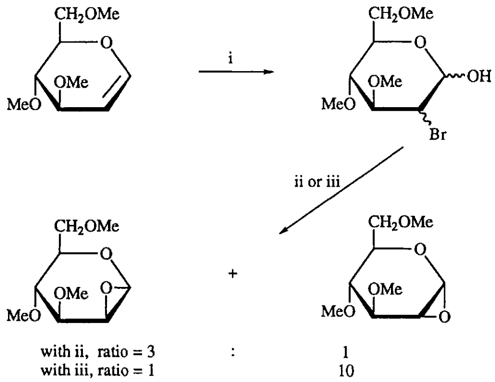


7

$R^1 = CH_2OBn, R^2 = R^5 = H, R^3 = R^4 = OBn$
$R^1 = CH_2OTr, R^2 = R^5 = H, R^3 = R^4 = OBn$
$R^1 = R^2 = R^4 = H, R^3 = R^5 = OBn$

A new stereoselective synthesis of 1,2-anhydro-sugars from glycals has been reported (Scheme 3).[14] Although little selectivity is observed in the initial bromohydrin formation, the resulting anhydro bond forming step using metal hydrides is selective. These latter observations were attributed to interconversion of the bromides prior to cyclization and modification of the cyclization step by the metals.



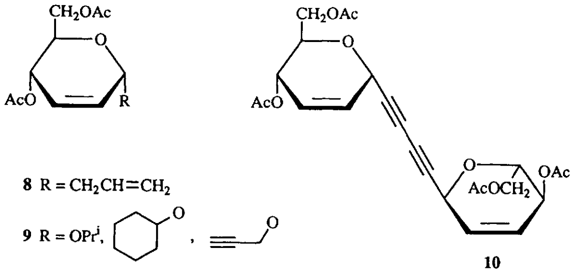
Reagents: i, *N*-Bromoacetamide, H_2O; ii, NaH; iii, KH, 18-crown-6

Scheme 3

Methanol can be added to tri-*O*-acetyl-D-glucal under catalysis with triphenylphosphonium bromide to give the corresponding 2-deoxyglycoside with high α-selectivity. By adding sodium methoxide to the same pot followed by 6-*O*-tritylation, a highly crystalline product in multikilogram quantities can be obtained.[15]

Several methods for preparing 2,3-unsaturated glycosides from glycals have appeared. Thus tri-*O*-acetyl-D-glucal was converted to the *C*-allyl glycoside **8** on treatment with allyltrimethylsilane in the presence of a neutral activator, DDQ with high α-selectivity.[16] In a similar way, glycals are converted into a wide range of *O*-glycosides such as **9** by treatment with alcohols and DDQ.[17] The preparation of acetylenic *C*-glycoside **10** has been achieved by coupling 1,4-bis(trimethylsilyl)-1,3-butadiyne with tri-*O*-acetyl-D-glucal in the presence of tin (IV) chloride,[18] and the conversion of acetylated glycals with the Reformatsky reagent $^tBuO_2CCH_2ZnBr$ in the presence of trimethylsilyl triflate into unsaturated glycosides such as **11** has also been reported.[19]

The selective oxidation of the allylic alcohol group of glycals using palladium salts to produce 1,5-anhydro-2-deoxy-hex-1-eno-3-uloses is illustrated in Scheme 4.[20] When the starting glycal is D-galactal a mixture of C-4 epimers results, but no epimerization is seen in the case of D-glucal. Peracylated and per-benzylated glycals can also be oxidized to analogous hex-1-enopyran-3-ulose derivatives with the hypervalent iodine reagent, [hydroxy(tosyloxy)-iodo]benzene [21] or using *N*-bromosuccinimide with a catalytic amount of dibenzoyl peroxide in the presence of potassium carbonate.[22]

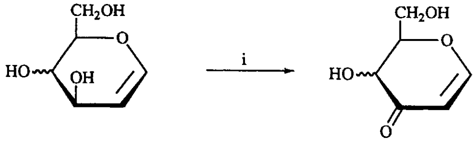


8 R = $CH_2CH{=}CH_2$

9 R = OPr^i,

11 R = $CH_2CO_2Bu^t$ (α : β mix.)

10



Reagents: i, PdX_2 (X = Cl or OAc), NaOAc, Bu_3N, DMF

Scheme 4

The use of lactal for preparing gangliosides is mentioned in Chapter 4 and the preparation of other *C*-glycosides and phenylseleno glycosides from glycals is mentioned in Chapter 3. The preparation of branched-chain unsaturated compounds from glycals is covered in Chapter 14 and the preparation of spiro-glycosides from glycals are referred to in Chapters 3 and 14. Glycals as starting materials for the preparation of nucleosides is covered in Chapter 20 and the use of a protected glycal for preparing the antibiotic monensin will be found in Chapter 24. The use of 6-*O*-(triisopropylsilyl)-D-glucal as a starting material for the synthesis of the protein kinase C inhibitor, staurosporine, is covered in Chapters 10 and 24.

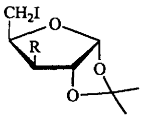
2 Other Unsaturated Derivatives

A review on the reactions of unsaturated monosaccharides with carbenes has appeared.[23]

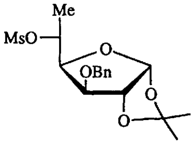
Full details of earlier papers (Vol. 22, p. 141, ref. 22 and Vol. 25, p. 208, ref. 52) on the preparation of 6-deoxy-5-enopyranosides by treating 6-bromo- or 6-tosyl-6-deoxy derivatives with DBU in DMSO have been reported.[24]

The effect of bulky substituents in the 3-position of furanose derivatives **12** on the zinc-induced ring opening to give 4,5-dideoxypent-4-enose compounds (see Vasella, Vol. 13, p. 122), has been studied.[25] With small substituents like fluorine and methoxy the usual ring opening occurs, but with benzyloxy or tosyloxy groups, only dehalogenation takes place. Interestingly, sugar substrates that contain differentially positioned azide groups always dehalogenate in preference to undergoing the dealkoxyhalogenation reaction.

Full details of an earlier paper (Vol. 23, p.40, ref. 178) on the synthesis of a range of difluoromethyl *C*-glycosides by difluoromethylenation of sugar lactones followed by hydrogenation of the glycosylidene derivatives has appeared.[26]



12 R = OMe, F, OBn, OTs



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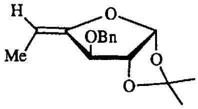
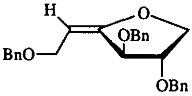


14



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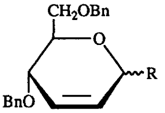


16 R = CH(NO$_2$)CO$_2$Et, C(NO$_2$)(CO$_2$Et)$_2$ CAc$_2$CO$_2$Me

Treatment of the α-D-*gluco* derivative **13** with tetra-*n*-butylammonium fluoride in DMF yielded the E-configured elimination product **14**, whereas the corresponding C-5 epimer of **13** (β-L-ido) gave the Z-isomer of **14** together with some 5,6-elimination product (a 5,6-dideoxy-5-ene).[27]

Treatment of the 1,5-ditriflate derivative of 2,3,4,6-tetra-*O*-benzyl-D-glucitol with tetra-*n*-butylammonium acetate gave unexpectedly the tetrahydrofuran derivative **15**.[28] (See Chapter 18 for a different course for the reaction when the corresponding 1,5-dimesylate or ditosylate is used.)

FAB mass spectra of alkali metal-cationized unsaturated *C*-glycosides such as **16** are useful for molecular weight determinations of these compounds.[29]

The synthesis of methyl 3,4,6-trideoxy-α-L-*glycero*-hex-3-eno-pyranosid-2-ulose from L-fucose and its use in the total synthesis of the antibiotic kalafungin has been disclosed.[30]

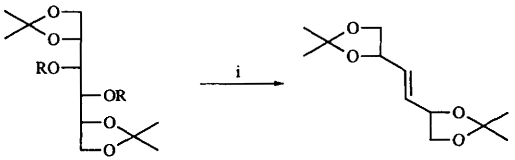
Dramatic rate increases for Tipson-Cohen eliminations applied to vicinal dimesylate or ditosylate sugar derivatives to produce 2,3- and 3,4-unsaturated hexose compounds have been brought about by the use of microwave fields.[31]

A full account of a preliminary communication (Vol.25, p. 144, and p. 158) on the deoxygenation of primary and secondary vicinal thionocarbonates or xanthates to give olefins on treatment with phenylsilane, triphenyl- or triethylsilane has appeared.[32]

Scheme 5 illustrates the ability of reagents with P-H bonds such as dialkylphosphites or hypophosphorous acid and its salts to act as radical reducing agents for the conversion of *vic*-diols to alkenes *via* thionoesters.[33] Dodecene added to the reaction mixture minimizes by-products.

Magnesium in methanol has been shown to cleave allylic alkoxy-*C* bonds with allylic rearrangement (Scheme 6).[34]

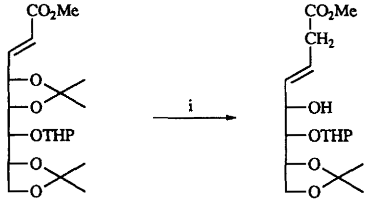
Addition of carboethoxymethylenetriphenylphosphorane to aldehyde **17**, in which the C-4 hydroxyl is unprotected, resulted in the Z-configurated product **18**.[35] On the other hand, if the C-4 hydroxyl group is protected as its Tbdms ether the E-isomer is formed.



R = C(=S)SMe

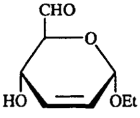
Reagents: i, H_3PO_2, Et_3N, AIBN, dodecene

Scheme 5

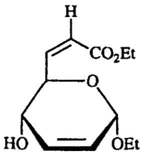


Reagents: i, Mg, MeOH

Scheme 6



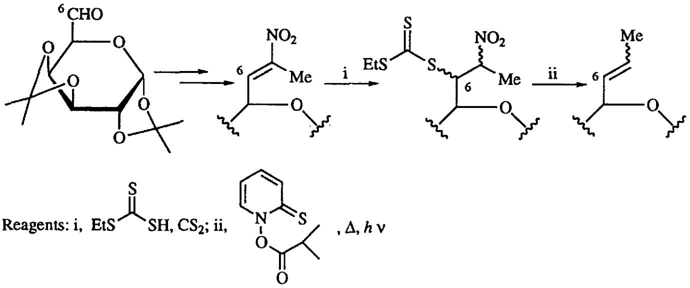
17



18

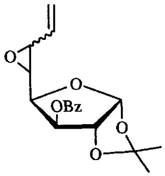
A new olefin synthesis is illustrated in Scheme 7. The key steps involve initial formation of a nitro-olefin, then conversion to a β-nitrotrithiocarbonate followed by radical induced formation of the olefin.[36]

The use of nitro-olefins as starting materials for conversion into nitro-epoxides is mentioned in Chapter 10. The preparation of 2,3-unsaturated nucleosides is covered in Chapter 20 and the synthesis of derivatives of 3-hydroxy-2(5H)-furanose (isotetronic acid) from benzylidene acetal derivatives of D-ribono-1,4-lactone is dealt with in Chapter 16. The addition of Grignard reagents to levoglucosenone and the oxypalladation reaction of 3-hydroxy-4,5-hexadienal to produce branched-chain unsaturated sugars are mentioned in Chapter 14.

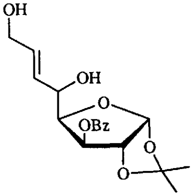


Scheme 7

The reaction of vinyl epoxide **19** with triphenylsilanol in the presence of a palladium catalyst affords, after de-silylation, olefin **20**.[37]

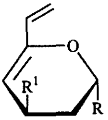


19

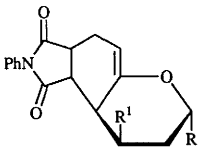


20

The diastereofacial selectivity of the Diels-Alder addition of *N*-phenylmaleimide to dienopyranoside **21** to give adduct **22** has been compared with the reaction of the carbocyclic analogue of **21**.[38] It was shown that the dienophile added to the face opposite to the methoxy group in all cases. See Chapter 24 for the Diels-Alder addition of dienes to levoglucosenone derivatives.



21 R = OMe, R^1 = H
or R = H, R^1 = OMe



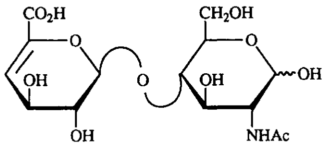
22 R = OMe, R^1 = H
or R = H, R^1 = OMe

The use of enzymes (heparinases) to digest heparin and heparan sulfate to produce unsaturated disaccharides such as **23** has been reported.[39]

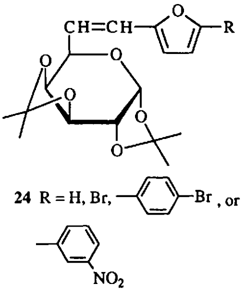
The preparation of the unsaturated derivatives **24** as a Z/E mixture by treatment of a 6-phosphorane with 2-furaldehyde and its derivatives has been disclosed.[40] The reaction was also applied to 6-phosphoranes of D-glucose and D-tagatose derivatives.

The synthesis of sugar-derived β-ketophosphonates and their use in Wittig-Horner reactions have been described (Scheme 8).[41]

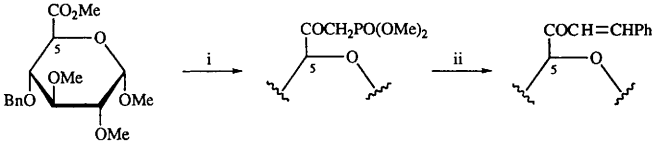
The ring contraction of 6,7-dideoxyhept-6-enopyranosides to produce cycloalkanes is mentioned in Chapter 18, and in Chapter 24 the preparation of the polyene antibiotic restricticin will be found. The synthesis of 2-chloro-4-nitrophenyl-*O*-(6-deoxy-α-D-*xylo*-hex-5-enopyranosyl)-(1→4)-tris[*O*-α-D-glucopyranosyl-(1→4)]-β-D-glucopyranoside as a substrate for human amylases is covered in Chapter 4.



23



24 R = H, Br, , or



Reagents: i, $LiCH_2PO(OMe)_2$; ii, PhCHO, $CsCO_3$, Pr^iOH

Scheme 8

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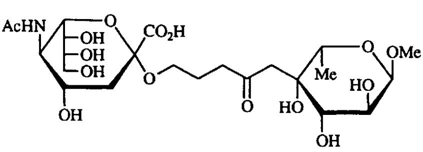
14
Branched-chain Sugars

1 Compounds with an R-C-O Branch

The synthesis of compound **1** as a novel mimic of the Sialyl Lewis X determinant has been achieved from the L-fucose-based ketophosphonate **2** which is made from methyl 2,3-di-*O*-benzoyl-α-L-fucopyranoside.[1]



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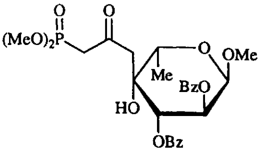
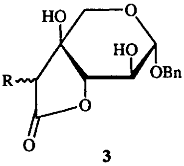


2

The preparations of β-oxy-γ-butyrolactones such as **3** (R= H or Me), by treating epoxyketone **4** with $LiCH_2CO_2{}^tBu$ or $LiCH(Me)CO_2{}^tBu$ followed by treatment with TFA, have been reported.[2]



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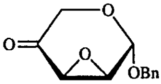
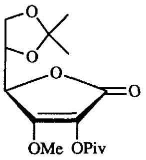


4

The *O*-methylated L-ascorbic derivative **5** can be transformed into the 2-*C*-methyl compound **6** by treatment with methyl iodide and lithium iodide *via* an oxygen-to-carbon methyl transfer process.[3]

The treatment of the *syn* or *anti*-α-alkoxy-β-hydroxy-β-methyl derivatives **7** or **8** with Raney nickel followed by hydrogenolysis over palladium afforded racemic 2-*C*-methyl-erythrono-1,4-lactone **9** and racemic 2-*C*-methyl-threono-1,4-lactone **10**, respectively.[4] The reactants **7** and **8** were prepared in a stereoselective fashion from aluminium triflate-mediated aldol reaction of ethyl pyruvate and (E) or (Z)-1-benzyloxy-2-ethylthio-2-trimethylsilyloxyethene respectively.



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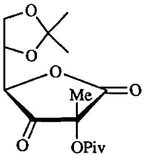

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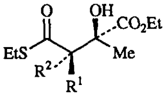
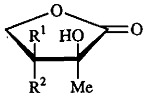
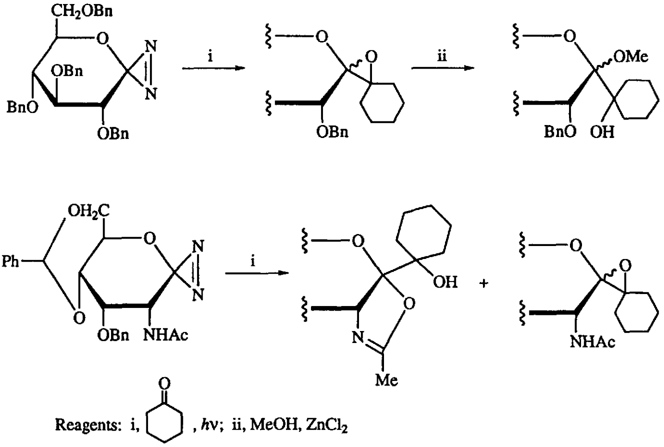


7 $R^1 = OBn, R^2 = H$
8 $R^1 = H, R^2 = OBn$



9 $R^1 = OH, R^2 = H$
10 $R^1 = H, R^2 = OH$

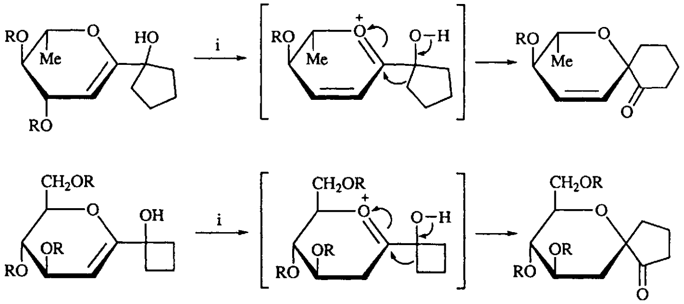
Glycosyl diazirines can be converted into spirooxiranes which can be further elaborated as shown in Scheme 1.[5] The Scheme also illustrates that diazirines with participating *N*-acetylamino groups in the 2-position can result in the formation of oxazolines.



Reagents: i, cyclohexanone, *hν*; ii, MeOH, $ZnCl_2$

Scheme 1

Glycals substituted at C-1 with a tertiary cyclic carbinol on treatment with camphorsulfonic acid undergo a Ferrier-rearrangement or pinacol-like rearrangement depending on the size of the cyclic carbinol ring (Scheme 2).[6] Thus with cyclopentanol derivatives the former rearrangement is operative with migration of the methylene carbon to the axial position of the pyran ring. In the case of cyclobutanol compounds pinacol-like products are formed.

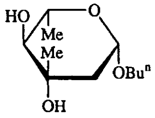


R = Tbdms
Reagents: i, Camphorsulfonic acid, CH_2Cl_2

Scheme 2

1,2-Addition of methylmagnesium bromide to levoglucosenone afforded 1,6-anhydro-3,4-dideoxy-2-*C*-methyl-β-D-*threo*-hex-3-enopyranose which was characterized as its 3,5-dinitrobenzoyl ester.[7] A similar result was also obtained using phenylmagnesium bromide.

The synthesis of racemic olivomycose derivative **11** has been achieved from dihydropyrone **12** by treatment with methylmagnesium bromide then borane-methyl sulfide complex followed by sodium perborate.[8] The dihydropyrone, in turn, was prepared by trapping the acyl ketene produced on pyrolysis of dioxinone **13** with butyl vinyl ether.



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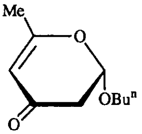

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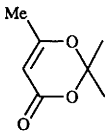
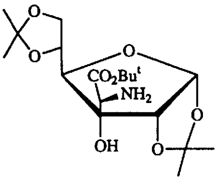


13

The reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose with the anion derived from *t*-butyl *N,N*-dibenzylaminoacetate followed by hydrogenolysis has led to the branched-chain sugar **14** as a single diastereomer.[9] The same starting material has been used to prepare the stannylmethyl compound **15** by addition of Ph_3SnCH_2Li.[10] Compound **15** was further elaborated to **16** by treatment with TFA and to **17** by reaction with iodine.

A formal synthesis of methyl D-mycarosides is illustrated in Scheme 3.[11] (The L-form of the dihydropyran intermediate has previously been converted into L-mycarose; *Chem. Ber.*, 1978, **111**, 3484).

The synthesis of the acetylenic branched-chain sugar **18** in 9 steps from D-xylose as an intermediate in the preparation of 10-membered dienediynes related to neocarzinostatin has been reported.[12]



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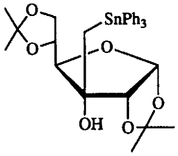

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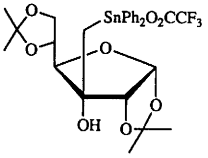

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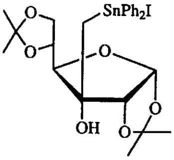

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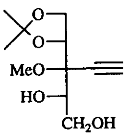

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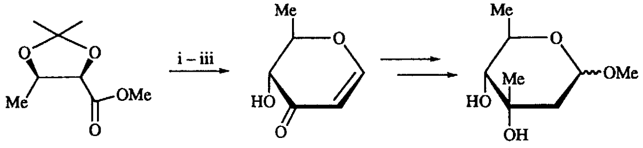
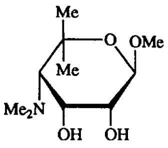


Reagents: i, Me_3SnCH_2Li; ii, HCO_2Me; iii, H_2SO_4

Scheme 3

A synthesis starting from (*R*)-2,3-epoxy-3-methyl-1-butanol has proved that the amino-sugar of the enediyne glycoside antibiotic C-1027 is the D-*ribo*-hexose compound **19**.[13]

The chemo-enzymatic synthesis of spyhydrofuran, **20** has been reported.[14] (See Vol. 26, p. 311, ref. 51 for preliminary report).



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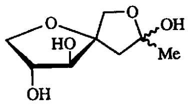
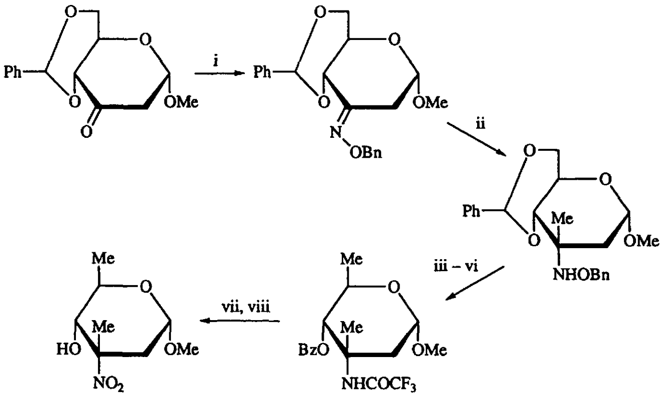


20

The synthesis of the trisaccharide of olivomycin A is covered in Chapter 4 and the synthesis of α-L-olivomycosides is mentioned in Chapter 3.

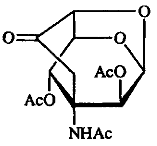
2 Compounds with an R-C-N Branch

Scheme 4 illustrates a new stereoselective route to methyl α-D-decilonitrose in which the key step involves the addition of a methyl group to an oxime ether using the *in situ* generated reagent "$MeCeCl_2$".[15] The same methodology has been applied using methyl 2,6-dideoxy-α,β-L-*erythro*-hexopyranosid-3-ulose as starting material leading to the formation of methyl α-L-decilonitrose and methyl α-L-avidinosamine.



Reagents: i, NH_2OBn; ii, MeLi, $CeCl_3$; iii, H_2, Pd/C; iv, $(CF_3CO)_2O$, py; v, NBS, $BaCO_3$; vi, Ra-Ni, H_2, Et_3N; vii, NaOMe/MeOH; viii, MCPBA

Scheme 4



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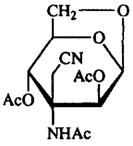
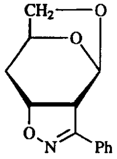


22

Two routes to the tricyclic ketone **21**, which represents the core structure of tetrodotoxin, have been reported.[16] The best route (8 steps) involves the preparation of the cyanomethylacetamido derivative **22** from which **21** is obtained by treatment with *t*-butylhyponitrite. The isolation of antibiotic AC6H which contains a 3-amino-*C*-3-methyl sugar is mentioned in Chapter 19.

3 Compounds with an R-C-H Branch

The regio- and face-selective cycloadditions of benzonitrile oxide and *C*, *N*-diphenylnitrone to racemic 6,8-dioxabicyclo[3.2.1]oct-3-ene have been studied.[17] In the former case the *exo*-isomers **23**(major) and **24**(minor) were formed, whereas in the latter case the *exo,endo*-adduct **25** is formed preferentially.



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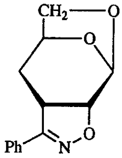

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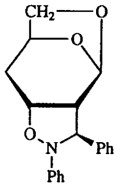
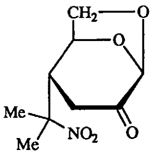


25

Regioselective Michael additions of nitroalkanes to levoglucosenone under cathodic electrolysis conditions have been reported and can be illustrated by the use of 2-nitropropane to give derivative **26**.[18]

Addition of nitromethane to levoglucosenone in the presence of tetramethylguanidine gives a 10:1 mixture of the bis adducts **27** and **28** *via* an initial 1:4 adduct.[19] When levoglucosenone is present in excess the main product is **29**. The use of levoglucosenone derivatives for making branched-chain sugars as intermediates for the synthesis of (+)-grandisol and (-)-tetrodotoxin is mentioned in Chapter 24.



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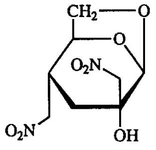

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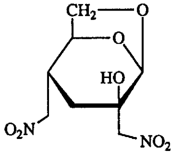

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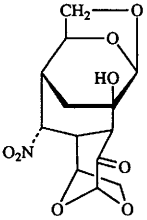
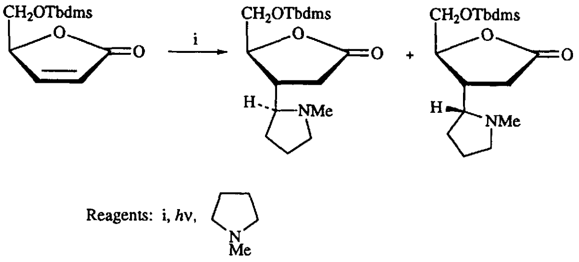


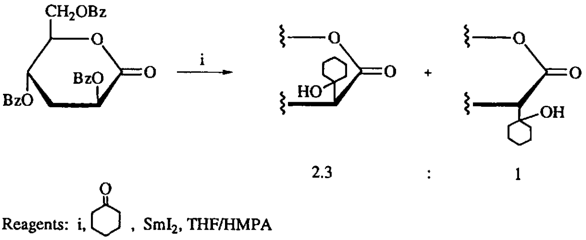
29

Scheme 5 illustrates the light-induced addition of *N*-methylpyrrolidine to butenolides.[20] By use of trimethylsilylpyrrolidine in a similar way, followed by base treatment, a 4-substituted 1-azabicyclo[3.3.0]octan-2-one, the ring skeleton of the alkaloid lindelofidine, can be obtained.

A direct deoxygenation/carbonyl addition procedure for preparing branched-chain lactones is depicted in Scheme 6.[21] Several other examples are given in the report and the reaction is also applicable to 1,4-lactone derivatives.



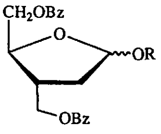
Scheme 5



Scheme 6

A new route to branched deoxypentofuranosides such as **30**, which involves photolysis of cyclobutanone derivatives like **31** in the presence of an alcohol (R= Me), has been reported.[22]

A synthesis of the branched-chain nucleoside analogue precursor **32** has been prepared by sequential treatment of dimethyl (2S)(3S)-2-allyl-3-hydroxyglutarate (prepared by yeast reduction of dimethyl 2-allyl-3-oxoglutarate) with ozone, acid resin and methanol then LAH.[23] Branched-chain nucleosides are covered in Chapter 20 and the preparation of *C*-linked glycosides and nucleosides are mentioned in Chapters 3 and 20 respectively.



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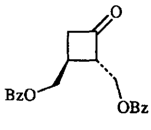

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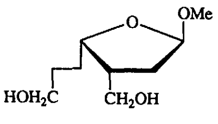
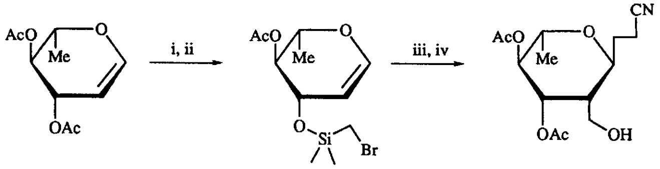


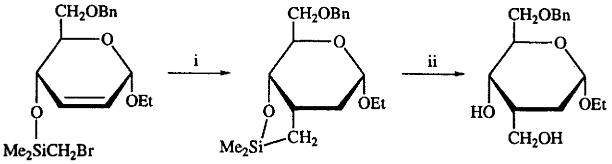
32

The stereoselective branching of L-rhamnal at C-1 and C-2 *via* a silicon tethered radical cyclization is illustrated in Scheme 7,[24] and allyl alcohol groups which are protected as their (bromomethyl)dimethylsilyl ethers undergo a radical-induced cyclization to give branched-chain sugars as shown in Scheme 8.[25]



Reagents: i, $Ba(OH)_2.8H_2O$; ii, $ClSiMe_2CH_2Br$, Et_3N; iii, Bu_3SnH, CN, AIBN; iv, Ac_2O, KF then MCPBA, KF

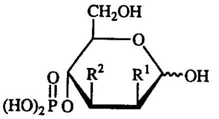
Scheme 7

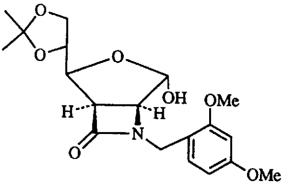


Reagents: i, Bu_3SnH, AIBN; ii, H_2O_2, Na_2CO_3, MeOH, THF

Scheme 8

A branched-chain analogue **33** of one of the two monosaccharide portions of lipid A has been synthesized from the known (M. Shiozaki Vol. 23, p. 100) β-lactam **34**.[26]





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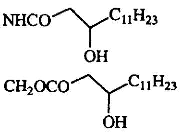
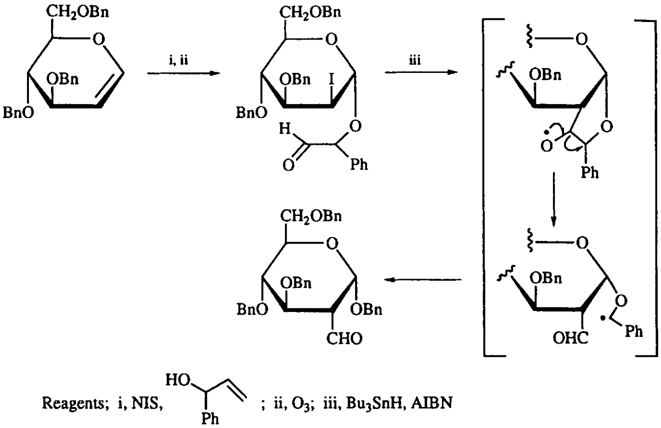


34

A route to alkyl-2-deoxy-2-*C*-formylglucopyranosides by a radical cyclization-fragmentation process is shown in Scheme 9.[27]

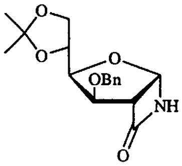
Stable bicyclic β-lactam products like **35** have been obtained by treating furanoid glycals with trichloroacetyl isocyanate.[28] (See also Chapter 14 in Vol. 25 and 26 for similar work).

The conversion of the 2-deoxy-2-iodo anhydride **36** into the 2-*C*-allyl compound **37** by treatment with allyltributyltin has been described; after de-acylation tricyclic product **38** was obtained by treatment with NBS and re-acetylation.[29]



Reagents; i, NIS, ; ii, O_3; iii, Bu_3SnH, AIBN

Scheme 9



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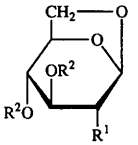
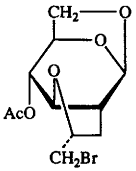
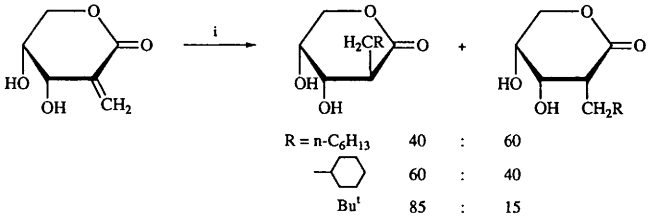


36 $R^1 = I, R^2 = Ac$
37 $R^1 = CH_2CH{=}CH_2, R^2 = Ac$



38

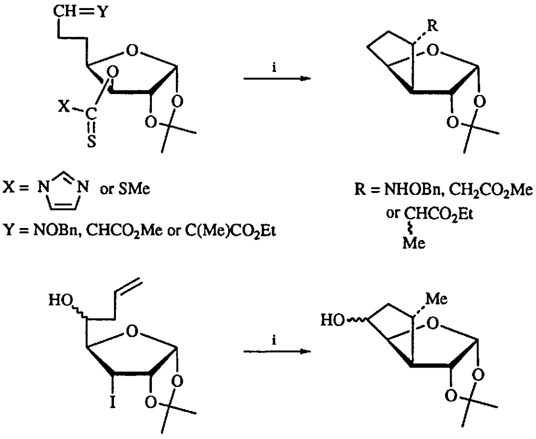
The stereoselectivity of radical additions to 2-*exo*-methylene lactones in the preparation of 2-*C*-alkyllactones by a process which is related to one used for the formation of *C*-disaccharides (Vol. 22, p. 38, ref. 188) has been studied (Scheme 10).[30]



Reagents: i, RI, Bu_3SnH, AIBN

Scheme 10

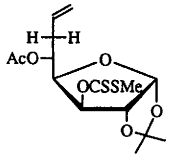
Full details of a preliminary communication (Vol. 26, p. 303) on the preparation of annulated furanoses by radical cyclization of diacetoneglucose-derived precursors have been reported (Scheme 11).[31] Several other examples are also covered in the paper.



Reagents: i, Bu_3SnH, AIBN

Scheme 11

Treatment of xanthate **39** with tributyltin hydride and AIBN affords the expected product **40** together with the unexpected *S*-methyl dithiocarbonate compound **41** which is thought to arise by radical isomerization.[32]



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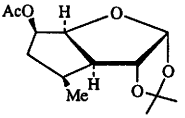

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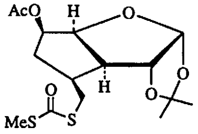
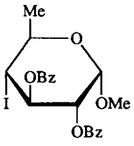


41

The direct introduction of a hydroxymethyl group into the pyranoid ring of the iodide **42** to give an analogue **43** (with very little *galacto*-derivative formed) of the B ring sugar of calicheamycin has been achieved using a one-pot procedure utilizing triphenylgermane, sodium cyanoborohydride and carbon monoxide under high pressure.[33]

1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose has been transformed in several steps into the *C*-3 furanoid lactone derivative **44** as a synthon for sesquiterpene lactones.[34]

The use of 2-chloromethyl-3-trimethylsilyl-1-propene to generate methylenetetrahydrofurans has been demonstrated by the conversion of aldehyde **45** into **46**.[35]



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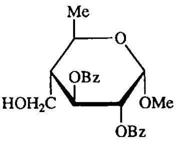

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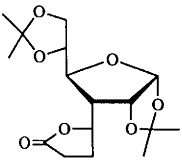

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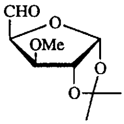

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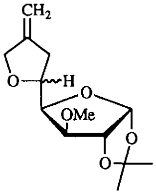
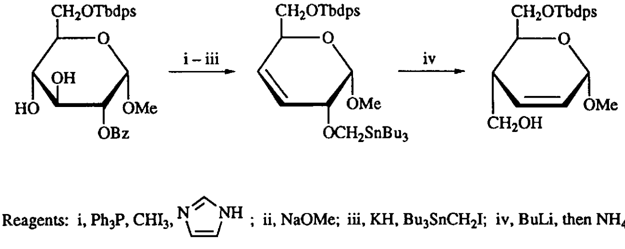


46

The preparation of a synthetically useful 4-*C*-hydroxymethyl-hex-2-enopyranoside by use of a Still-Wittig rearrangement of a stannyl ether has been described (Scheme 12).[36]



Reagents: i, Ph$_3$P, CHI$_3$, ; ii, NaOMe; iii, KH, Bu$_3$SnCH$_2$I; iv, BuLi, then NH$_4$Cl

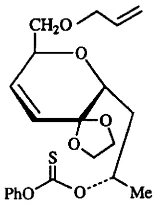
Scheme 12

Several products were observed, following radical generation from **47** with tributyltin hydride and AIBN, including derivatives **48** and **49**.[37]

An improved synthesis of the 3-*C*-cyano branched-chain sugar **50** has been achieved by treating nitromethyl-sugar **51** under the Garegg and Samuelsson conditions (triphenylphosphine, imidazole and iodine) for the conversion of a vicinal diol to an alkene.[38]

The boron trifluoride-induced aldol reaction between isopropylidene-D-glyceraldehyde and 2-(trimethylsilyloxy)furan followed by treatment with trimethylsilyl chloride and dimethylcopper lithium gave lactone **52**.[39] This compound was converted into 2,3-dideoxy-3-*C*-methyl-D-*manno*-heptose by treatment with DIBAL then hydrochloric acid, and into 2,3-dideoxy-2,3-di-*C*-methyl-D-

glycero-D-*galacto*-heptose by treatment first with lithium hexamethyldisilazane and methyl iodide then DIBAL and acid.



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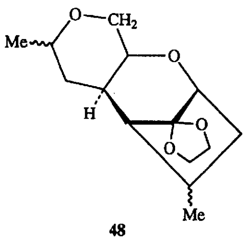

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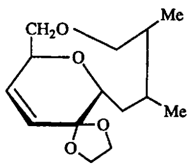

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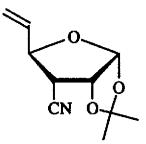

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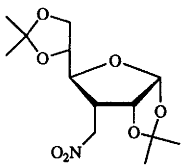

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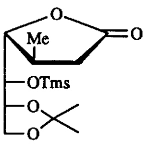
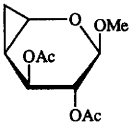


52

The cyclopropane derivative **53** has been prepared by reaction of either the diiodo compounds **54** or **55** with diethylamine in the presence of palladium on charcoal.[40] Other examples are given.



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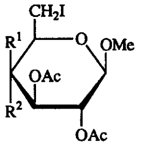


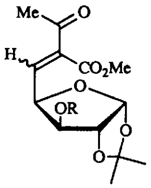
54 $R^1 = I, R^2 = H$
55 $R^1 = H, R^2 = I$

1,2-*O*-Isopropylidene-3-*O*-methyl (or benzyl)-α-D-*xylo*-pentodialdo-1,4-furanose, on treatment with methylacetoacetate, affords the α-acylacrylate **56** which undergoes a Michael addition with malononitrile to give the 2-amino-4H-pyran derivative **57**.[41]

The 1-deoxyhepturonolactone **58** can be *C*-methylated to give the methyllactone **59** which can be equilibrated with strong base to give mainly the isomer **60**.[42] This lactone has been further elaborated to give doubly branched heptano-1,4-lactones such as the L-*glycero*-L-*altro*-derivative **61** or the corresponding D-*glycero*-L-*altro* compound **62**.

Full details of earlier papers (Vol. 22, p. 137, ref. 9; p.140, ref. 18 and 19; p. 152, ref. 39 and

40) on the preparation of 2-and 3-*C*-formyl glycals and dieno-pyranoside **63** have appeared.[43] The synthesis of 9-alkylanthracyclinone by a stereocontrolled alkylation of 4-cyanofuranoses is covered in Chapter 24.



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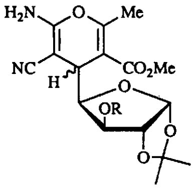

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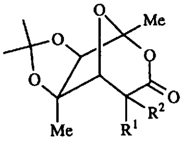
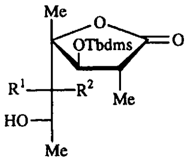
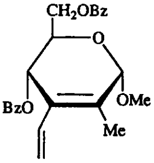


58 $R^1 = R^2 = H$
59 $R^1 = H, R^2 = Me$
60 $R^1 = Me, R^2 = H$



61 $R^1 = OH, R^2 = H$
62 $R^1 = H, R^2 = OH$



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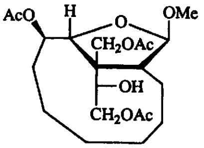
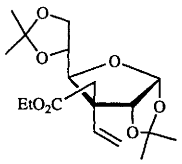


64

4 Compounds with an R-C-R or C=R branch

Expansions of a preliminary report (*Tetrahedron Lett.*, 1992, **33**, 8023) on the preparation of racemic bridged and branched methylfuranosides such as **64** from a non-carbohydrate source (an oxepin derivative) have appeared.[44]

The conversion of the known (K. Tadano *et al.*, Vol. 21, p. 142), doubly branched sugar **65** in 6 steps affords intermediate **66** which can undergo an off-template orthoester-Claisen rearrangement on treatment with methyl triethylorthoformate.[45] The product of the reaction, **67**, is obtained as a 1:3 mixture of (R)/(S) isomers.



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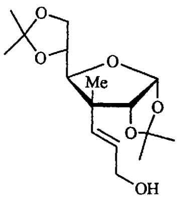

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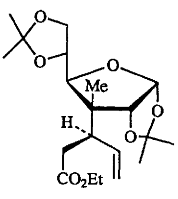
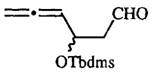


67

The intramolecular oxypalladation of 3-*t*-butyldimethylsilyloxy-4,5-hexadienal **68** (prepared in 7 steps from 1,3-propanediol) gave the 2-deoxy-*erythro*-furanoside **69** as a potential side-chain-branched nucleoside.[46]



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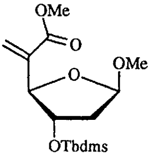
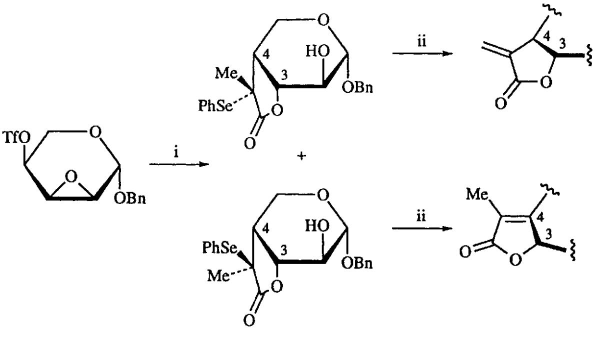


69

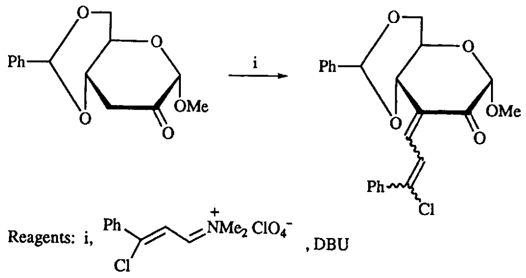
The synthesis of α-methylene-γ-butyrolactones from an epoxytriflate is illustrated in Scheme 13.[2] (See earlier this Chapter for the preparation of β-oxy-butyrolactones from epoxy ketones). The epimeric intermediate selenoderivatives eliminate in different ways as shown.



Reagents: i, LiCMe(SePh)CO_2Li–HMPA; ii, H_2O_2–AcOH

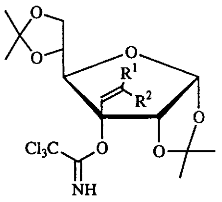
Scheme 13

The use of 3-chloro-3-phenylprop-2-enylidenedimethylyiminium perchlorate in the synthesis of *C*-3-exocyclic methylene derivatives has been reported (Scheme 14).[47]



Scheme 14

Overman rearrangement of the diacetoneglucose derived allylic trichloroacetimidate **70** by heating in xylene gives the branched-chain compound **71**.[48] Oxidative cleavage of the double bond with concomitant loss of the trichloroacetimidate affords access to D-amino acids.



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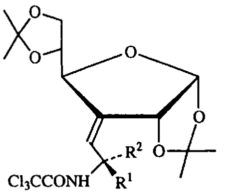
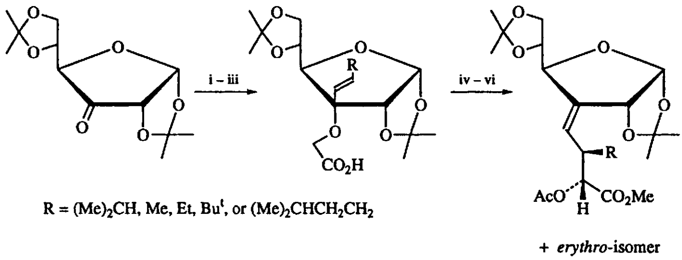


71

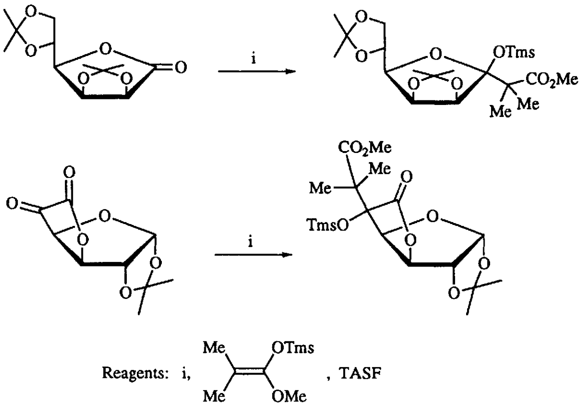
The same group have utilized a [2,3]-Wittig rearrangement for preparing exomethylene derivatives (Scheme 15), of which the double bond can be oxidatively cleaved to give 3-alkylmalic acids.[49]



Reagents: i, R—≡—Li; ii, LAH; iii, NaOH, DMSO, $BrCH_2CO_2Me$;
iv, LDA; v, CH_2N_2; vi, Ac_2O/Py

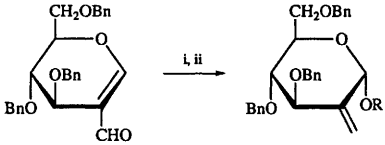
Scheme 15

Aldol-like additions using fluoride-mediated reaction of lactones or α-ketolactones with silyl ketene acetals, are depicted in Scheme 16.[50]



Scheme 16

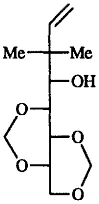
The synthesis of 2-*C*-methylene glycosides by a displacement process with allylic rearrangement of 2-*C*-acetoxymethylglycals has been reported (Scheme 17).[51] The synthesis of chiral pyrano[2,3-*b*][1]-benzopyrans from 2-*C*-acetoxymethylglycals is mentioned in Chapter 24.



Reagents: i, $NaBH_4$; ii, Ac_2O then ROH, $BF_3.OEt_2$

Scheme 17

The diastereoselective addition of tributylprenylstannane to 2,4:3,5-dimethylene-L-xylose affords the alcohol 72. This was further elaborated into the trioxadecalin part of mycalamide B, a member of the recently dicovered family of protein and DNA synthesis inhibitors.[52]



72

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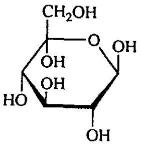
15

Aldosuloses, Dialdoses, and Diuloses

A review on naturally occurring dicarbonyl monosaccharides has included coverage of aspects of their metabolism, analysis, separation, identification and synthesis.[1]

The synthesis of sixteen methyl D-hexopyranosid-2-, 3-, or 4-ulosides by bis(tributyltin)-oxide - bromine oxidation of unprotected methyl glycosides has been described. Axial hydroxy groups in 1,2-*cis*-diols are preferentially oxidised by this system. The structures of some of the products were confirmed by independent syntheses involving oxidation of partially protected derivatives.[2] In related work some carbohydrate 1,2-diol dibutylstannylene acetals have been regiospecifically oxidized by NBS (rather than bromine) to give α-hydroxyketones. A ^{119}Sn n.m.r. study on the stannylene acetals has shown some of them to be dimers.[3]

High field ^{1}H and ^{13}C n.m.r. studies of aqueous solutions of D-*xylo*-hexos-5-ulose have provided evidence for the presence of at least six isomeric forms and one anhydro form. The dominant isomeric form was the β-pyranose **1** (67%) with the next most abundant form being the anhydro structure **2**.[4]



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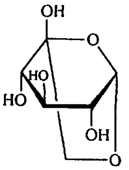

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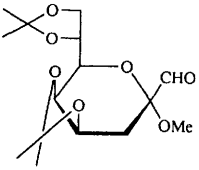

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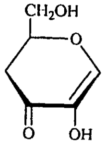

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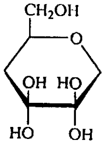

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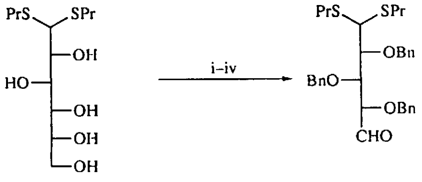
2-Substituted thiazoles, which on deprotection afford aldehydes, have been utilized in the synthesis of derivatives of dicarbonyl sugars such as the methyl glycoside **3**.[5] Various procedures for the selective oxidation of both protected and unprotected glycals at the allylic position are discussed in Chapter 13. The pyrone **4** and the diketone dihydrate **5** have been isolated from different *Ascomycetes*. The authors unexpectedly claim **4** and **5** as separate compounds, not interconverted on isolation and characterization.[6]

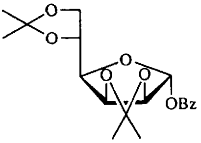
Some aldohexose dithioacetals have been selectively protected at *O*-2-3, and -4 and the 5,6-diol units have been cleaved with sodium periodate to afford pentodialdose derivatives. Thus the D-glucose dithioacetal **6** gave pentodialdose **7** (Scheme 1).[7] Ethereal periodic acid has been used to selectively cleave terminal *O*-isopropylidene groups and hence to cleave the released diols in a one pot process. Thus di-*O*-isopropylidene mannose derivative **8** gave the pentodialdose ester **9**.[8] Periodic acid has also been used to leave methyl α-D-xylopyranoside only at the C-2 - C-3 site.[9]



6 **7**

Reagents: i, $Me_2C(OMe)_2$, Pyridinium tosylate; ii, BnBr, NaH, DMF; iii, HOAc, H_2O; iv, $NaIO_4$

Scheme 1



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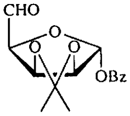

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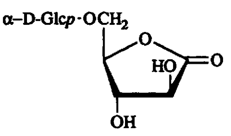
16

Sugar Acids and Lactones

1 Aldonic Acids and Aldonolactones

D-Gluconic acid can be prepared in nearly quantitative yield by the selective oxidation of glucose using a catalyst containing Pd, Pt and Bi on active charcoal,[1] and a continuous electrochemical oxidation of lactose to sodium lactobionate has been described.[2] In contrast with the corresponding oxidation of fructose, aerial oxidation of maltulose in the presence of potassium hydroxide gives a high yield of 5-*O*-α-D-glucopyranosyl-D-arabinonic acid, which can be lactonized to give **1**. Various transformations of the γ-lactone ring of **1** were also described, including the formation of the 2,3-dideoxy-2-ene by benzoylation followed by SmI_2 reduction, and the 2-*O*-benzoyl-3-deoxy-2-ene by benzoylation followed by treatment with DBU.[3] The *O*-formylated derivative **2** of methyl D-arabinonate has been obtained in 77% yield by ozonolysis of tri-*O*-acetyl-D-glucal, followed by work-up with Et_3N-Ac_2O.[4]



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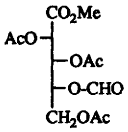

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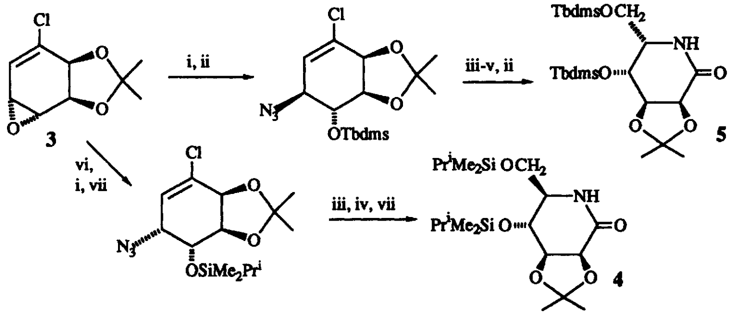
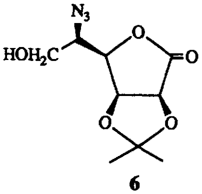


Reagents: i, NaN_3; ii, TbdmsCl; iii, O_3, MeOH, H_2O; iv, $NaBH_4$, $CeCl_3$; v, H_2, Pd/C; vi, LiCl; vii, Pr^iMe_2SiCl

Scheme 1

In an interesting approach to aldonolactones and lactams, the cyclohexene epoxide **3**, obtained from chlorobenzene using microbial dihydroxylation, was converted as outlined in Scheme 1 into the lactam **4** related to mannojirimycin, and into the epimer **5**;[5] the route to **4** could be adapted for the preparation of the azidolactone **6**, which was used as a precursor for (+)-kufunensine (Chapter 18).[6]



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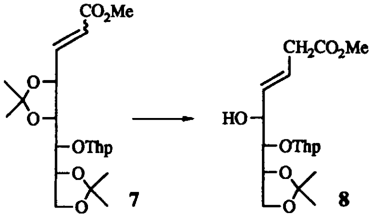
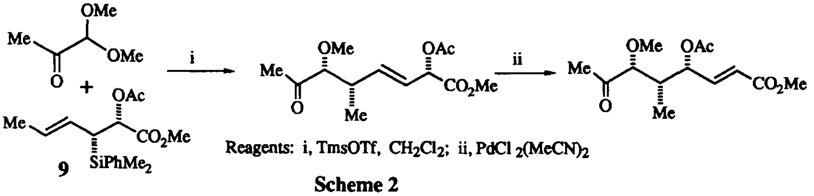


7 **8**

The α,β-unsaturated ester **7** can be transformed reductively into the β,γ-unsaturated system **8** in high yield using magnesium in methanol.[7] Reaction of the chiral crotyl silane **9** with various aldehydes and acetals offers a diastereoselective approach to branched β,γ-unsaturated esters, as in the example in Scheme 2, and, as indicated, stereospecific allylic rearrangement gave the α,β-unsaturated system. Similar reactions were also described using the C-2 epimer of **9**.[8]

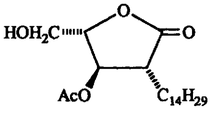


Reagents: i, TmsOTf, CH_2Cl_2; ii, $PdCl_2(MeCN)_2$

Scheme 2

A range of aldonamides with molecular weights and structures similar to sucrose have been synthesized by reaction of 1-amino-1-deoxy-D-glucitol or 2-amino-2-hydroxymethyl-1,3-propanediol with monosaccharide lactones,[9] whilst aldonamides have also been reported from interaction of aldonolactones with ethanolamine, diethanolamine, and related species.[10] Staudinger-type reactions between azides of type $RCH_2CH_2N_3$, where R is a perfluoroalkyl group, Ph_3P and lactobionic acid have given lactobionamides fluorinated in the amine unit, as non-ionic surfactants,[11] whilst interaction of diamines $H_2N(CH_2)_nNH_2$ (n = 6-12) with glucono-δ-lactone or lactobionic acid has given bis-gluconamides and bis-lactobionamides, also with surfactant activity.[12]

A series of papers from Marquez' laboratory describes conformationally restricted analogues of diacyclglycerol. Compounds such as **10** have been described, prepared from *R*-5-oxo-tetrahydrofuran-2-carboxylic acid, along with their enantiomers, made from D-ribono-lactone;[13] also reported were alkylidene systems such as **11**,[14] with **10** and **11** proving the most active in their class in inhibiting the binding of phorbol dibutyrate to protein kinase C. Molecular modelling suggested **12** as a good candidate for testing for binding to protein kinase C; it was synthesized from 5,6-*O*-isopropylidene-D-galactono-1,4-lactone by deoxygenations, and was indeed biologically active.[15]



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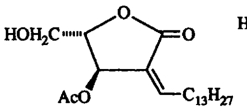

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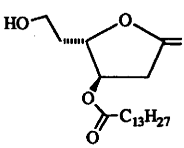
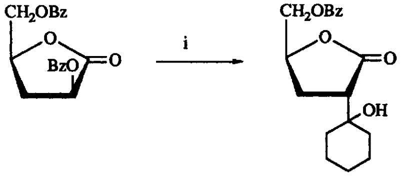


12

Treatment of 3-deoxy-aldonolactone esters with SmI_2 in the presence of a ketone causes serial deoxygenation and carbonyl addition, as in the example in Scheme 3; 1,5-lactone esters could be used equally well.[16] A paper describing a photochemical route to C-3 branched 2,3-dideoxy-aldonolactones is mentioned in Chapter 14.



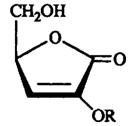
+ C-2 epimer (3.4:1)

Reagents: i, SmI_2,THF-HMPA, cyclohexanone

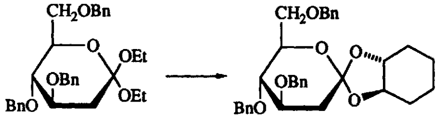
Scheme 3

Compounds of type **13** have been prepared from D-ribonolactone *via* its 3,4-*O*-benzylidene derivative, which was alkylated at O-2, and then subjected to base-catalysed elimination.[17]

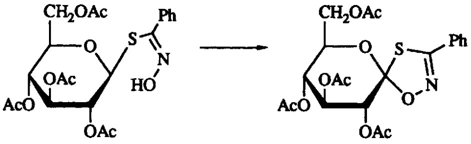
The ortholactone **14** could be prepared from the *O*-benzylated 2-deoxylactone by sequential treatment with triethyloxonium tetrafluoroborate and sodium ethoxide. Subsequent orthoester exchange could be effected with 1,2-diols to give spiroortholactones such as **15**.[18] When the glucosyl thiohydroximate **16**, or its α-anomer, was photolysed in the presence of NBS, the spiro-oxathiazole **17** was obtained in 50% yield.[19]



13, R=Me, Bn



14 **15**



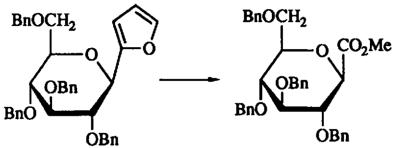
16 **17**

Some references to acetals of aldonolactones are mentioned in Chapter 6, and a paper on the regioselective acylation of aldono-1,4-lactones is discussed in Chapter 7. See Chapter 8 for a paper on deoxy-fluoroaldonolactones, and Chapter 9 for some sugar lactones with amino-substituents. The synthesis of 5-thio-D-glucohydroximo-1,5-lactone is discussed in Chapter 11.

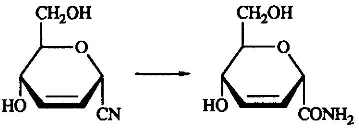
2 Anhydroaldonic Acids and Lactones

Routes to *C*-glycosyl carboxylates involving furans as intermediates have been developed. The β-anomer **18** was made by addition of 2-lithiofuran to the gluconolactone derivative, followed by reduction with Et_3SiH; low temperature ozonolysis and methylation then gave ester **19**. Alternatively, direct *C*-glycosidation of furan with 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose gave the α-anomer of **18**, convertible to the α-analogue of **19**.[20]

The immobilized enzyme preparation "SP409", possessing both nitrilase and amidase activity, has been used for the hydrolysis of glycosyl cyanides. The α-nitrile **20** underwent hydrolysis to the amide **21**, whilst the corresponding β-anomer was converted, at a faster rate, into the analogous carboxylic acid.[21]

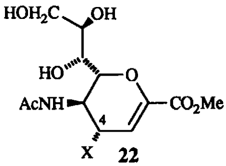


18 **19**



20 **21**

Sialic acid derivatives **22** (X=N_3, SAc) have been made by attack by azide and thioacetate nucleophiles on the corresponding 4,5-oxazoline.[22]



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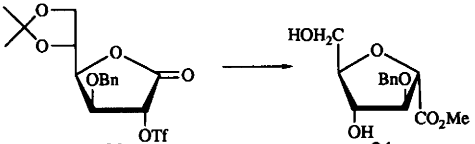
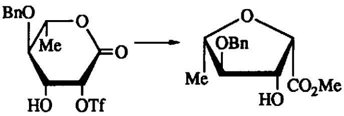
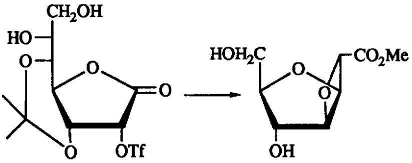


23 **24**

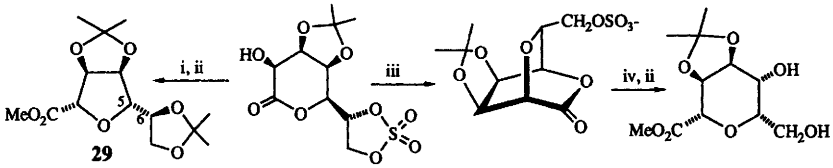


25 **26**



27 **28**

The base-catalysed ring-contraction of δ-lactone 2-triflates to homochiral tetrahydrofurans (Vol. 26, p. 169) now has a complementary acid catalysed procedure, as exemplified by the conversion of **23** to **24**, and of **25** to **26**, on treatment with HCl in methanol at room temperature. Under these conditions, the triflate **27** gave the expected product, but with K_2CO_3 in MeOH the bicyclic oxetane **28** was obtained in 86% yield, a result rationalized by a mechanism involving initial β-elimination from **27**.[23] Cyclic sulfates can also be used to make anhydroaldonic acids, as indicated in Scheme 4; the formation of **29**, involving inversion at both C-5 and C-6, was assumed to proceed via a 5,6-epoxide.[24]

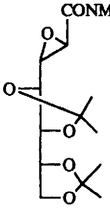


Reagents: i, K_2CO_3, MeOH; ii, Me_2CO, H_2SO_4; iii, NaH, DMF; iv, MeOH

Scheme 4

Wittig reactions of unprotected D-aldopentoses with stabilized ylids can give rise to anhydroaldonic acids and lactones by intramolecular Michael reactions on the initial α,β-unsaturated esters, but this process can be suppressed by the use of cupric acetate in the reaction mixture, when good yields of the acyclic products (as their tetra-*O*-acetyl derivatives) can be isolated.[25]

Condensation of the stabilized sulfur ylid *N*,*N*-dimethyl-2-dimethylsulfuranylidene-acetamide ($Me_2S{=}CHCONMe_2$) with *aldehydo*-sugars gave mixtures of the two diastereomeric *trans*-epoxyamides, such as **30**. When hemiacetals were used, the reaction proceeded with considerable stereoselectivity, and the initial epoxyamide underwent intramolecular cyclization; when 2,3-*O*-isopropylidene-D-ribose was employed, the product **31** could be isolated in 85% yield, and the reaction with di-isopropylidene-D-mannose was also investigated.[26]



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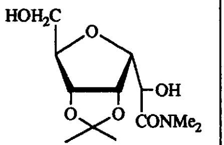

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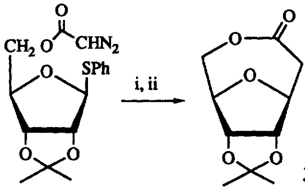
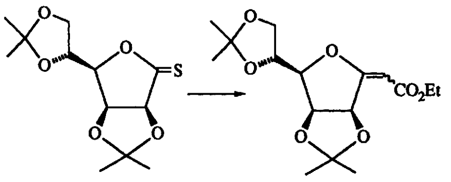
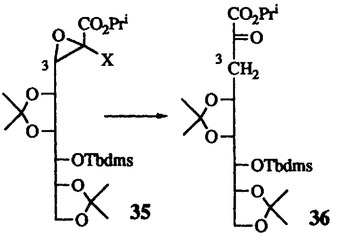


Reagents: i, $Rh_2(OAc)_4$; ii, Ra Ni

Scheme 5





A new route to the lactone **32**, of use in the synthesis of *C*-nucleosides, is indicated in Scheme 5,[27] and the methanolysis product of **32** has been made, as its enantiomer, by a sequence involving an enantioselective formation of a silyl enol ether using a chiral base.[28]

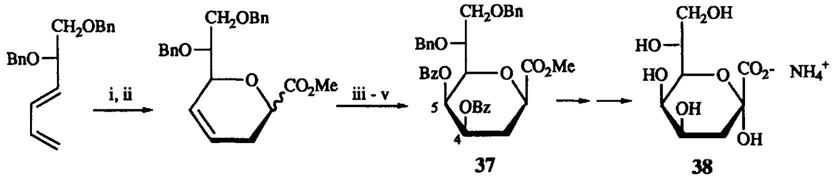
The glycothiono-*O*-lactone **33** (for preparation, see Chapter 11) could be converted to the enoate **34** by treatment with ethyl diazoacetate and $Rh_2(OAc)_4$.[29]

3 Ulosonic and Aldaric Acids

A review, in Czech, on naturally-occurring dicarbonyl monosaccharides includes discussion of ulosonic acids, covering their metabolism, analysis, identification and synthesis.[30]

Oxidation of D-gluconic acid in alkaline solution using Pt-Pb electrodes gives selectively 2-keto-D-gluconic acid,[31] whilst the methyl ester of 2-keto-D-gluconic acid can be obtained by oxidation of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose with potassium permanganate, followed by esterification and hydrolysis.[32] Electrochemical oxidation of diacetone-L-sorbose at a nickel foam electrode can give diacetone-2-keto-L-gulonic acid in up to 90% yield.[33]

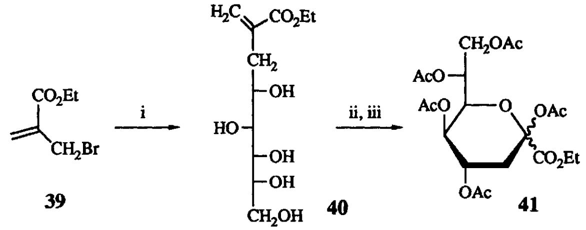
There have been further reports on routes to 3-deoxy-2-ulosonic acids. A new synthesis of Kdo involves the synthesis of epoxyester **35** (X=Br or Cl) by a Darzens reaction, followed by reaction with magnesium iodide and subsequent reduction of the 3-iodocompounds with bisulfite to give **36**; deprotection by sequential acid and base treatment led to the isolation of Kdo ammonium salt (**38**) in 63% overall yield from the *aldehydo*-sugar.[34] In another approach (Scheme 6) a hetero-Diels-Alder reaction was employed, followed by hydroxylation and then inversion at both C-4 and C-5; conversion of **37** to Kdo ammonium salt (**38**) involved functionalization at C-2 by phenylsulfenylation of an enolate.[35]



Reagents: i, $HCOCO_2Bu$; ii, MeOH, H^+; iii, OsO_4, NMNO; iv, Tf_2O, Py; v, $BzO^{-+}NBu_4$

Scheme 6

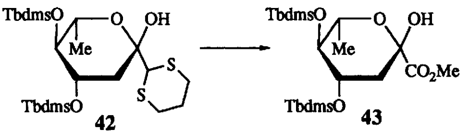
In a new direct and potentially very useful approach to 3-deoxy-2-ulosonic acids, reaction of unprotected D-arabinose with the allylic bromide **39** in the presence of indium metal in aqueous ethanol gave the adduct **40** (73%) with 4:1 selectivity in favour of the *threo*-stereochemistry (Scheme 7). Ozonolysis followed by acetylation then gave the ulosonate **41** epimeric with Kdo at C-4. Use of D-ribose in an analogous sequence gave the product epimeric with Kdo at C-5 (5:1 *threo*-selectivity),[36] and the method was extended to the case of *N*-acetyl mannosamine, thus giving a very short synthesis of NeuNAc.[37]

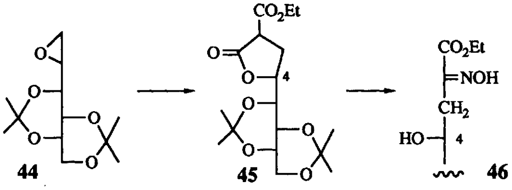


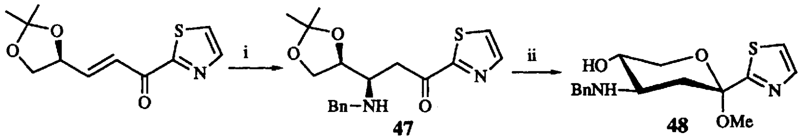
Reagents: i, D-arabinose, In powder, H_2O-EtOH; ii, O_3; iii, Ac_2O, Py

Scheme 7

Reaction of D-mannose with oxaloacetic acid gives crude 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (Kdn), isolable as its hexa-*O*-acetyl methyl ester.[38] The adduct **42** could be obtained in good yield by addition of 2-lithio-1,3-dithiane to the lactone; on treatment with $HgCl_2$ and HgO in aqueous methanol, deprotection was accompanied by oxidation to give **43**, thus providing a route to 3-deoxy-2-ulosonates by one-carbon chain extension.[39] There has been an additional report on the use of Wittig reactions of *aldehydo*-sugars for synthesis of 3-deoxy-2-ulosonic acids,[40] and treatment of acetalated 1,2-anhydroalditols such as **44**, or 1-iodoalditols, with diethyl malonate gave lactones such as **45** which on *C*-nitrosation led to the oximes of 3-deoxy-2-aldulosonates (e.g. **46**).[41]





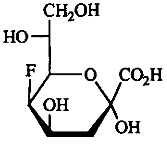


Reagents: i, $BnNH_2$, -70°C; ii, HCl, MeOH

Scheme 8

In an exploratory study from Dondoni's laboratory directed towards aminated ulosonic acids, it was found that the β-amino ketone **47** could be produced with 80% d.e. by low-temperature Michael addition (Scheme 8), but that **47** equilibrated to a 1:1 mixture of diastereomers on standing at room temperature. Methanolysis of **47** gave the ulosonic acid precursor **48**, and the same reaction was also carried out on the *erythro*-epimer.[42]

Enzymic and microbiological methods of synthesis also continue to be prominent in this area. 2-Keto-3-deoxy-D-gluconate (3-deoxy-D-*erythro*-2-hexulosonate, Kdg) has been prepared by aldol condensation of D-glyceraldehyde with pyruvate using *Aspergillus niger*,[43] whilst a strain of *Alcaligenes entrophus*, when grown on pyruvate and gluconate as carbon sources, excretes the 6-phosphate of Kdg into the broth.[44] The Kdo aldolase from a strain of *Aureobacterium barkerei* has been used for the synthesis of Kdo from D-arabinose and pyruvate. A range of other aldoses could also serve as substrates, although the enzyme prefers substrates with *R*- configuration at C-3 and, less strongly, *S*-configuration at C-2. Thus, for example, 3-deoxy-D-*arabino*-2-heptulosonic acid was prepared from D-erythrose and pyruvate, the fluoro analogue **49** of Kdo from 2-deoxy-2-fluoro-D-arabinose and pyruvate, and 5-deoxy-Kdo with 2-deoxy-D-ribose as substrate.[45] The use of aldolases in the synthesis of sialic acids has been reviewed,[46] and sialyl aldolase has been employed in the synthesis of 8-deoxy-NeuNAc and 8-deoxy-Kdn, and in the preparation of the 6-deoxy-compounds **50** from 3-deoxy-D-*arabino*-hexose and pyruvate.[47] Use of *N*-Cbz-mannosamine in a condensation with pyruvate catalysed by NeuNAc aldolase gave *N*-Cbz neuraminic acid, which could then be converted to the α-methyl glycosides of various *N*-acylneuraminic acids,[48] whilst other similar glycosides of NeuNAc, *N*-acylated with long chain alkanoyl units, were made by deacetylation of NeuNAc methyl ester-α-methyl glycoside, followed by coupling to the *N*-hydroxysuccinimidyl ester of the fatty acid.[49] These methyl α-sialosides had the ability to inhibit the binding of influenza virus to erythrocytes.



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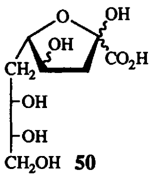

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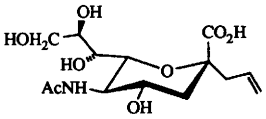

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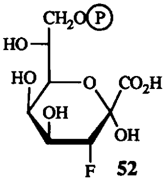
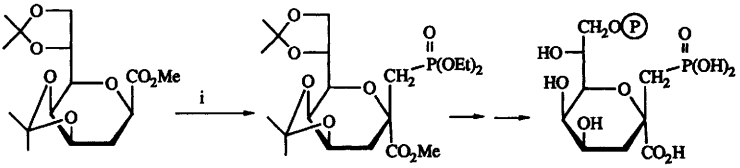


52

The *C*-glycoside **51** of NeuNAc has been incorporated into a polyacrylamide backbone to give a neuraminidase-resistant hemagglutination inhibitor.[50] The same *C*-glycoside **51** has also been linked, via a spacer arm, to a long-chain dialkynoate unit; liposomes containing this conjugate were polymerized, and liposome preparations with certain sialoside concentrations were found to bind influenza virus very effectively.[51]

In studies on the mechanism and stereochemistry of Kdo-8-phosphate synthase, use of stereospecifically fluorinated analogues of phosphoenolpyruvate led to the conclusion that the *si*-face of phosphoenolpyruvate was involved in bonding to D-arabinose-5-phosphate; thus the fluorinated analogue **52** was produced from (*E*)-3-fluoro-phosphoenolpyruvate; specifically deuterated materials were also used.[52] The reaction shown in Scheme 9 was the key to the synthesis of the phosphonate **53**; this proved to be a competitive inhibitor of Kdo-8-phosphate synthase, providing evidence that a cyclic glycosyl β-phosphate was an intermediate in the enzymic reaction.[53]



53

Reagents: i, LDA, $TfOCH_2PO(OEt)_2$

Scheme 9

Kinetic evidence based upon secondary deuterium isotope effects has indicated that a sialidase isolated from a leech cleaves the glycosidic link with the pyranose ring adopting a normally disfavoured conformation.[54]

During structural analysis of sialic acid-containing carbohydrates by the reductive cleavage method, it was found that permethylated sialosides are only cleaved slowly using BF_3 and $BH_3.Me_2S$ or $Et_3SiH-BF_3$, although reduction of the carbomethoxy group caused rapid cleavage. Thus, for example, permethylated 3'-sialyl-lactose was cleaved only at the galactose-glucose link and not at the sialyl-galactose bond.[55]

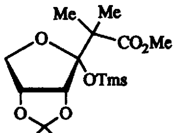
References to glycosides and oligosaccharides containing 3-deoxy-2-ulosonic acids can be found in Chapters 3 and 4.

Silyl ketene acetals react in fluoride-mediated processes with lactones to give 3-ulosonic acid derivatives, as in the formation of **54** from 2,3-*O*-isopropylidene-D-erythronolactone. α-Ketolactones undergo reaction with these acetals at the ketone function.[56]

A platinum-on-alumina catalyst has been used for the oxidation of aldopentoses to aldaric acids.[57]

4 Uronic Acids

A new and potentially useful method for the selective oxidation of primary alcohols in carbohydrates to uronic acids involves the use of sodium hypochlorite in the presence of 1 mole % of 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO). Thus, for example, the methyl uronate **55** could be obtained in 55% yield from methyl β-D-glucopyranoside using this method, followed by methylation.[58] Calcium hypochlorite in a solvent mixture of CH_3CN and MeOH, containing some acetic acid, has been used to prepare the methyl 5-deoxyuronate **56** from the corresponding primary alcohol; several other non-carbohydrate cases were also described.[59] The sodium uronates from methyl and butyl α-D-glucopyranoside have been prepared by catalytic oxidation using Adams' catalyst in an aqueous medium at pH 6-7; this is a lower pH value than used previously, and the water purity influences the yield.[60] The use of potassium permanganate and copper sulfate can effect an interesting oxidative degradation of otherwise protected furanosides with a carbonyl or alcohol function at C-5, as in the conversion of **57** to **58**.[61]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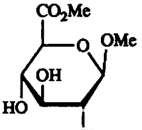
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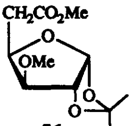
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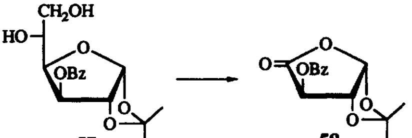
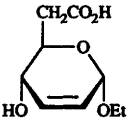

57 **58**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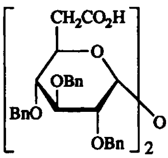
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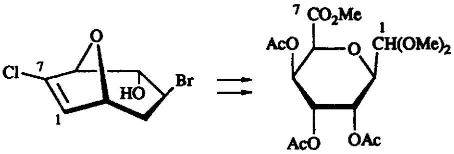
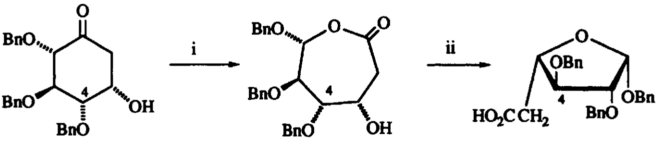

61 **62**

The immobilized enzyme preparation SP409, referred to above, can also be used to prepare certain uronic acid derivatives, as in the synthesis of **59** from the corresponding nitrile.[21]

There have been further reports from Baer's laboratory about the synthesis of the bis-heptosiduronic acid derivative **60** from α,α-trehalose (see Vol. 24, p.183), and the use of **60** to prepare dicorynomycolate[62] and dimycolate esters[63] as analogues of cord factors.

Ozonolysis of **61**, obtained from the Diels-Alder adduct of 1-cyanovinyl acetate and furan, was a key step in the synthesis of the 2,6-anhydrohepturonic acid derivative **62**. Although the work was carried out in the racemic series, the ultimate starting material, a 'naked sugar', is available as either enantiomer.[64]

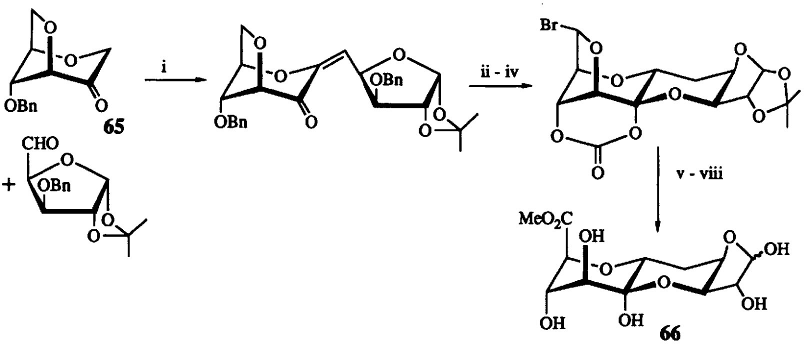
In a novel approach to rare saccharides, cyclohexanones such as **63**, accessible from Ferrier rearrangements, could be manipulated as indicated in Scheme 10; similar chemistry could be carried out with O-4 (cyclohexanone numbering) linked via a glycosidic bond to another sugar unit, to give a disaccharide analogue of **64**.[65]


63 **64**

Reagents: i, MCPBA; ii, TsOH, CH_2Cl_2

Scheme 10

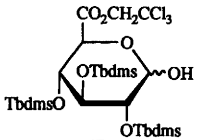
The undecuronic acid unit **66**, found as the glycosyl component of the herbicidin class of nucleoside antibiotics, has been synthesised as outlined in Scheme 11. The bicyclic structure of **65** was necessary to restrict enolization to the desired sense.[66]



Reagents: i, KOBu^t; ii, H_2, Pd/C; iii, Im_2CO; iv, Br_2, hν; v, NaOMe; vi, Ag_2CO_3, Me_2CO, H_2O; vii, I_2, KOH, MeOH; viii, TFA

Scheme 11

In the area of glucuronide conjugates, the glucuronic acid derivative **67**, which has protecting groups removable under non-reducing conditions, has been prepared and used in the synthesis of glucuronides of α,β-unsaturated acids.[67] 5β-Cholestane-3α,7α,12α,25-tetraol, and its 24-*nor*-analogue have been coupled regioselectively at O-3 with methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucuronate using $SnCl_4$ as catalyst to give uronate glycosides.[68] Tertiary amines have been converted into quaternary glucuronides, thought to be biological metabolites, by reaction with methyl (2,3,4-tri-*O*-acetyl-α-D-glucopyranosylbromide)uronate.[69]



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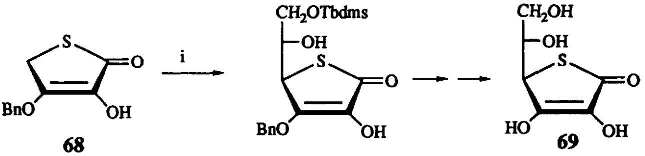
Other papers dealing with glycosides of uronic acids can be found in Chapters 3 and 4.

5 Ascorbic Acids

A full account has been given of the conversion of L-galactonolactone, a product of the sugar-beet industry, into L-ascorbic acid in 40% overall yield (see Vol. 26, p. 176).[70]

The *threo*-selective aldol condensation of **68** with *t*-butyldimethylsilyloxyacetaldehyde was the key step in the synthesis of racemic thioascorbic acid **69** (Scheme 12).[71]

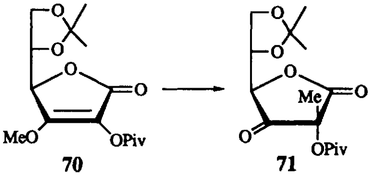


68 69

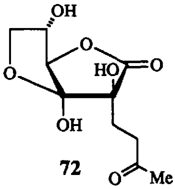
Reagents: i, LDA, then TbdmsOCH$_2$CHO

Scheme 12

Treatment of the L-ascorbic derivative **70** with lithium iodide and methyl iodide in DME gave the *C*-methylation product **71** with high diastereoselectivity, and a similar result was found with the equivalent D-isoascorbic precursor.[72] 'Ketobutylbutyrolactone' (KBBL, **72**) is an immunostimulant derived from condensation of ascorbic acid with methyl vinyl ketone; on treatment with methanol in the presence of Amberlyst resin (H$^+$ form), a mixture of the two spirocyclic ketals **73** is formed, whilst more vigorous conditions (MeOH, HCl) cause rearrangement to give **74**. This structure for **74** was confirmed by X-ray crystallography, and is a revision of an earlier proposal (Vol. 17, p.151).[73]



70 **71**



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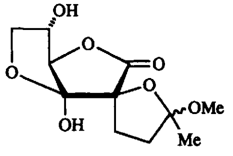

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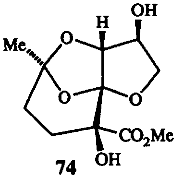

74

The diastereomers of 5,6-*O*-benzylidene-L-ascorbic acid have been separated preparatively as their dimethyl ethers.[74]

Udenfriend's reagent (Fe^{2+}, EDTA, O$_2$, ascorbic acid) hydroxylates benzene to phenol; evidence based on the inhibitory effects of alcohols has led to the conclusion that hydroxyl radicals are involved in this process.[75]

Quantum mechanical interpretations of the nucleophilic addition of L-ascorbate to formaldehyde have been presented. The data indicate that the anionic form of ascorbate in water has high electron density at C-2, whilst C-1 and C-3 are significantly positive.[76,77]

A report has been given on the morphological and chemical stability of Vitamin C crystals.[78]

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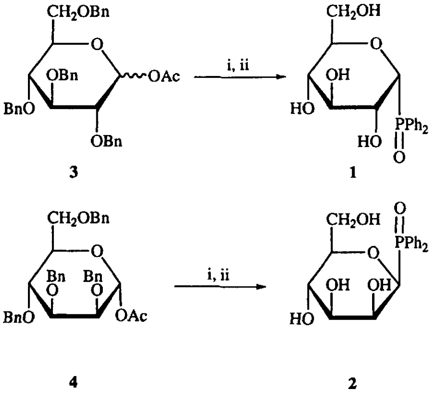
17

Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

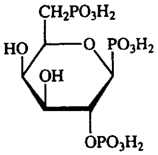
The preparation of "P in the ring" sugar analogues has been reviewed (in Japanese).[1] 1,2-*Cis*-glycosyl phoshine oxides **1** and **2** have been prepared from the corresponding glycosyl acetates **3** and **4** (Scheme 1).[2] This procedure was utilized in the synthesis of the galactose 2-*O*-phosphate bisphosphonate **5**, an analogue of D-*myo*-inositol 1,4,5-trisphosphate.[3] Preparations of 5-deoxy-5-hydroxyphosphinyl-D-mannopyranose[4] and 5-deoxy-5-methoxyphosphinyl-L-fucopyranose[5] have been reported. Previous reports of the synthesis of 6-deoxy-6-phenylphosphinyl-D-fructopyranose derivatives (SPR Vol. 25 p. 195) have been elaborated including the preparation of the corresponding 1,2-anhydro derivatives.[6]



Reagents: i, $MeOPPh_2$, TMSOTf; ii, Pd/C, MeOH, H_2

Scheme 1

Alkylation of cyclic phosphonate **6** afforded almost entirely the diastereomers **7** (Scheme 2) which, on hydroxylation, gave the furanose analogues **8**.[7] Procedures for the conversion of L-ascorbic acid and D-isoascorbic acid into the chiral building blocks **9** and **10** have been described.[8] Lithiated diethyl difluoromethylphosphonate has been utilized in displacement reactions applied to a number of primary sugar triflate derivatives affording the corresponding chain-extended difluoromethylphosphonate derivatives,[9] and the synthesis of fluorinated vinyl phosphonate **11** has been described.[10]



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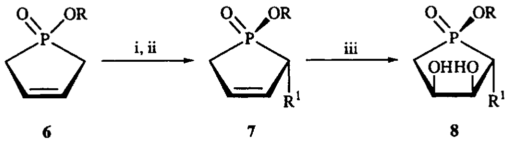
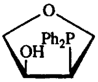


R = Me or Pr^i; R^1 = Me or CH_2OBn

Reagents: i, LDA; ii, R^1X; iii, OsO_4, $NaClO_3$

Scheme 2



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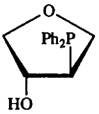

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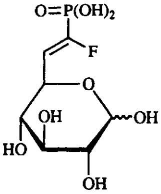

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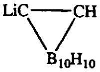

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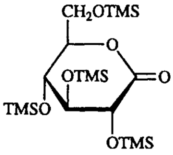

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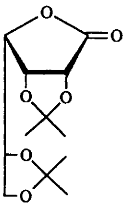

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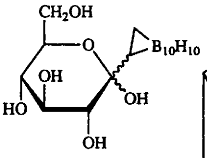

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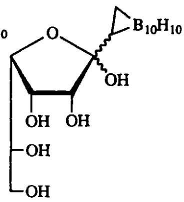

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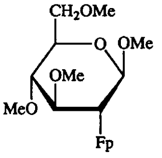
2 Other Carbon-bonded Derivatives

Monolithiated carborane **12** has been added to protected aldono-1,4- and 1,5-lactones such as **13** and **14**, and the products deprotected to afford carbohydrate carboranes **15** and **16**, respectively. Some 2-bromo (or iodo)-2-deoxy sugar derivatives have been treated with a dicarbonyl-(cyclopentadienyl)iron(II) nucleophile affording *C*-bonded derivatives such as **17-19**,[12] and the carbohydrate cobaloximes **20-22** have been prepared from iodides **23-25**.[13]



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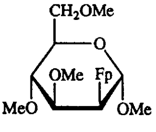

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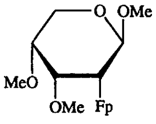

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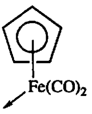
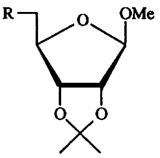
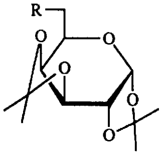
Fp =

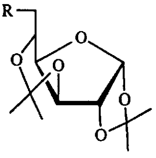




20 R = ←Co–B
23 R = I

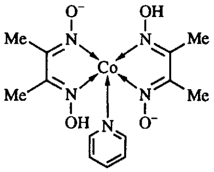


21 R = ←Co–B
24 R = I



22 R = ←Co–B
25 R = I

Co–B =



3 Oxygen-bonded Derivatives

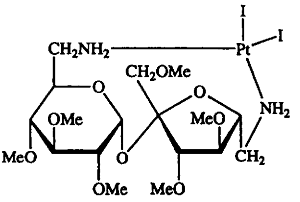
The synthesis, structures and function of carbohydrate-metal coordination compounds has been reviewed.[14] Complexes of some heptofuranose derivatives containing primary-secondary 1,3-diol moieties with molybdenum tetraacetate have been studied and their CD spectra have allowed assignment of the configurations of the secondary alcohol centres.[15] Aldoses of the *arabino-* and *xylo-* series have been shown to form tetradentate acyclic complexes with molybdate ions in aqueous acidic media,[16] and the structure and conformation of molybdate complexes with 5-deoxy-L-arabinose and 5-deoxy-L-ribose have been studied.[17] Molybdate complexes of D-allose, D-altrose, D-gulose and D-idose have been studied by NMR methods.[18]

The interaction of D-glucuronic and D-galacturonic acids with trivalent lanthanide ions has been studied. It was shown that the carboxylate group and O-5 are involved in complex formation but that simple uronic acids do not form sufficiently stable complexes to act as detoxifying agents.[19] A copper(II) ethylenediamine complex with methyl α-D-mannopyranoside has been prepared,[20] and 5-indolylboronic acid complexes with glucose, fructose and several di- and tri-saccharides have been studied.[21] Phenylboronic acid along with an ionophore have been used simultaneously with a cation to transport *p*-nitrophenyl β-D-glucopyranoside through a liquid organic membrane,[22] while M.O. studies of some borate-xylopyranose chelates have been reported.[23] The regiospecific oxidation of dibutylstannylene acetals with NBS (instead of bromine) has been described and some new carbohydrate examples have been reported.[24]

4 Nitrogen-bonded Derivatives

D-Glucosamine and either ammonia, 1,2-ethylenediamine, or 1,10-phenanthroline have been shown to form complexes with Co(III) ions,[25] and the cobalt (ethylenediamine . D-glucosamine) complex is formed from the α-pyranose anomer of the sugar.[26] Aldose oximes on catalytic hydrogenation afford bis(polyhydroxyalkyl)amines. These compounds and their *N*-carboxymethyl derivatives react with borate ions to give macrocyclic diborate esters which can sequester Ca^{2+}, Cu^{2+} and Cd^{2+} ions.[27] The coordination of some divalent transition metal ions to 2-amino-2-deoxy-D-*glycero*-D-*gulo*-heptonic acid in aqueous solution has been studied.[28]

The platinum complexes **26** and **27** of sucrose derivatives have been synthesized as cisplatin analogues.[29] The diamines **28** and **29** were prepared from D-mannitol and converted into the Pt complexes **30** and **31**. The complexes **32** and **33** were also prepared - again as cisplatin analogues.[30] Similarly, the complexes **34**-**36** were prepared from L-arabinose.[31]



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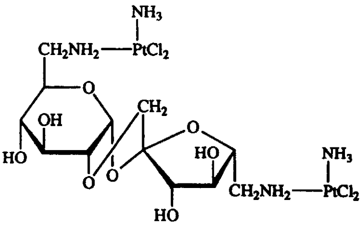

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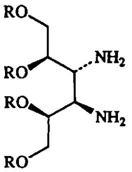
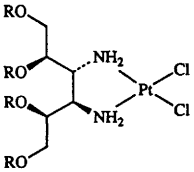
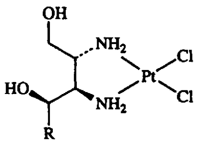


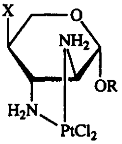
28 R = H
29 R = Me



30 R = H
31 R = Me



32 R = H
33 R = CH_2OH



34 X = OMe, R = H
35 X = OMe, R = Me
36 X = H, R = H

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18
Alditols and Cyclitols

1 Alditols

1.1 Acyclic Alditols.-1,2:5,6-Di-*O*-isopropylidene-D-mannitol and -D-talitol undergo direct elimination reactions with Garegg's reagent (triiodoimidazole, imidazole and TPP) to give the (E)- and (Z)-3,4-dideoxy-D-*threo*-hex-3-enitol derivatives respectively.[1]

The structure of the bisacetal formed from glucitol and *p*-isobutylbenzaldehyde has been shown to be 1,3:2,4-bis(*O*-*p*-isobutylbenzylidene)glucitol, by oxidative cleavage then reduction of the latter into the corresponding xylitol derivative.[2] A conformational analysis of the 1,3-dioxane rings was also performed.

Further reports on the hydrogenation of glucose[3,4,5] or fructose[6], in the presence of ruthenium catalysts, have appeared.

The borotritiide reduction of various carbonyl-containing carbohydrates to give alditols or glycosides with characteristically divergent specific radioactivities has been disclosed.[7]

The thermodynamics of hydration of C-4 to C-6 polyhydric alcohols[8] and some thermodynamic functions of activation for viscous flow[9] and a volumetric study[10] of D-mannitol and D-glucitol in aqueous solution have been reported.

A report has appeared on the synthesis and taste properties of maltitol and maltose analogues to test the hypothesis that H-bonding is responsible for sweetness.[11]

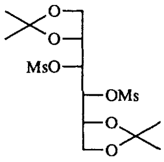
The mild periodate oxidation of 3- and 6-*O*-substituted 2-acetamido-2-deoxy-D-galactitols and 4- and 6-*O*-substituted D-glucitols have been studied, and the major sites of oxidation shown as expected to be *threo*-diol moieties.[12] The products were characterized by ms of thin layer chromatography samples of the corresponding 1,2-di-*O*-palmitoyl-sn-*glycero*-3-phosphoethanolamine derivatives.

The D-mannitol derived dimesylate **1** underwent a double displacement with inversion on treatment with tetrabutylammonium azide. Subsequent simple chemical transformations gave the amines **2** and **3** as intermediates for cisplatin-like antitumor agents.[13] Other similar analogues are also described.

The conversion of *O*-benzyl protected *aldehydo*-hexoses derived from D-allose, D-glucose, D-galactose and D-mannose into 3-deoxy-2-octulosonic acids (see Chapter 16) and their subsequent reduction-deprotection to produce the corresponding 3-deoxy-D-*glycero*-D-*allo*/*altro*-, 3-deoxy-D-*glycero*-L-*manno*/*gluco*-, 3-deoxy-D-*glycero*-D-*gulo*/*ido*- and 3-deoxy-D-*glycero*-D-*galacto*/*talo*-octitols has been reported[14] and the per-acetylated or -methylated derivatives used as GC standards.

A convenient method for measuring absolute configurations of alditols can be found in Chapter 22 and the solid state ^{13}C CP/MAS NMR experiments and X-ray analysis of threitol are covered in

Chapters 21 and 22 respectively. The preparation of some polyhydroxy carbocyclic compounds is covered in Chapter 24.



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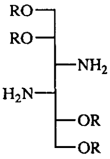
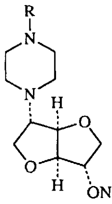
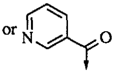


2 R = H
3 R = Me



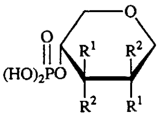
4 R = H, PhS(CH$_2$)$_3$, or 

1.2 Anhydro-Alditols.-The uses of 1,4:3,6-dianhydroglucitol and -dianhydromannitol to prepare high molecular weight polyesters, polyurethanes and polycarbonates has been reported.[15]

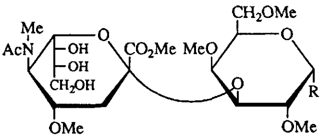
The synthesis of 5-deoxy-5-(4-piperizin-1-yl)-1,4:3,6-dianhydro-L-iditol-2-nitrates **4** together with various stereoisomers as anti-ischemic agents has been described.[16,17] (See also Vol. 26, Chapter 18, ref. 29). The preparation of chiral auxiliaries derived from 1,4:3,6-dianhydroglucitol is mentioned in Chapter 24.

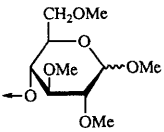
The preparation of the 1,5-anhydroxylitol and 1,5-anhydro-D-arabinitol trisphosphates **5** and **6** respectively as mimics for *myo*-inositol phosphates has been described.[18]

The regioselective reductive-cleavage of the galactose-glucose link in the sialic acid containing trisaccharide derivative **7** with borane-dimethylsulfide complex in the presence of boron trifluoride or by triethylsilane afforded anhydro derivative **8**.[19]



5 R^1 = OPO(OH)$_2$, R^2 = H
6 R^2 = OPO(OH)$_2$, R^1 = H



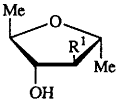
7 R = 

8 R = H

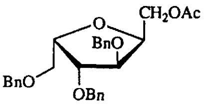
Treatment of 3,4-di-*O*-acetyl-2,5-anhydro-1,6-di-*O*-tosyl (or mesyl)-D-mannitol with LAH gave the expected product **9** together with the deoxy derivative **10**.[20]

The reaction of the 1,5-dimesylate or -ditosylate of 2,3,4,6-tetra-*O*-benzyl-D-glucitol with tetrabutylammonium acetate afforded a good yield of the 2,5-anhydro-L-iditol derivative **11** through nucleophilic attack by O-2 at C-5 and displacement at C-1 with acetate.[21] (See Chapter 14 for a different course of the reaction when the ditriflate is used).

The synthesis of 1-amino-2,6-anhydro-1-deoxyheptitols such as **12** by treating the corresponding 1-*O*-acetyl sugar with trimethylsilylcyanide followed by hydrogenation has been reported.[22]



9 $R^1 = OH$
10 $R^1 = H$



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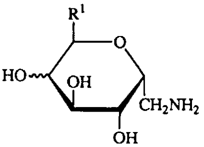
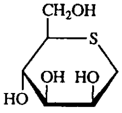


12 R^1 = Me or CH_2OH

Full details of a preliminary communication (S.J. Mantell *et al.*, Vol. 26, p. 310) of the synthesis of epimeric 3-hydroxymuscarines from L-rhamnono-1,4- or 1,5-lactones have appeared.[23]

The synthesis of the anhydrothioalditol **13** as an analogue of deoxymannojirimycin has been reported.[24] The anhydro linkage is introduced by treating the intermediate bromothioacetate derivative **14** with sodium methoxide to give bicyclic compound **15**. Subsequent de-silylation, benzylation, acid hydrolysis, hydride reduction and catalytic hydrogenolysis furnished **13**.



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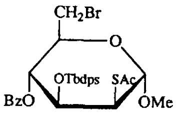

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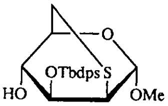
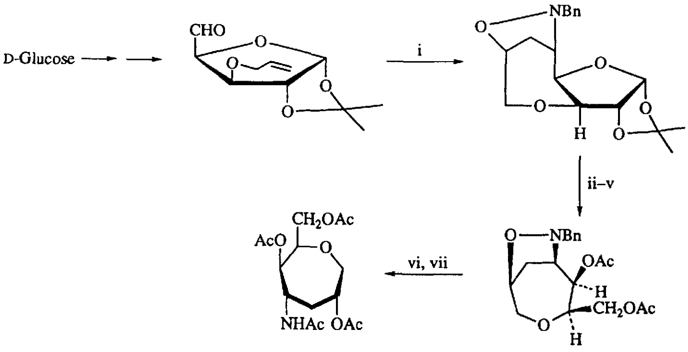


15

A preparation of an oxepane (a 1,6-anhydroheptose derivative) is illustrated in Scheme 1.[25]

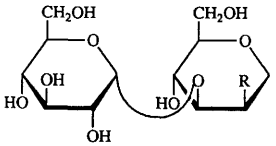
The synthesis by standard methods of the disaccharide derivatives **16** and **17**, as potential mannosidase inhibitors, has been described.[26]

The introduction of 3,6-anhydro linkages into (1→4)-α-D-glucans is mentioned in Chapter 4, and the synthesis of various 1,4-anhydropentitols as abasic derivatives of nucleosides in order to study relative strength of various guache and anomeric effects that affect the pseudorotational equilibrium of the pentofuranose moiety of nucleosides is covered in Chapter 21.



Reagents: i, BnNHOH, Δ; ii, H_2SO_4; iii, IO_4^-; iv, $NaBH_4$; v, Ac_2O/Py; vi, H_2, Pd/C; vii, Ac_2O/Py

Scheme 1



16 R = OH
17 R = H

1.3 Amino- and Imino-Alditols.-A review on the chemical modifications of aza sugars including the synthesis of analogues of 1-deoxynojirimycin and its *manno*-isomer,[27] as well as one on the aldolase-catalysed aldol condensations in the synthesis of aza sugars, has appeared.[28]

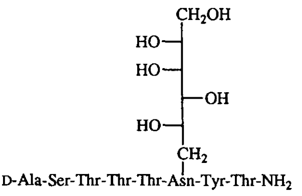
The preparation of the neoglycopeptide derivative **18** has been described from intermediate **19**, itself made from 1-amino-1-deoxy-D-glucitol.[29]

The riboflavin analogue **20** has been made in order to study its binding to riboflavin synthetase.[30]

The study by NMR spectroscopy of complexing of the mono[6(1-pyridino)-6-deoxy]-α-cyclodextrin with various inorganic anions,[31] and a study of H/D exchange rates of the H's of the pyridino ring of the same molecule has been reported.[32]

The reductive amination of L-rhamnose and L-fucose to afford 1-amino-1,6-dideoxy-L-mannitol and-L-galactitol respectively has been described.[33]

D-Glucose and L-arabinose have been converted into 1,3-diamino-1,3-dideoxy-D-threitol and D-erythritol respectively as potential glycosidase inhibitors.[34] The same paper also describes the preparation of unusual urea and thiourea derivatives such as **21** and **22** also as potential glycosidase inhibitors.



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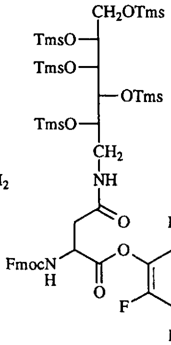

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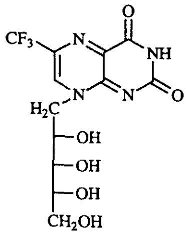

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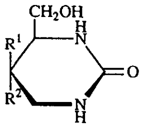
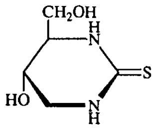


21 $R^1 = OH, R^2 = H$ or $R^2 = OH, R^1 = H$

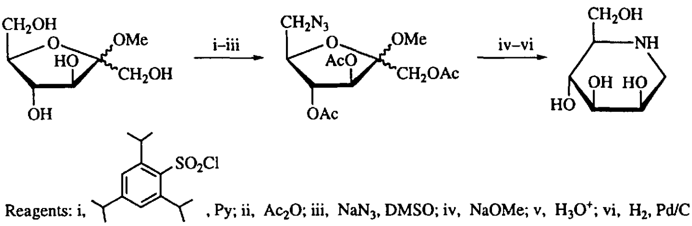


22

The synthesis of polyamino dextran 3-fluorosalicylaldehyde as a non-invasive ^{19}F probe is mentioned in Chapter 4.

The biosynthesis of 1-deoxynojirimycin from D-glucose by a *Bacillus subtilus* variation *niger* strain was studied using ^{13}C-labelled precursors.[35]

A short route from fructose to deoxymannojirimycin is illustrated in Scheme 2.[36] The same group have also prepared 1-deoxygalactonojirimycin from sorbose.[37]

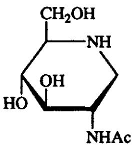


Reagents: i, , Py; ii, Ac_2O; iii, NaN_3, DMSO; iv, NaOMe; v, H_3O^+; vi, H_2, Pd/C

Scheme 2

A synthesis of 2-acetamido-1,2-dideoxynojirimycin **23** from *N*-acetyl-D-glucosamine in six steps and 10% overall yield has been reported.[38] The key step involves double reductive-amination of keto-aldehyde **24**.

The preparation of 1-deoxy-L-idonojirimycin following reaction of the dimesylate **25** with benzylamine, followed by hydrogenolysis, has been described.[39]



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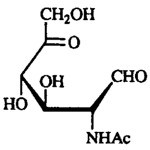

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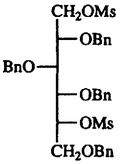
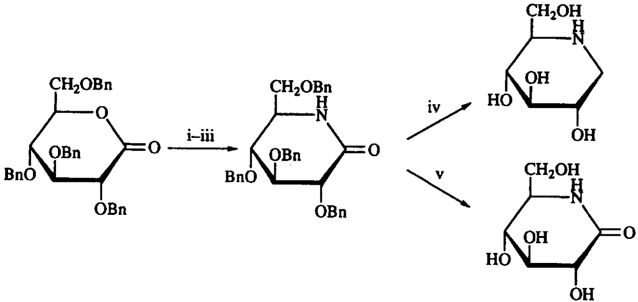


25

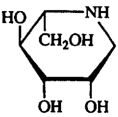
A simple route to 1-deoxynojirimycin and 5-amino-5-deoxy-D-gluconolactam is depicted in Scheme 3.[40]



Reagents: i, NH_3; ii, DMSO, Ac_2O; iii, $NaCNBH_3$, HCO_2H; iv, LAH; v, H_2, Pd/C

Scheme 3

The synthesis of 1,5-dideoxy-1,5-imino-L-mannitol **26** and -L-rhamnitol **27** by the L-rhamnulose 1-phosphate aldolase-catalysed reaction of dihydroxyacetone phosphate and 3-azido-2-hydroxypropanal, followed by hydrogenolysis and phosphatase treatment, has been described.[41]



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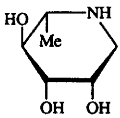
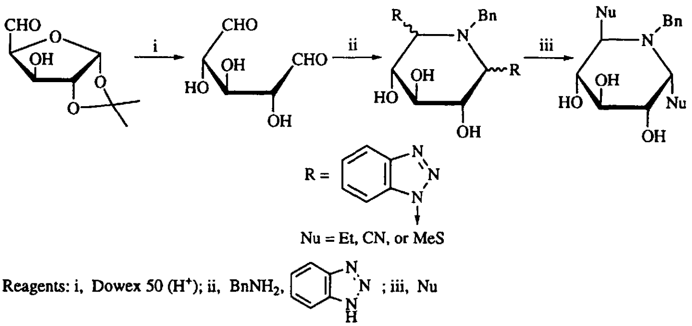


27

An alternative synthesis to 1-deoxy-L-rhamnojirimycin **27** has been reported starting from 2,3-*O*-isopropylidene-D-gulono-1,4-lactone and proceeding through an intermediate 2,3-*O*-isopropylidene-δ-L-rhamnono-lactam.[42] The methyl group is introduced by bromination of the 6-OH group of the starting material followed by hydrogenolysis.

An interesting synthesis of 2,6-disubstituted trihydroxypiperidines is shown in Scheme 4.[43]



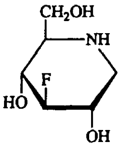
Nu = Et, CN, or MeS

Reagents: i, Dowex 50 (H$^+$); ii, BnNH$_2$, ; iii, Nu

Scheme 4

The fluorinated deoxynojirimycin derivative **28** has been prepared from the known **29** (*Carbohydr. Res.*, 1992, **225**, 99) by de-benzoylation or desilylation followed by hydrolysis and hydrogenation.[44]

The synthesis of α-L-homofuconojirimycin **30** from the known compound **31** (Vol. 23, p. 181, ref. 31), by reaction with tetrabutylammonium fluoride then hydrogenaton and acidolysis, has been reported.[45] If compound **31** is hydrogenated before de-silylating, 6-*epi*-α-L-homofuconojirimycin is produced.



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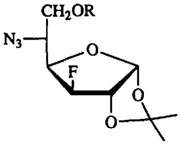
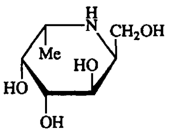


29 R = Bz or Tbdps



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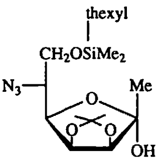
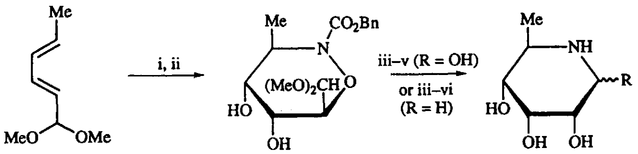


31

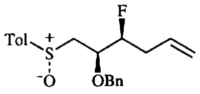
The preparation of racemic 6-deoxyallonojirimycin and 1,6-dideoxyallonojirimycin by a hetero-Diels-Alder approach is illustrated in Scheme 5.[46]



Reagents: i, O=N−CO$_2$Bn; ii, OsO$_4$, NMNO; iii, H$_2$, Pd/C; iv, SO$_2$; v, Ba(OH)$_2$; vi, H$_2$, Pd/C

Scheme 5

A non-carbohydrate process has been developed from the chiral sulfoxide **32** to produce the fluorinated dideoxynojirimycin derivative **33**.[47]



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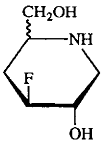

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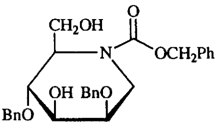


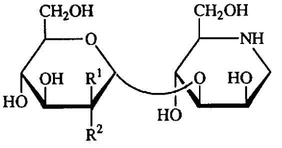
34

The effects of 1-deoxynojirimycin, 4-*O*-α-D-glucopyranosyl-1-deoxynojirimycin and their *N*-substituted derivatives on the thermal stability of cyclodextrin glycosyl transferase, glucoamylase and β-amylase have been described.[48]

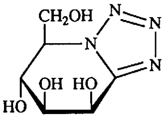
The preparations of derivatives of 3-*O*-(α-D-glucopyranosyl)-deoxymannojirimycin in which the imino-alditol portion has been modified to analogous 2-deoxy, 2-*O*-methyl, 4-deoxy, 4-*O*-methyl, 6-deoxy, 6-*O*-methyl and *N*-alkyl groups, have been described and tested for glycosidase activity.[49]

Treatment of the known deoxymannojirimycin derivative **34** (Vol. 23, p. 180, ref. 25) with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl chloride or -mannopyranosyl chloride led to derivatives **35**.[50] See also Chapters 3 and 4 for related imino-alditol glycosides and imino-alditol oligosaccharides, respectively.

The synthesis of the mannojiritetrazole **36** by a similar route used to that of the *gluco*-derivative (Vol. 25, p. 131 and p. 206) has been described.[51]



35 $R^1 = OH, R^2 = H$
or $R^1 = H, R^2 = OH$



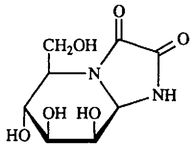
36

A multistep synthesis of (+)-kifunensine **37**, a potent glycosidase inhibitor, starting from microbial oxidation of chlorobenzene has been reported.[52]

The synthesis of D-gluconohydroximino-1,5-lactam and its analogues as β-glucosidase inhibitors is covered in Chapter 9.

In the field of 1,4-dideoxy-1,4-imnoalditols, the mannoaldonolactone **38** has been used as a starting material for the preparation of the L-*allo*-configured 1,4-dideoxy-1,4-iminohexitol **39**, and starting from a D-gluconolactone derivative a D-*talo*-iminohexitol is formed. The corresponding enantiomeric iminohexitols were prepared from the appropriate enantiomeric 1,4-lactones.[53] In a related way L-*galacto*- or D-*ido*-1,4-iminohexitols can be prepared as shown in Scheme 6.[54]

The synthesis of the first 2-acetamido-1,4-dideoxy-1,4-iminohexitol to be examined as a reversible competitive inhibitor of hexosaminidase is depicted in Scheme 7.[55]



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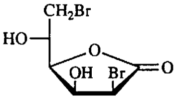

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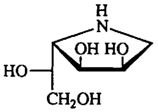

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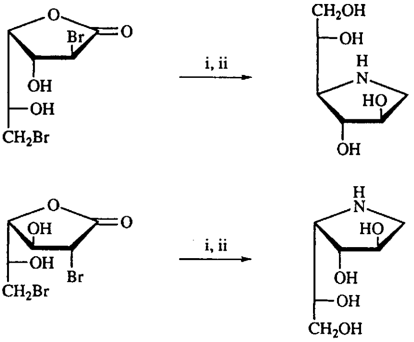
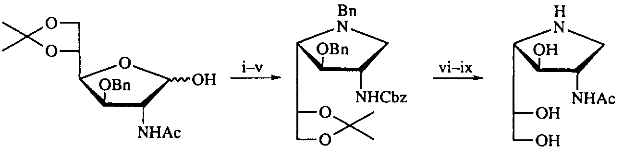


Reagents: i, $NaBH_4$; ii, NH_3

Scheme 6



Reagents: i, $NaBH_4$; ii, NaOH; iii, $(Cbz)_2O$; iv, MsCl; v, $BnNH_2$; vi, HCl; vii, Ac_2O/Py; viii, NaOMe; ix, H_2, Pd/C

Scheme 7

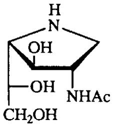
Benzyl-2-acetamido-2-deoxy-α-D-glucopyranoside has been used as starting material for the preparation of 2-acetamido-1,4-imino-1,2,4-trideoxy-D-galactitol **40**.[56]

Dehydroproline and lyxose precursors have been used to prepare D- and L-forms of 1,4-dideoxy-1,4-iminoribose.[57,58]

The use of (S)-pyroglutamic acid as a non-carbohydrate starting material for the preparation of 1,4-dideoxy-1,4-imino-D-arabinitol **41** has been reported,[59] whilst a synthesis of 1,4-dideoxy-1,4-imino-L-arabinitol from the D-lyxono-1,4-lactone **42**, in which the key steps involve inversions at C-2 and C-4 by sulfonate displacement reactions, has also been described.[60]

A double displacement reaction with benzylamine of the dimesylate **43**, derived from D-ribose, was the key step in the preparation of imino-L-lyxitol **44**.[61] The same paper describes an interesting *threo*-selective Michael addition of ammonia to enoates such as **45** derived by Wittig elongation of hemiacetal-sugar derivatives followed by standard chemistry to afford compounds **46.** Other similar examples are also reported.

A facile synthesis of the pyrrolidine **47** from 1,3:4,6-di-*O*-benzylidene-D-mannitol has been described.[62]



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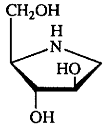

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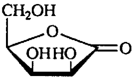

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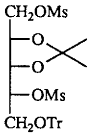

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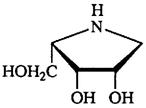

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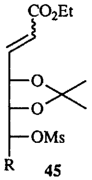

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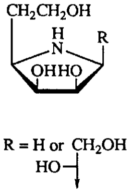

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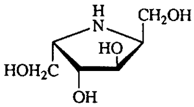
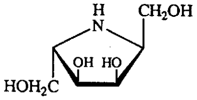


47

The synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol from (R)-serine and of 2,5-dideoxy-2,5-imino-L-talitol **48** from D-ribonolactone has been achieved.[63]

A new route to aza-sugars is depicted in Scheme 8 which involves an unusual PCC oxidative-degradation process.[64]



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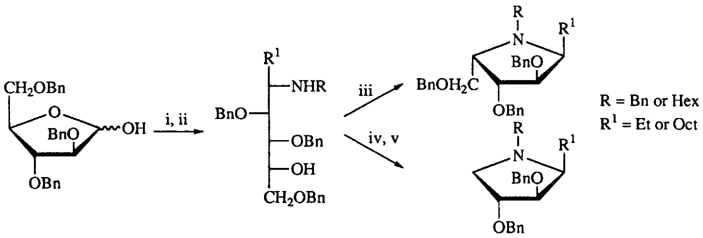


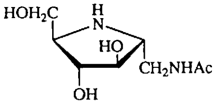
Reagents; i, RNH_2; ii, R^1MgX; iii, Tf_2O; iv, PCC; v, $BH_3.Me_2S$

Scheme 8

The preparations of aza-sugars **49**[65] and **50**[66], by aldolase catalysed addition of dihydroxyacetone phosphate to azido aldehydes followed by hydrogenolysis have been reported as has the use of immobilized glucose isomerase followed by hydrogenolysis to convert azido sugars **51** and **52** into the 2,5-imino-D-mannitol and -D-glucitol derivatives **53** and **54**, respectively.[67]

The preparation of a potential transition state inhibitor of nucleoside hydrolase, **55**, from the known (Vol. 22, p. 181, ref. 36) aza-sugar **56** has been described.[68] Functionality was introduced into **56** by *N*-chlorination followed by strong base treatment to give an imine which was further reacted with a protected lithiated imidazole.

The addition of *N*-Tms pyrrolidine under the influence of light to the butenolide **57**, followed by treatment with potassium *t*-butoxide, gave azabicyclo derivative **58**, which contains the basic ring skeleton of the pyrrolizidine alkaloid lindelofidine.[69]



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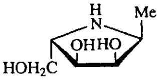

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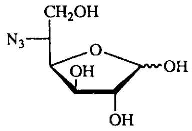

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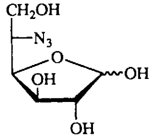

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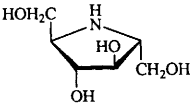

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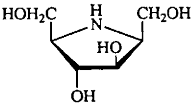

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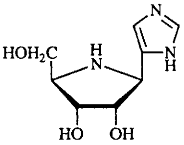

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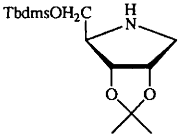

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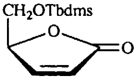

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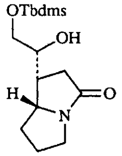


58

The synthesis of quinolizidine alkaloids and of pyrrolidines as precursors of retronecine are mentioned in Chapter 24

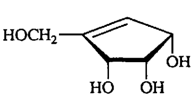
2 Cyclitols

Reviews on the enzymic asymmetric synthesis of cyclitols from cyclopentadiene, benzene and cycloheptatriene[70] and on the conversion of carbohydrates to functionalized cyclohexanes and cyclopentanes[70a] have appeared.

2.1 Cyclopentane and Cyclobutane Derivatives.-The isolation of the unsaturated cyclitol **59** from *Streptomyces citricolor* has been described[71] and proposed as a biosynthetic precursor of aristeromycin and neplanocin A.

The synthesis of polyoxygenated cyclopentane derivatives such as **60** by 5-*exo*-dig. radical cyclization of 1,2,6-trideoxy-6-iodo-L-*arabino*-hex-1-ynitol compounds have been reported.[72]

The preparation, as a precursor for carbocyclic nucleosides, of the simple aminopentane derivative **61** from S-aspartic acid[73] and the isolation from a sponge[74] of six cyclopentane glycolipids such as **62** which display insect antifeedent activity on a fish species have been described.



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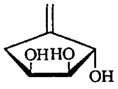

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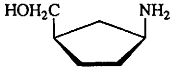

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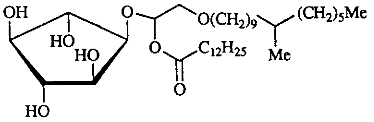

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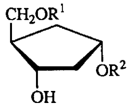
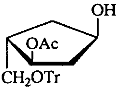


63 R^1 = Tr, Bu, Me, or $PhCH_2$, R^2 = H

64 R^1 = Tr, R^2 = Ac



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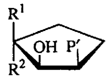
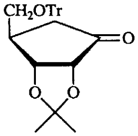


P′ = OPO_3^{2-}

66 R^1 = H, R^2 = CH_2OH

67 R^1 = CH_2OH, R^2 = H



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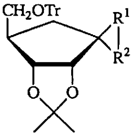


69 R^1 = O, R^2 = CH_2

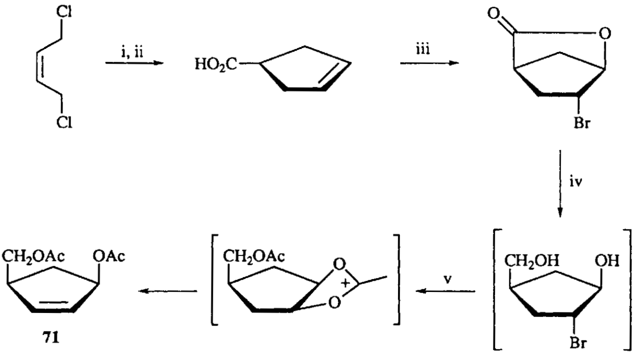
70 R^1 = CH_2, R^2 = O

Kinetic resolution of a series of mono-alkylated cyclopentane triol derivatives **63** using vinyl acetate and *Pseudomonas fluorescens* lipase has been reported.[75] Best results were seen with R^1= Tr leading to products **64** and **65** with > 99% ee.

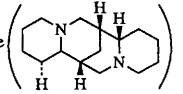
A racemic synthesis of the cyclopentane phosphate derivatives **66** and **67** as potential inhibitors and substrates of inositol monophosphatase has been described. The products were compared with the furanose ring equivalent.[76]

The synthesis of α- and β-D,L-*ribo*-carbahex-2-ulofuranoses from racemic norbornen-2-one has been achieved.[77] The keystep involves the addition of either dimethylsulfoxonium methyl ylide or bromomethyllithium to the known (Vol. 24, p. 200, ref. 49) ketone **68** to afford the intermediate spiro-epoxides **69** and **70**.

A simple and straightforward synthesis, over the current Prins reaction route, of the acetylated cyclopentene diol **71**, a useful precursor for the preparation of carbocyclic nucleosides, has been achieved from non-carbohydrate sources (Scheme 9).[78]



CO_2Me
Reagents: i, CO_2Me, LiH; ii, NaOH, then H^+, then Δ (180 °C); iii, TMSBr, DMSO, Pr^i_2NEt;
iv, $[(MeOCH_2CH_2O)_2AlH_2]Na$;
v, Ac_2O, cat. DMAP, (–)-Sparteine

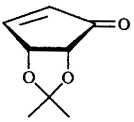


Scheme 9

A short synthesis of the carbocyclic analogue of 5-phosphoribosyl-1-pyrophosphate from the known (C.R. Johnson *et al.*, *Tetrahedron*, 1984, **40**, 1225) chiral ketone **72** has been described.[79]

Syntheses of carba-α-D-arabinofuranose and of the carba-nucleosides (+)-cyclaradine and (+)-1-carba-β-D-arabinofuranosyluracil from key intermediate nitro-compound **73** have been reported.[80]

A short synthesis of Ohno's lactone, **74** in 54% overall yield from (+)-(1R)-*endo*-5-norbornene-2-carboxylic acid, as a useful carbocyclic nucleoside precursor, has been reported.[81] See Chapter 20 for the synthesis of carbocyclic tiazofurin and other carbocyclic nucleosides.



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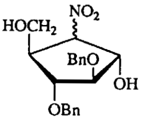

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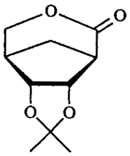
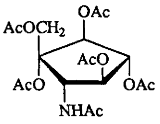


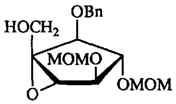
74

The preparation of (-)-allosamizoline from a 2-amino-2-deoxy-D-glucose derivative in which the cyclopentane ring is formed by an intramolecular nitrile oxide cycloaddition reaction to a terminal olefin has been reported.[82] Also a detailed paper on the synthesis of racemic allosamizoline from non-carbohydrate sources, employing a Pd^0 catalysed isomerization-cyclization strategy to prepare oxazolidinones from *meso*-cycloalkenediols has appeared.[83] (See Trost *et al.*, *J. Am. Chem. Soc.*, 1991, **112**, 1261 for a preliminary account). Modification using Pd^0 with chiral ligands leads to asymmetric induction.

The preparation of the hexaacetate **74a** from the epoxide **75** (prepared in eleven steps from methyl 4,6-O-benzylidene-α-D-glucopyranose) in order to establish the absolute configuration of trehazolin has been reported.[84]



74a



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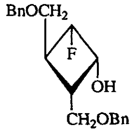
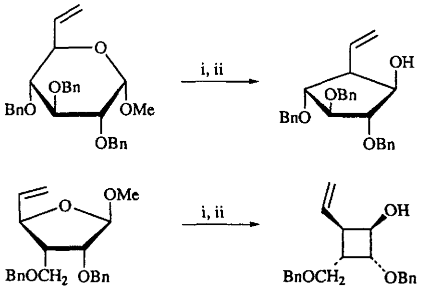


76

The isolation from fermentation broths of trehalamine, the aglycone of trehazolin, is mentioned in Chapter 19.

The direct ring contraction of hept-6-enose and hex-5-enose derivatives to cyclopentane and cyclobutane compounds, respectively has been described (Scheme 10).[85]



Reagents: i, Cp_2ZrCl_2, BuLi(2 equiv.); ii $BF_3.OEt_2$

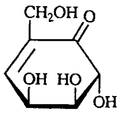
Scheme 10

The synthesis of the cyclobutane derivative **76**, as well as its enantiomer, by a non-carbohydrate method has been achieved.[86] These compounds are useful for preparing nucleobase analogues.

2.2 Inositols and other Cyclohexane Derivatives.-A series of eleven new carba-sugars, termed Gabosines A-K, have been isolated from several *Streptomyces* strains and are typified by compounds

77 and **78**.[87]

The formation of 2,3-dihydroxyacetophenone by treating pentoses or hexuronic acids with dilute mineral acid has been shown to proceed through the intermediate **79**.[88]



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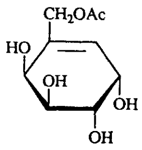

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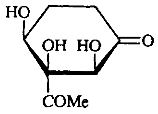
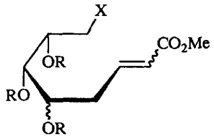


79

A detailed study on the radical cyclization of various protected sugars **80** (R= alkyl, silyl or acetals, X= Br or I), on treatment with tributytin hydride and AIBN to produce branched-chain cyclitols **81**, has been disclosed.[89]

The Ferrier reaction of 5,6-unsaturated hexopyranoses has been utilised on several occasions for preparing the carbocyclic analogues of lipid X,[90] ring cleaved analogues, **82** and **83** of lycoricidine and narciclasine alkaloids,[91] and the carba-sugars **84**,[92] which are related to allosamizoline.



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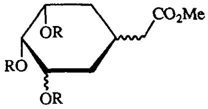

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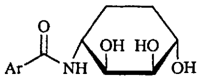

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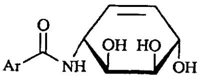

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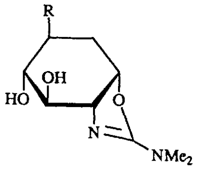
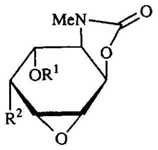


84 R = CH_2OH or OH

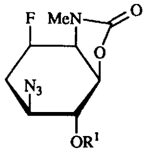
The use of lipases and esterases for the kinetic resolution of several bicyclic carbamate derivatives **85-87** which are intermediates in Prinzbach's route from benzene (see Vol. 23, p. 191, ref. 6 and 7) have been described.[93] The same methodology has been used to resolve intermediates en-route from tropilidene to diamino-tetradeoxycycloheptitols.

A synthesis has been reported of (+)-fortamine from the known conduritol derivative **88**.[94]

The preparation from the known ketolactone **89** of carba-α and -β-D-glucopyranose as well as validamine, in which the key step is a stereoselective addition of nitromethane to the keto function, has been described (Scheme 11).[95]



85 R^1 = H or Ac, R^2 = H
86 R^1 = H or Ac, R^2 = OBn



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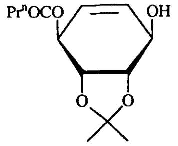

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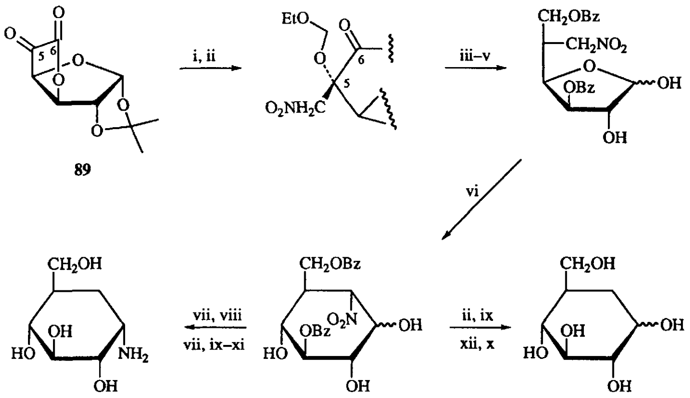
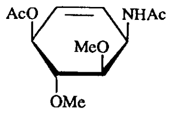


Reagents: i, $MeNO_2$–KF; ii, $\diagup\!\!\!\diagdown$OEt–H^+ ; iii, $NaBH_4$; iv, BzCl–py; v, TFA; vi, CsF; vii, Ac_2O–H^+; viii, NH_3(l); ix, Bu_3SnH; x, NaOMe/MeOH; xi, NH_2NH_2; xii, PPTS

Scheme 11

The preparation of a conduramine derivative **90** by hetero-Diels-Alder reaction of α-chloronitroso sugar derivatives with cyclohexadienes has been reported.[96] (See Vol. 25, p. 210, ref. 73 for similar work).



90

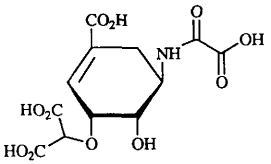
Methodology has been developed using mutant enzymes and ^{1}H NMR analysis to identify the rate limiting steps in the conversion of glucose to aromatics.[97] Dehydroquinate (DHQ) synthase, enoylpyruvyl shikimate 3-phosphate (EPSP) and chorismate synthase have been identified as such rate limiting enzymes.

The syntheses of [5-^{2}H] labelled 5-epishikimic acid and [6-^{2}H] labelled shikimic acid have been achieved from L-shikimic acid.[98] The synthesis of several deuterated and ^{13}C derivatives of shikimic acid has been described in order to study the biosynthesis of ansatrienin (a member of the ansamycin antibiotics).[99] These derivatives were also used in feeding experiments to determine the biosynthesis of the cyclohexanecarboxylic acid starter unit of ω-cyclohexyl fatty acids in *Alicyclobacillus acidocaldarius*.[100]

Evidence (NMR) has been presented that a type (II) dehydroquinase transforms 3-dehydroquinate to 3-dehydroshikimate with anti-stereochemistry.[101]

The synthesis of an EPSP synthase inhibitor **91**, which relies on a malonate group to mimic a phosphate group, has been reported[102] and the EPSP analogue **92** has been prepared to study inhibition of EPSP synthase.[103]

A report on the addition of aliphatic amines to 3-dehydroquinate derivatives to give 3-alkylamino-4-hydroxybenzoates and 3-dehydroshikimate has appeared.[104] The synthesis of phosphate analogues **93-95** as potential inhibitors of DHQ synthase has been described.[105]



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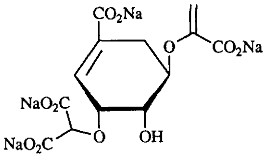

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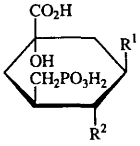
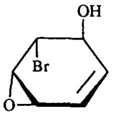


93 $R^1 = R^2 = H$
94 $R^1 = H, R^2 = OH$
95 $R^1 = OH, R^2 = H$

Both enantiomers of methyl shikimate have been obtained following microbial oxidation of benzene.[106]

The isolation of conduritol A from an extract of *Gymnema sylvestre* and its effects on intestinal glucose absorption have been described.[107]

The stereoselective opening of allylic epoxides with dilithium tetrachlorocuprate (Li_2CuCl_4) or dilithium tetrabromonickelate (Li_2NiBr_4) has been reported and used to convert the epoxide **96** into the bromoconduritol derivatives **97** and **98** respectively, as potential antiviral agents.[108]



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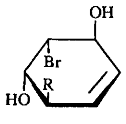


97 R = Br
98 R = Cl

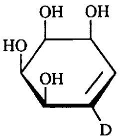
The replacement of the oxirane ring in cyclophelitol by thiirane, aziridine and *N*-alkylaziridine rings has been reported.[109]

L-Quebrachitol has been used as a starting material for the preparation of (-)-conduritol F, (+)-conduritol B and cyclophelitol in which the key step is a selective de-*O*-methylation in the presence of cyclohexylidene acetal groups.[110] (See Vol. 25, p. 210, ref. 74 and p. 235, ref. 101 for preliminary work).

The microbial oxidation of benzene and its derivatives using *Pseudomonas putida* have been used in several cyclitol syntheses. These include the preparation of conduritol D and the deuterated compound **99**[111], D-*chiro*-inositol and D-*chiro*-3-inosose for which the key step involves a one pot oxidation-protection to an epoxy-acetonide derivative,[112,113] and racemic quebrachitol.[114] Also reported are the syntheses of (+)-D-*chiro*-inositol, *allo*-inositol, *muco*-inositol and *neo*-inositol from a halogenated conduritol epoxide.[115]

An efficient synthesis of racemic *proto*-quercitol **100**, which involves photooxidation of 1,4-cyclohexadiene to give the *endo*-adduct **101** followed by three simple steps, has been reported.[116]

An unusual reaction of myo-inositol with a mixture of sulfur tetrafluoride and hydrofluoric acid produced the sulfite ester of the difluorooxabicycloheptanediol **102**.[117]



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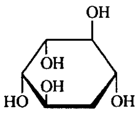

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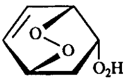

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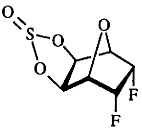


102

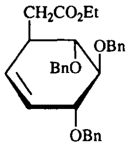
Molecular mechanics calculations of hexa-*O*-methyl-*scyllo*-inositol indicates the most stable conformation is all-equatorial with all O-Me bonds eclipsing the axial C-H (H attached to the same C atom as the O-Me group).[118]

A report has appeared demonstrating that 2-deoxy-*scyllo*-inosose is an early intermediate in the biosynthesis of 2-deoxystreptamine.[119]

The synthesis of the branched-chain conduritol **103** by treating the alcohol **104** with *N,N*-dimethylacetamide dimethylacetal to effect a [3,3]-sigmatropic Claisen rearrangement has been described.[120]

The conversion of D,L-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol into D,L-1-thio-*myo*-inositol has been reported (Scheme 12).[121]

Treatment of 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol with TPP-imidazole-iodine gives, selectively, the iodide **105** which was converted into the thio-derivative **106** by standard chemical transformations.[122]



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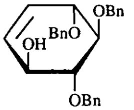

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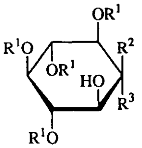
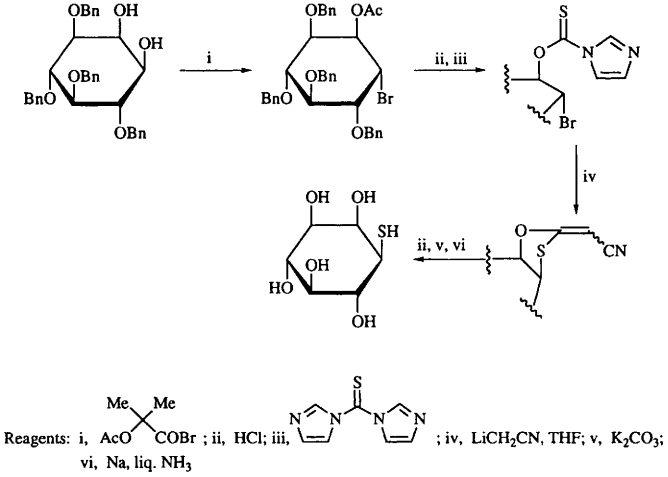


105 $R^1 = Bn, R^2 = H, R^3 = I$

106 $R^1 = R^3 = H, R^2 = SH$



Reagents: i, AcO–C(Me)(Me)–COBr ; ii, HCl; iii, $(Im)_2C=S$; iv, $LiCH_2CN$, THF; v, K_2CO_3; vi, Na, liq. NH_3

Scheme 12

The synthesis of a range of 3-modified 1D-*myo*-inositols by nucleophilic displacements applied to triflate **107** with chloride, thiolacetate and azide (followed by reduction to amine) has been reported.[123]

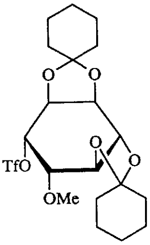
The selective acylation of *myo*-inositol orthoformate **108** at the equatorial site with vinyl acetate and a lipoprotein lipase has been reported as a method for preparing enantiomerically pure *myo*-inositol derivatives.[124] Orthoesters derived from *scyllo*-inositol have been transformed into enterobactin (a siderophore) analogues with hydrophilic properties **109**(R= H, X= Ph) or lipophilic properties **109** (R= $C_{10}H_{21}$, X= Ph).[125]

The benzylation of 1,2-*O*-isopropylidene-*myo*-inositol in the presence of dibutyltin oxide affords 3,4,6- and 3,5,6-triethers as easily isolable major products.[126]

The synthesis of fluoroscyllitol derivatives like **110**[127] and of DL-1-deoxy-1-fluoro-6-*O*-methyl-*chiro*-inositol,[128] by use of DAST as the fluorinating agent, has been described.

L-Quebrachitol has been used as the starting material to prepare the following *myo*-inositol derivatives to study phosphatidylinositol-3'-kinase: 3-deoxy-3-methylene-, 3-deoxy-3-(hydroxymethyl)- and 3-deoxy-3-(iodomethyl)-D-*myo*-inositol as well as 3-deoxy-3-

phosphonomethyl-D-*myo*-inositol.[129]



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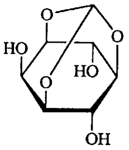

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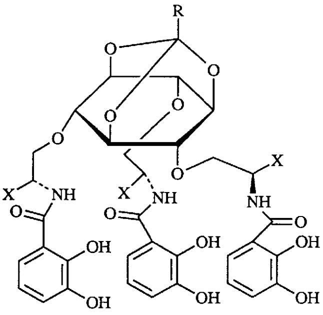

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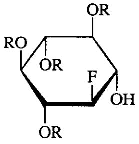
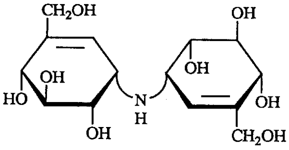


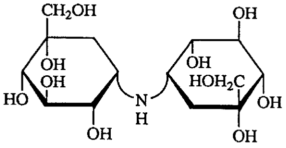
110 R = C_6H_{13}

The use of L-quebrachitol in the synthesis of (-)-oudemansin X and the synthesis of a chiral trihydroxy A ring intermediate for 1α,2β,2S-trihydroxyvitamin D3 are mentioned in Chapter 24.

In the area of carba-disaccharides, the synthesis of dicarba-α,α-trehalose, together with the analogues **110a** and **111** have been reported as potential trehalase inhibition.[130]

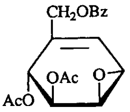


110a



111

Several 1,4-imino-linked carbadisaccharides containing 2-amino-2-deoxy-5a-carba-glucopyranosyl residues as analogues of the potent α-glucosidase inhibitor, acarviosine have been prepared,[131] and the preparation of a *manno*-configurated (1→6)-imino-linked unsaturated derivative using the reaction of methyl 6-amino-6-deoxy-α-D-mannopyranose with epoxide **112** has been reported.[132]



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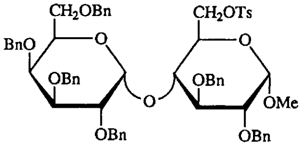

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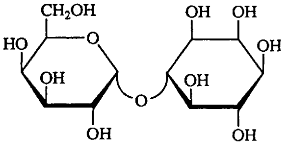


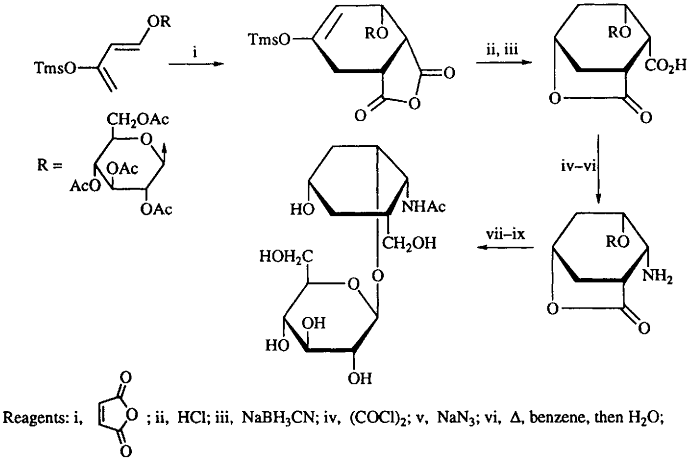
114

The absolute configuration of 4-α-D-glucopyranosyl-*myo*-inositol, synthesized by enzymatic *trans*-glycosylation by a known procedure (M. Sato *et al.*, *Biotechnology Letters*, 1992, **14**, 659; **13**, 69), has been proved by synthesis starting with 1L-1,3,4,5-tetra-*O*-benzoyl-*myo*-inositol.[133]

The preparation of 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol 1-phosphate as a potential insulin second messenger using (-)-quinic acid as the source of the inositol moiety has been achieved.[134]

The conversion of the glucose ring of the disaccharide **113** into an inositol ring of compound **114** and a related compound by way of a Ferrier reaction and standard chemical transformations has been disclosed.[135]

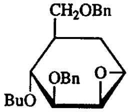
The synthesis of carbadisaccharides by way of a Diels-Alder approach has been reported (Scheme 13).[136]



Reagents: i, ; ii, HCl; iii, $NaBH_3CN$; iv, $(COCl)_2$; v, NaN_3; vi, Δ, benzene, then H_2O; vii, LAH; viii, Ac_2O, Py; ix, IRA-400 (^-OH)

Scheme 13

The anhydrocyclitol **115** has been used as a 5a-carbahexopyranosyl donor for preparing a variety of oxygen-linked 5a-carba-di- and tri-saccharides.[137]



115

The synthesis of sodium 1D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol sn-2,3-dipalmitoyloxypropyl phosphate and the related 1L-*myo*-inositol derivative have been prepared to develop an *in vitro* assay for the α-D-Man*p*-(1→4)-α-D-Glc*p*-NH_2-(1→6) phosphatidyl inositol α-D-mannosyl transferase and related systems.[138]

The preparation of some sulfur-linked carbadisaccharides are mentioned in Chapter 3.

2.3 Inositol Phosphates and Derivatives.-A monograph on the chemical synthesis and biological significance of inositol phosphates has appeared.[139]

Studies by potentiometric and ^{31}P NMR methods of *myo*-inositol 1,4,5-triphosphate (Ins (1,4,5) P3) have given data on protonation sequence.[140]

The synthesis of *myo*-inositol 1,4,6-triphosphate from *myo*-inositol as a new synthetic Ca^{2+}-mobilizing agonist at the Ins(1,4,5)P3 receptor has been described,[141] and in an expanded version of earlier work (*J. Org. Chem.*, 1989, **54**, 5851 and Vol. 24, p. 206, ref. 103) the synthesis from quinic acid of Ins(1,4,5)P3 and of Ins(1,3,4,5)P4 have also been described.[142]

A full report on the synthesis of 1D-3-deoxy-Ins(1,4,5)P3 (see Vol. 24, p. 206, ref. 104 for a preliminary account) together with two novel dideoxy and trideoxy compounds, 1D-2,3-dideoxy-Ins(1,4,5)P3 and 1D-2,3,6-trideoxy-Ins(1,4,5)P3, have been described.[143]

D,L-2,3-*O*-Cyclohexylidene-*myo*-inositol has been kinetically resolved using a lipase in the presence of acetic anhydride and further converted into Ins(1,4,5)P3.[144]

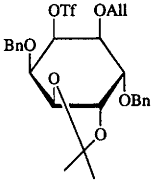
The preparations of the known (Vol. 22, p. 172, ref. 21 and Vol. 24, p. 206, ref 95) 3,6-di-*O*-benzoyl D,L-*myo*-inositol 1,2,4,5-tetrakisphosphate and Ins(1,2,4,5)P4 have been described and their ability to release Ca^{2+} at the Ins(1,4,5)P3 receptor studied.[145]

The syntheses of racemic 2-deoxy-2-fluoro-*myo*-inositol 1,4,5-triphosphate and of 2-deoxy-2-fluoro-*scyllo*-inositol 1,2,4-triphosphate as novel Ins(1,4,5)P3 agonists using the intermediate triflate **116** have been reported.[146]

The first synthesis of the 4,5-diphosphonate analogue **117** of D,L-4,5-*myo*-inositol 4,5-diphosphate has been described by two different routes using either phthalic acid or the Diels-Alder adduct derived from butadiene and dimethylfumarate as starting materials.[147]

The preparations of the racemic methyl phosphonate **118**[148] and phosphonate **119**[149] from *myo*-inositol and quebrachitol, respectively, have been reported.

The preparation of *myo*-inositol 1,4,5-triphosphate 3-*O*-methylene carboxylate, **120** as an analogue of Ca^{2+} mobilizing Ins(1,3,4,5)P4 has been described.[150]



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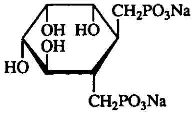

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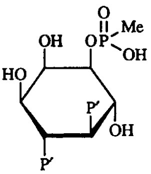
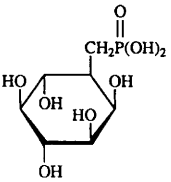


118 $P' = OPO_3^{2-}$



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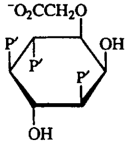
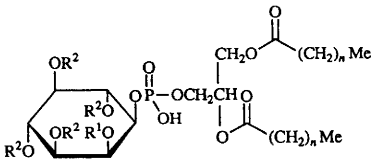


120 $P' = OPO_3^{2-}$

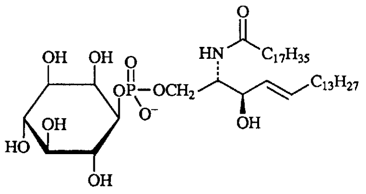
The synthesis of racemic phosphatidyl-2-*O*-alkylinositol **121** as a potential inhibitor of phosphatidyl inositol specific phospholipase C (PI-PLC)[151] and a short, convenient route to protected phosphatidyl inositol **122**[152] have been achieved.



121 R^1 = Me or n -C_7H_{15}, R^2 = H, *n* = 6
122 $R^1 = R^2$ = Bn, *n* = 4 or 5

The D-*erythro*-ceramide-1-phosphoinositol **123** has been prepared from *myo*-inositol and resolved *via* an intermediate (-)-menthyl carbonate derivative.[153]

The preparation of the octadecylphosphodithionyl-1-*myo*-inositol **124** as a potential PI-PLC inhibitor,[154] and the synthesis of the trismethylene sulfonic acid derivative **125** as an analogue of trideoxy *myo*-inositol 1,4,5-triphosphate in which the cyclitol ring is formed by a Diels-Alder reaction of di-(+)-menthyl fumarate and 2-benzyloxymethyl-1,3-butadiene,[155] have been reported.



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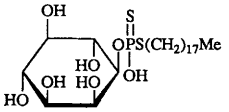

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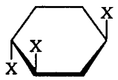

125 $X = CH_2SO_3^-Na^+$

The synthesis of D-mannose 1,4,6-triphosphate as an analogue of L-*myo*-inositol 1,4,5-triphosphate is covered in Chapter 7.

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19
Antibiotics

The synthesis of bioactive compounds containing carba-sugars has been reviewed.[1]

1 Amino-Glycoside Antibiotics

As is customary, this section contains reference to antibiotics comprising amino-sugars glycosidically linked to various aglycons - not just cyclitol derivatives. The title is sometimes used for this latter group exclusively.

Reviews have appeared on carba-amino sugars and their α-glucosidase inhibitory activity,[2] and on the chemistry and enzymic preparation of complex chiral and bio-active azamono- and oligo-saccharides and their derivatives.[3]

Derivatives of istamycin B, including its 3-*O*-demethyl and various 2′-*N*-acyl and *N*-amidinyl derivatives, have been prepared in the search for compounds less toxic than the parent.[4] Further analogues of 1,6-anhydro methyl acarviosin have been synthesized, particularly 2′-substituted compounds ($OH \rightarrow NH_2$,F).[5]

Allosamidin has been converted to its demethyl and didemethyl analogues by treatment with methylamine and ammonia respectively, and 6- and 6″-*O*-acyl derivatives were also prepared.[6] A study of the biosynthesis of allosamidin suggests that one *N*-methyl group is introduced before cyclization of the oxazoline ring.[7] A synthesis of the cyclopentane-based (-)-allosamizoline moiety of allosamidin is mentioned in Chapter 18.

3-Deoxy-3-fluoro-D-glucose has been used to prepare 4-amino-3-fluoro-2-hydroxybutanoic acid derivatives which were coupled to kanamycin A and B via amide links to N-1 of the streptamine unit.[8]

Synthesis of 5-deoxy-5-fluoro- and 5,5-difluoro-netilmicin involved DAST treatment of the epimeric alcohol or ketone derivative.[9] Analogous derivatives of arbekacin have been prepared and had lower toxicities than the antibiotic.[10] New 2″-amino derivatives of the antibiotic have also been reported.[11]

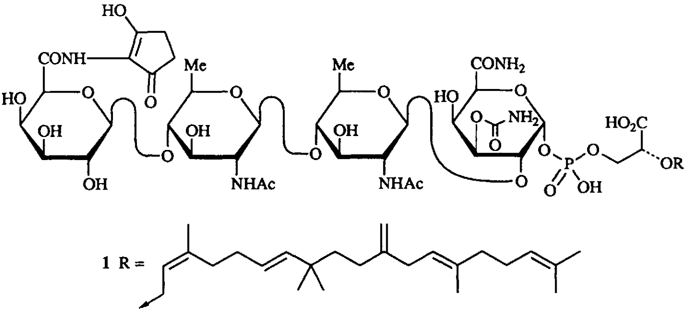
N-Benzamido derivatives of kanamycin A and tobramycin containing a chromium complex in the benzoic acid unit have been synthesized; their potential in metallo-immuno assay detection of these antibiotics was not apparently fulfilled.[12]

Pathogenic *Nocardia* bacteria can inactivate rifampicin by forming β-D-glucopyranosyl derivatives of this antibiotic.[13]

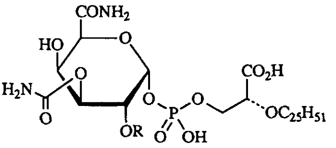
Complete ^1H and ^{13}C n.m.r. assignments have been made for apramycin and sisomicin, as well as for polyacetyl derivatives of kanamycins A and B and tobramycin.[14] N.m.r. data and molecular mechanics calculations have been used to establish conformations of sisomicin and a polyacetyl derivative.[15]

Syntheses of components of calicheamicins and esperamicins are mentioned in Chapters 10 and 11.

A new antibiotic, moenomycin C_1, has been isolated and assigned structure **1**. It lacks the C-4 branching in unit F present in the other moenomycin antibiotics. The smallest degradation product to retain activity was the corresponding trisaccharide lacking the terminal galacturonic acid unit and having a saturated alkyl ether unit.[16] The reducing terminal disaccharide in this degradation product was synthesized.[16] Moenomycins C_3 and C_4 have also been isolated from a flavomycin complex, and characterized as close analogues of the C_1 antibiotic, but with the 4-C-methyl-D-glucuronic acid unit present in moenomycin A.[17] The disaccharide **2**[18] and the trisaccharide **3**[19] have also been synthesized, the latter being as active as moenomycin A.



1 R =



2 R = β-D-Glc*p* NAc
3 R = β-D-Glc*p* NAc-(1 → 4)-β-D-Glc*p* NAc

2 Macrolide Antibiotics

Vicenistatin, isolated from *S.* sp. HC34, contains the amino-sugar vicenisamine (4-methylamino-2,4,6-trideoxy-β-D-*ribo*-hexopyranose) attached to a 20-membered macrolide ring.[20] An unnamed macrolactam dissaccharide antifungal antibiotic from the culture broth of *Actinomadura* sp. SCC 1840 contains the disaccharide unit α-D-Glcp(1→2)-α-L-mycosamine attached to a 14-membered macrolide ring.[21]

Antibiotic PC-766B, a new macrolide antibiotic obtained from *Nocardia brasiliensis*, contains 2,6-dideoxy-β-D-*arabino*-hexopyranose attached to a 16-membered macrolide ring through a 6-membered hemi-ketal ring on a sidechain.[22]

The macrolide anitbiotics quartromicins A1, A2, and A3, obtained from *Amylolatopsis orientalis* contain two α-D-galactopyranose residues separately attached as *O*-glycosides to a 32-membered carbon ring.[23]

3″-Epierythromycin A has been synthesized from a desosaminyl erythronolide precursor using the glycal rearrangement glycosylation procedure with a glycal obtained from cladinose.[24]

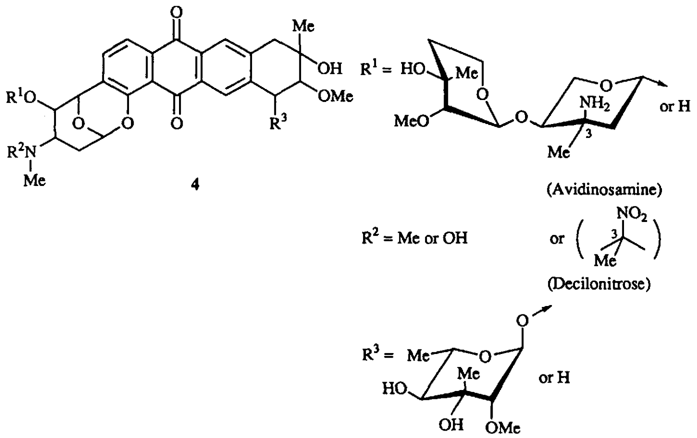
The solution conformation of azithromycin, which contains desosamine and cladinose attached to a 15-membered aza-lactone ring, has been determined from ^{1}H n.m.r. data and molecular mechanics calculations.[25] ^{1}H and ^{13}C n.m.r. data for tylosin have been reported.[26] Conformational space searching has been used to assess the selectivities of *O*-methylation of erythromycin derivatives.[27]

The synthesis of the digitoxose disaccharide unit of kijanimycin is referred to in Chapters 3 and 8.

3 Anthracycline and Related Polycyclic Antibiotics

Respinomycins, novel anti-leukaemia compounds produced by *S. xanthocidicus*, have been shown to have the general structure **4**.[28]

Other new antibiotics are the dactylocyclines **5** from *Bacillus licheniformis*, [29] rubomycins F and H obtained from *S. coeruleorubidus*, which contain *N*-carboxy-methyl or -ethyl daunosamine,[30] and TAN-1120, produced by *S. triangulatus* subsp. *angiostaticus*, which contains the cyclic derivative **6** of daunosamine, being a close relative of barminomycin.[31] (See Vol. 25, p. 228).



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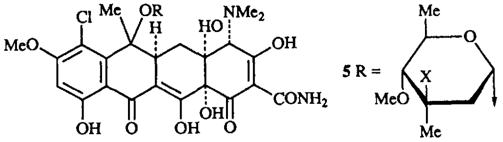
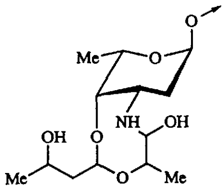


5

X = NHOH, NO_2, NHOAc, or OH

(Absolute configuration not known)



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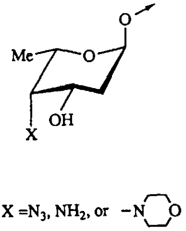
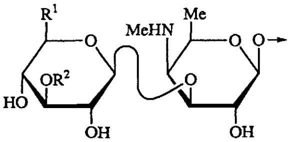


7 X = N_3, NH_2, or

A 5-deoxypyranoanthracycline analogue of idarubicin has been synthesized using a conventional glycosylation procedure.[32] Isodoxorubicin derivatives have been made incorporating the isomeric 4-amino-sugar units **7** and giving a highly active antitumour agent ($X=NH_2$).[33] 3′-*N*(β-D-glucopyranosyl)thiocarbamoyl-daunorubicin has been made using tetraacetyl-D-glucopyranosyl isothiocyanate.[34]

Anthracyclines incorporating a disaccharide unit have been prepared by glycosylating the aglycon with an α-L-daunosaminyl-(1→3)-α-L-rhamnopyranosyl unit using a glycal procedure and giving a product only marginally active.[35] Otherwise a microbial glycosidation method with a mutant strain of *S. galilaeus* and the anthracyclinone monosaccharide was used. Addition of rhodinose or 2-deoxyfucose as the additional sugars again gave less active products.[36]

New congeners of pradimicin A which contains the disaccharide unit **8** attached to a pentacyclic aglycon have been reported. Pradimicins L and FL contain the D-glucose unit **9**,[37] pradimicin S the corresponding D-glucopyranosyl 3-sulphate **10**,[38] and pradimicins T1 and T2 contain in addition a β-L-xylopyranosyl unit elsewhere on the aglycon.[39] Pradimicin analogues containing modified sugars have been synthesized, notably with modified D-xylose units, some of which are as active as pradimicin A. Structure-activity relationships clarified the role of the sugar moiety in the antifungal properties.[40] Another paper describes the synthesis of conventional *N*-substituted derivatives of the amino-sugar unit, the 4-*N*-cyano derivative of pradimicin C showing most promise.[41] Pradimicins H and FH, which are 11-hydroxy analogues of pradimicins A and FA-1, have been converted to 11-*O*-L-xylosyl derivatives on being fed to an actinomycete strain to give broad spectrum antifungal agents.[42]

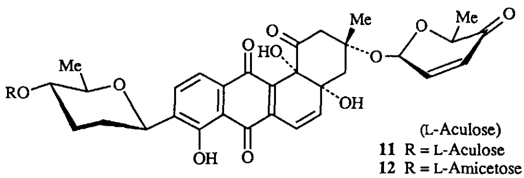


8 $R^1 = R^2 = H$
9 $R^1 = CH_2OH, R^2 = H$
10 $R^1 = CH_2OH, R^2 = SO_3H$

The tetrocarcin antibiotic AC6H is related to tetrocarcin A in having the nitro-sugar in the latter (decilonitrose) reduced to the corresponding amino-sugar.[43]

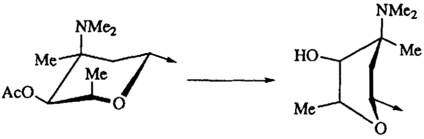
Antibiotic D329C, obtained from a mutant strain of *S. chartreusis*, is a chartreusin analogue with a digitalose→fucose→fucose trisaccharide unit instead of the digitalose→fucose disaccharide present in chartreusin.[44]

Two new angucycline group antifungal compounds, Sch 47554, **11** and Sch 47555, **12**, have been isolated from the *Streptomyces* strain SCC2136.[45]



(L-Aculose)
11 R = L-Aculose
12 R = L-Amicetose

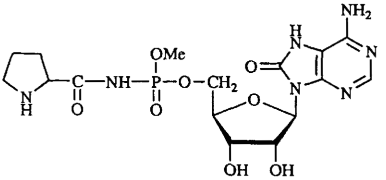
Deacetylation of the vancosamine moiety in saptomycins D and E (see Vol. 25. p. 227) causes a conformational change from chair to boat form shown in Scheme 1; it makes little difference to their antibiotic activity.[46]



Scheme 1

4 Nucleoside Antibiotics

Phosmidosine, an antibiotic from *S. durhamensis*, has been characterized as the nucleoside derivative **13**.[47]



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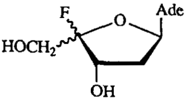


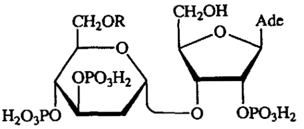
14

Nucleocidin and the 2′-deoxy analogues **14** have been synthesized, besides other 4′-fluoro derivatives.[48]

A practical synthesis of toyocamycin has been described.[49]

Analogues of sangivamycin have been synthesized. 5′-Substituted derivatives, including sulphamate, mesylate and nitrate esters, and its 5′-azido-5′-deoxy analogue, are more potent enzyme inhibitors than the parent.[50] 2′ and 3′-Stereo-isomers of sangivamycin together with 2′- and 3′-deoxy and/or fluoro compounds have been prepared conventionally and their conformations determined.[51]

The inositol 1,4,5-trisphosphate agonists adenophostins A and B **15** and **16**, respectively, have been isolated from the culture broth of *Penicillium brevicompactum*.[52]



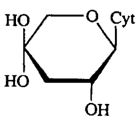
15 R = H
16 R = Ac

Compounds related to agrocin 84, including 9(3-deoxy-β-D-*threo*-pentofuranosyl) adenine and a 6-*N*-glucosylphosphorylated derivative of adenosine, have been synthesized.[53]

Molecular orbital studies of nebularine and isoguanosine have predicted conformational preferences for these compounds which were compared with those of the parent purine nucleosides.[54]

A synthesis of rebeccamycin has been described.[55]

A series of cytosine derivatives, including the compounds **17** and **18**, have been isolated from a fermentation broth of *S. griseochromogenes* fed with cytosine and L-arginine hydroxamate.[56]



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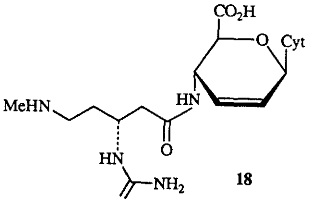

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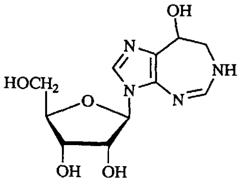


19

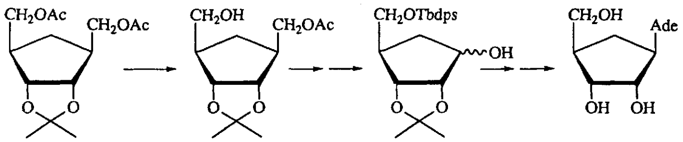
Two new cytotoxic compounds, the *C*-glycoside 9-deazaadenosine and its 5′-α-D-glucopyranoside derivative, have been isolated from broths of the cyanobacterium *Anabaena affinis*.[57]

5′Deoxypyrazofurin has been synthesized, using a modified Wittig approach to generate the *C*-glycoside from a 5-deoxy-D-ribose precursor.[58]

Syntheses have been reported for 2′-deoxyshowdomycin and its α-anomer, also using a Wittig procedure with 2-deoxy-D-*erythro*-pentose.[59]

Five carbocyclic nucleosides have been isolated from a fermentation broth of a *saccharothrix* species; of those, compound **19** showed post-emergence herbicidal activity.[60]

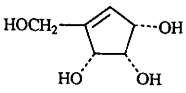
Aristeromycin **21** has been prepared from the *meso*-cyclopentane derivative **20** using lipase to achieve asymmetric hydrolysis leading to intermediates for (-)-aristeromycin, as outlined in Scheme 2.[61]



20 **21**

Scheme 2

The cyclopentenol **22** has been shown to be an intermediate in the biosynthesis of both aristeromycin and neplanocin A.[62]



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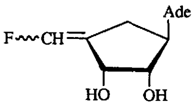

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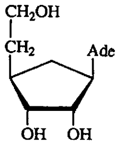

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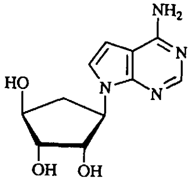
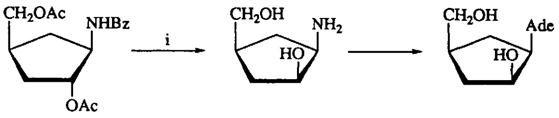


25

Syntheses have also been reported for 5′-deoxyaristeromycin,[63] (E) and (Z)-4′,5′-didehydro-5′-deoxy-5′-fluoro-aristeromycin **23**,[64] (-) homoaristeriomycin **24**, together with 5′-noraristeromycin and 7-deaza-5′-noraristeromycin **25**,[65] and of 5′-noraristeromycin using a chemo-enzymatic route from cyclopentadiene monoxide.[66] Other papers report syntheses of 7-deaza-4′deoxy-5′-noraristeromycin,[67] 5′-nor-2′- and 3′-deoxyaristeromycin,[68] 4′-epi-5′-noraristeromycin and 4′-deoxy-4′-fluoro-5′-noraristeromycin,[69] neplanocin A together with 5′-noraristeromycin,[70] and 3′-deoxy-*ara*-aristeromycin **27** by a surprising 2′-epimerization of the 3′-deoxy-aristeromycin precursor **26** (Scheme 3).[71]

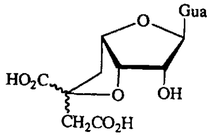


26

Reagent: i, 6N HCl

27

Scheme 3



28

Further work on griseolic acid analogues has been reported (see Vol. 25, p. 232), giving guanosine analogues, e.g. **28**, instead of adenine derivatives and its 3′,4′-stereoisomers together with carbocyclic analogues.[72] Other carbocyclic nucleoside derivatives of aristeromycin and a synthesis of carbovir are mentioned in Chapter 20, and a synthesis of the carbocyclic nucleoside precursor, Ohno's lactone, is referred to in Chapter 18.

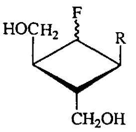
The syntheses of oxetanocin A and its carbocyclic analogues have been reviewed.[73] Syntheses have been recorded for carbocyclic analogues of oxetanocin A [74, 75, 75a] and cyclobutane intermediates for such compounds,[76] and such intermediates are also mentioned in Chapters 14 and 16. The fluorinated analogues **29** have also been made.[77, 78]

The synthesis of tunicamycin V using a 2-azido-2-deoxy-D-galactose derivative as starting material for a multistep sequence has been described.[79]

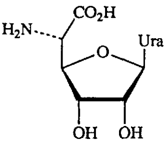
Degradation of polyoxin D yielded uracil polyoxin C, **30**, which was used to prepare analogues of both polyoxins and nikkomycins.[80, 81] Thymine polyoxin C has been synthesized.[82] N.m.r. data on polyoxin A have suggested a revised stereochemistry for the exocyclic double bond present on the azetan ring.[83]

Syntheses have been recorded for (-)-polyoxamic acid[84] and (+)-5-*O*-carbamoyl-polyoxamic acid.[85]

Reaction of nucleoside 5'-aldehydes with DAST has led to some fluorinated AZT analogues, e.g. **31**.[86]



29 R = Gua, Ura, or Cyt



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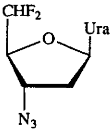


31

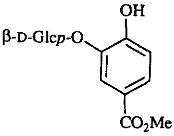
The undecose skeleton present in herbicidins has been synthesized from a 1,5:3,6-dianhydrohexulose percursor.[87]

A new drug delivery system for allopurinol has been developed which incorporates D-gluconic acid and D-mannose units on a polylysine backbone.[88]

Antibiotic 3'-amino-3'-deoxy nucleosides are mentioned in Chapter 20.

5 Miscellaneous Antibiotics

The glucoside **32**, isolated from the fern *Woodwardia orientalis*, has been shown to have antiviral activity.[89]



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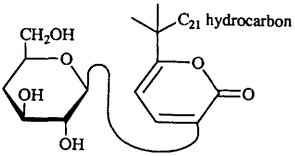
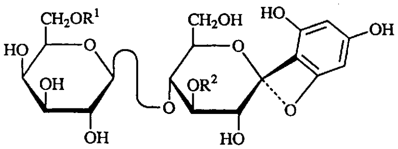


33

The novel antifungal antibiotic dactylfungin A, obtained from *Dactylaria parvispora* D500, has structure **33** containing a linear terpene hydrocarbon. The B isomer, from the same source, has the γ- instead of the α-pyrone as the central unit.[90] Spectroscopic evidence suggests a new inhibitor of adenosine triphosphatases, aquastatin A, obtained from the fungus *Fusarium aquaeductuum*, is a β-galactopyranoside of a dimeric dihydroxy-benzoic acid.[91] Spectroscopic evidence also suggests that novel cytocidal compounds oxapropalines A, B, and E, obtained from *S.* sp G324, are all α-rhamnopyranoside derivatives of a β-carboline chromophore.[92]

BU-4794F, a new β-1,3-glucan synthase inhibitor, isolated from the culture broth of the fungus *Gilmaniella* sp. FA 4459, is a novel member of the papulacandin group of antibiotics, and contains the disaccharide unit **34** which carries fatty acid substitutents.[93] Another papulacandin antibiotic, Mer-WF3010, from *Phialophora cyclaminis*, is a closely related analogue of **34** with a C_8 rather than C_{10} ester substituent.[94]



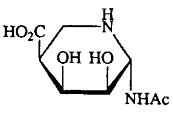
34 $R^1 = C_{10}$ acid, $R^2 = C_{16}$ acid

N-1,2-Dihydroxypropyl derivatives of siastatin B **35** and its 4-deoxy- and 3,4-didehydro-4-deoxy analogues which proved to be potent neuraminidase inhibitors have been synthesized.[95] 3-Episiastatin B and 3,4-diepisiastatin B have been prepared from siastatin B, and shown to have anti-influenza virus activity.[96]

Full details of the synthesis of racemic mannostatin A have been published (see Vol. 25, p. 236).[97]

The trehalase inhibitor trepazolin **36** has been synthesized from the corresponding amino-pentitol using a glucosyl isothiocyanate reagent to give a thiourea intermediate leading to the required oxazoline ring.[98, 99]

Trehalamine, the aglycone of trehazolin, has been isolated from microbial broths.[100] (See Vol. 25, p. 224).



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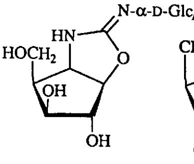

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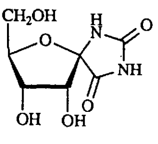

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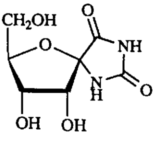

38

(+)-Hydantocidin **37** has been synthesized from fructose via a psicofuranose intermediate,[101, 102] and the spirostereoisomer, 1-epi-hydantocidin **38**, has also been prepared.[102, 103]

Chapter 10 contains a reference to spirohydantoins formed from mannofuranose.

D-Xylose isonicotinoylhydrazone, produced conventionally, shows *in vitro* anti-bacterial activity.[104]

Some 3-*O*-alkyl and 3-*O*-haloalkyl-D-glucose derivatives have been found to have antimicrobial properties. Compounds containing C_{12} and C_{14} alkyl groups were most effective.[105, 106]

Hydroxyjuglone glucosides and maltosides, prepared by an ortho-ester procedure, have been found to be more effective antifungal agents than the parent aglycone.[107]

The importance of the sugars present in vancomycin for stabilizing the dimers formed in solution has been studied using n.m.r. evidence.[108]

An antibiotic incorporating features of cyclitol and nucleoside antibiotics is mentioned in Chapter 9. 6-Deoxy-6-fluoro-glucosides, which are glucosidase inhibitors, are covered in Chapter 8. The synthesis of a trisaccharide fragment of some orthosomycin antibiotics is referred to in Chapter 3.

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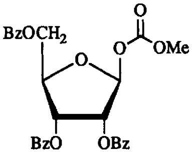
20
Nucleosides

1 General

A review on 'current concepts in antisense drug design' discusses the topical area of analogues, both phosphorus-containing and lacking phosphorus, that have been used as isosteric replacements for the phosphodiester link in oligonucleotides.[1] Krayevsky and Watanabe have jointly proposed the possibility for the existence of a general conformational motif in the active site of enzymes involved in nucleic acid metabolism; detailed examination of the sugar moieties of a large group of modified nucleosides indicates a distinct conformational similarity, with a flattening of the rings. The authors propose that during the enzyme process natural substrates should reflect these flattened conformations.[2]

2 Synthesis

With regard to new methods for the synthesis of β-D-ribofuranosyl nucleosides, it has been shown that the methyl carbonate **1** condenses in a highly stereoselective manner with silylated heterocycles in the presence of silver salts and diphenyltin sulfide.[3] The use of pentenyl glycosides has been extrapolated to the nucleoside field; the glycoside **2** coupled efficiently with various purines when activated by NIS and TfOH to give products β-linked at *N*-9, but the method was less effective in the 2-deoxy series.[4]



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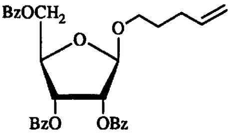
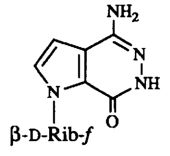


2

Standard condensation procedures have been used to prepare β-D-ribofuranosyl derivatives of some 6-azauracils,[5] 4-quinolones,[6] some 1,2-benzisoxazol-3(2*H*)-ones and 5-methyl-1,2-benzisothiazol-3(2*H*)-one,[7] 1,7-dideazapurines,[8] the pyrrolo[2,3-*d*]pyridazinone **3**, made by cyclization of a pyrrole nucleoside,[9] and some 8-substituted theophyllines (ribosylation at N-7).[10,11] Also reported has been the 5-iodoanalogue of tubercidin, together with some related 5'-modified compounds,[12] the imidazo[1,2-*a*]-1,3,5-triazinone **4** (an isoguanosine analogue),[13] the

1,2,4-triazolo[4,3-*b*]-1,2,4-triazole nucleoside **5**, which was the major regioisomer formed under the conditions used (see Vol. 18, p.190 for an alternative isomer),[14] the thieno[3,2-*d*] pyrimidinedione **6** and some related compounds modified at C-4,[15] and the thieno[3,4-*d*]pyrimidine **7** (for related *C*-nucleosides, see Section 10).[16]

Reduction of the 2'-ketonucleoside gave the precursor **8** of 2'-deuterio-*ara*-adenosine, and inversion of stereochemistry *via* the mesylate gave 2'-deuterio-adenosine. Similar work was also carried out on tubercidin (7-deazaadenosine).[17]



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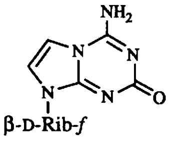

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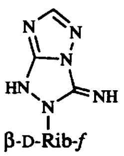

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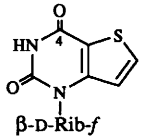

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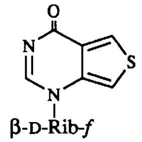

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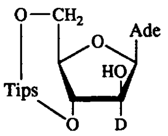

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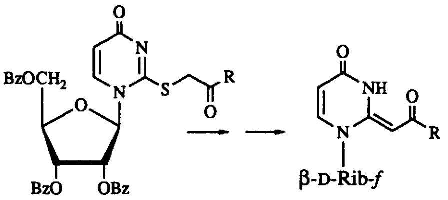


9 **10**

A range of 1',2'-*cis*-pyrimidine nucleosides (α-D-*ribo*-, α-D-*xylo*-, etc) have been made by NBS-promoted reaction of *O*-benzylated thioglycosides with the silylated pyrimidine.[18]

The pyrimidine derivatives **9** (R=Me, Et) could be made by direct glycosylation, and converted into 2-(2-oxoalkylidene)-4-pyrimidinones **10** by a sulfur extrusion process. 2'-Deoxyanalogues were made in an alternative way by opening of a 2,5'-anhydronucleoside with the appropriate enolate, and the arabinofuranosyl series was similarly accessible from 3',5'-di-*O*-Tbdps-2,2'-anhydrouridine and an enolate.[19]

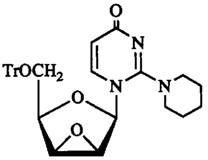
Reaction of methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside with silylated 6-methyl- or 6-ethyluracil gave a mixture of the N^1-glycosylated product and the N^1,N^3-disubstituted material. The equivalent reaction of 6-ethyl-2-thiouracil gave mostly the N^3-arabinofuranosyl derivative.[20]

β-L-Xylofuranosyl nucleosides have been prepared conventionally from all five of the nucleic acid bases[21] and from some 8-substituted theophyllines.[22] β-D-Glucopyranosyl derivatives of pyrrolidinone[23] and pentobarbital diastereomers[24] have been reported. Reaction of D-glucose hydrazone with acetylacetone gave 1-β-D-glucopyranosyl-3,5-dimethylpyrazole, and similar chemistry was carried out in the D-galactosyl and D-xylosyl series.[25]

3 Anhydro- and Cyclo-nucleosides

Dialkylamino compounds such as **11** are formed from 2',3'-di-*O*-mesyl-5'-*O*-trityluridine on treatment with the secondary amine, reaction proceeding via the 2,2'-anhydronucleoside. The presence of the 3'-*O*-mesyl group facilitates the opening of the anhydronucleoside by the amine, since the compound lacking this activation does not open with dialkylamines.[26]

The 8,2'-anhydrosystem **12** could be formed from 8-mercapto-3',5'-Tips-guanosine under Mitsunobu conditions (DEAD, TPP, DMF), and the 8,5'-anhydrocompound **13** could be similarly made from 2',3'-*O*-isopropylidene-8-mercaptoadenosine.[27]



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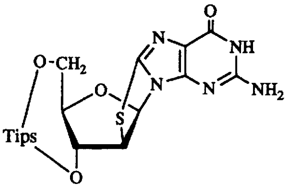

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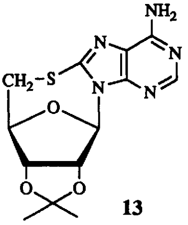
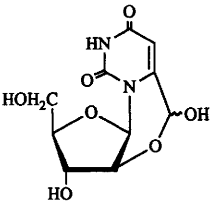


13

There has been a further report (see Vol. 26, p. 227-8) on the formation of intramolecular hemiacetals by uridine-6-carboxaldehyde and related compounds. The D-*ribo*- and 2'-deoxy-D-*ribo*-compounds form hemiacetals involving O-5', whilst the D-*arabino*-analogue forms the hemiacetal **14** involving O-2'.[28]

On oxidation and subsequent treatment with hydroxylamine, 3',5'-*O*-Tips-uridine was converted into a 2'-oximinocompound, shown to be in equilibrium with the cyclized structure **15**. Desilylation of the oxime, followed by reduction with BH_3.Py, gave the cyclic *N*-hydroxy compound **16**.[29]



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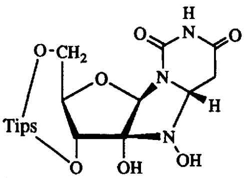

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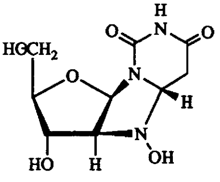

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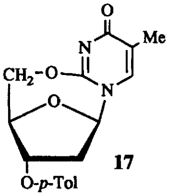

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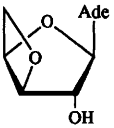


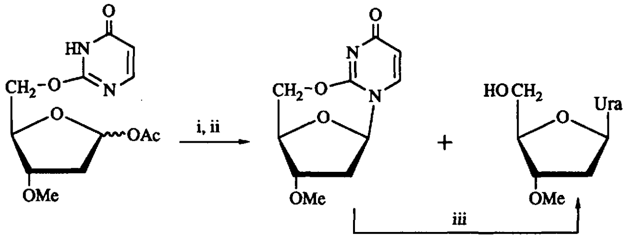
18

Treatment of the 2,5'-anhydride **17** with liquid hydrogen sulfide in pyridine gave the 2-thiono-pyrimidine, which could be oxidatively desulfurized to give the 2'-deoxy-4-pyrimidinone nucleoside.[30]

The oxetane **18** could be obtained by treatment of 5'-*O*-tosyl-β-D-xylofuranosyladenine with sodium methoxide, and this material proved to have interesting antiviral activity.[31]

A number of examples of the use of anhydronucleosides in the synthesis of other types of compounds can be found elsewhere in this Chapter.

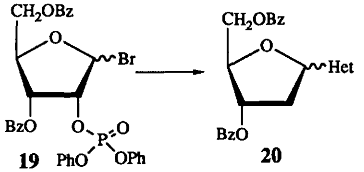
4 Deoxynucleosides



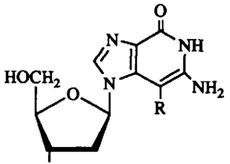
Reagents: i, TmsCl, hexamethyl disilazane; ii, TmsOTf, MeCN; iii, NaOH aq.

Scheme 1

Two laboratories have independently developed a new stereoselective approach to the synthesis of β-2'-deoxyribonucleosides by intramolecular glycosidation. One group have employed an intramolecular Vorbrüggen-type coupling, as outlined in Scheme 1,[32] whilst alternatively a thioglycoside can be used as the intramolecular glycosyl donor, activated by dimethyl(methylthio)sulfonium tetrafluoroborate.[33] In another new approach to 2'-deoxyribonucleosides, it was found that irradiation of the bromide **19** in the presence of Bu_3SnH and an *N*-heterocycle gave reasonable yields of nucleosides of type **20**, but without stereocontrol; it was assumed that the 2-deoxy-α-ribofuranosyl phosphate was an intermediate, produced by rearrangement of the initial anomeric radical.[34]



19 **20**



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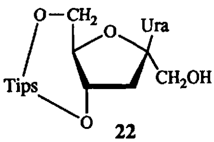


22

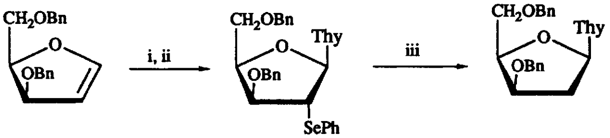
2-Thio-derivatives of 2'-deoxyuridine and 5-fluoro-deoxyuridine (FDU) have been produced as α,β- mixtures by conventional coupling,[35] whilst other workers have shown that, in the case of 2-thio-2'-deoxyuridine, the β-anomer can be produced stereoselectively at low temperatures, whilst the α-anomer is formed at higher temperatures.[36] Fairly conventional base-sugar couplings have also been used to make 2'-deoxyribonucleosides of 4-methoxycarbonylindole,[37] some 3-alkyl-3-deazaguanines **21**, made by cyclization of imidazole deoxynucleosides,[38] some hydantoin analogues of thymine,[39] 4-methoxy-pyrazolo[3,4-*d*]pyrimidine (the 2',3'-dideoxynucleoside was also made, and hydrolysed to the ddI analogue),[40] and 8-azaguanine, when products of glycosylation at all three nitrogen atoms in the triazole ring were obtained.[41]

Tin hydride reduction of the D-*ribo*-precursors was used to make 2'-deoxy-5-triflyloxyuridine, where the 2'-3'-dideoxycompound and the 2',3'-ene (d4 nucleoside) were also made; the 5-triflyloxy group can be used in Pd-catalysed substitutions to give a range of 5-substituted nucleosides.[42] Similarly prepared was the 2'-deoxyanalogue of N^2-,3-ethenoguanosine,[43] and the deoxyfructofuranosyl nucleoside **22**.[44] A way has been developed for the highly stereoselective introduction of deuterium at C-2' of deoxyribonucleosides, involving treatment of the 2'-bromo-2'-deoxy-3',5'-*O*-Tips-ribonucleoside with Bu_3SnD and Et_3B at low temperatures; the deuterium is introduced with retention of configuration to give the 2'-*R*-deuteriated 2'-deoxy-nucleoside (i.e. with deuterium α-oriented).[45]

It has been found that addition of ethylene glycol (10% v/v) has a beneficial effect on the enzymic synthesis of 2'-deoxynucleosides catalysed by crude *N*-deoxyribosyl transferases from *Lactobacillus leichmanii*, by inhibiting some of the contaminating enzymes that carry out unwanted hydrolyses or deaminations. A number of 2'-deoxynucleosides of 6-substituted nucleic bases were obtained in high yields on a preparative scale.[46] Other workers have reported the synthesis of 2-chloro-2'-deoxyadenosine by microbiological transglycosylation of 2'-deoxyguanosine using whole cells of an *E.coli* strain.[47]

The Birmingham group have reported that treatment of 3',5'-di-*O*-acetyl-2'-deoxyribonucleosides with sulfuric acid/acetic anhydride causes anomerization to a mixture which is rich in the α-nucleoside.[48]

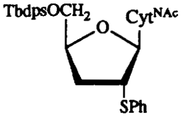
Furanoid glycals can be used in a stereoselective route to 2'-deoxy-β-D-*threo*-pentofuranosyl nucleosides, as illustrated by the case in Scheme 2, and 2'-deoxy-β-D-*arabino*-hexofuranosyl systems were similarly prepared.[49]



Reagents: i, PhSeCl, AgOTf; ii, $(Tms)_2Thy$; iii, Bu_3SnH, AIBN

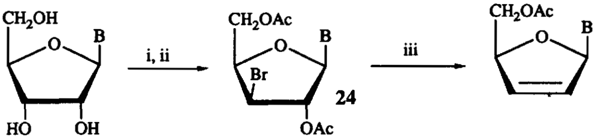
Scheme 2

In the area of 2',3'-dideoxynucleosides and the related 2',3'-enes (d4 systems), similar chemistry to that shown in Scheme 2 has also been employed for stereoselective access to these compounds. Thus the 2'-phenylthionucleoside **23** was prepared in 65% yield and with 18:1 β-stereoselectivity by treatment of the glycal with PhSCl and *N*-acetylcytosine in the presence of tin(IV) chloride; the phenylthiogroup can act as a precursor for the alkene or the saturated unit.[50] Other workers have reported similar results, but with the intermediate glycosyl chloride being separately prepared;[51] both these groups have earlier reported an alternative way of introducing the α-SPh group through sulfenylation of enolates (Vol. 24, p.229).



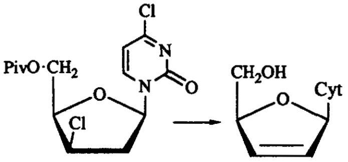
23

Barton's group have reported the synthesis of 2'.3'-enes by treatment of 2',3'-bis-xanthates with Et_3SiH[52] or Ph_2SiH_2[53] and dibenzoyl peroxide; the formation of the bis-xanthates is not easy, but the olefination is very efficient. Other workers have described the reductive cleavage of 2',3'-di-*O*-mesyl derivatives with Li_2Te, Na_2Te or Na_2Se as a route to d4 nucleosides,[54] and the ring-opening of 2',3'-orthoacetates and subsequent reductive elimination has also been developed as a general method for synthesis in the area (Scheme 3); alternatively, reduction of the intermediate bromoacetates **24** with tributylstannane gives access to 3'-deoxy systems.[55] A short synthesis of d4T has been reported, involving an elimination reaction on the 2,3'-anhydronucleoside,[56] whilst treatment of 5'-*O*-pivaloyl-2'-deoxyuridine with triphenylphosphine and carbon tetrachloride gives the D-*threo*-compound **25**, which on treatment with ammonia in chloroform, followed by potassium *t*-butoxide, provides a new route to d4C (**26**).[57]

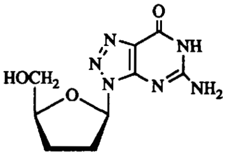


Reagents: i, $MeC(OMe)_3$, TsOH; ii, AcBr; iii, Zn/Cu

Scheme 3



25 **26**



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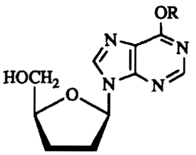


28

5-(Dialkylamino) derivatives of 2',3'-dideoxynucleosides have been made by base-sugar condensation,[58] as has dideoxy-8-azaguanosine (**27**), where products of glycosylation at N^2 and N^3 were also formed,[59] and various cytokine analogues (N^6-alkylated adenosine derivatives), along with dideoxydidehydro systems.[60] Treatment of 3'-deoxythymidine with thymidine phosphorylase from *E. coli* caused the formation of the glycosyl phosphate, which was coupled with various 6-alkoxypurines in the presence of purine nucleoside phosphorylase to give the dideoxynucleosides of type **28**.[61]

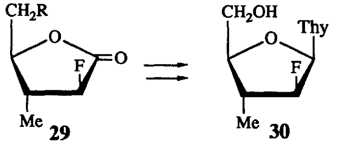
There has been an expanded account of work on the synthesis of 2',4'-dideoxy-β-D-*erythro*-hexopyranosyl nucleosides (see Vol. 26, p. 232),[62] and conventional Vorbrüggen-type condensation has been used to make 1-β-D-fucopyranosyl-uracil, -thymine and -cytosine, and 7-β-D-fucopyranosylguanine, the cytosine nucleoside showing good anti-leukaemic activity.[63]

5 Halogenonucleosides

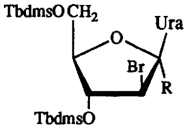
An improved synthesis of 2'-deoxy-2'-fluoroadenosine has been described, involving a sequence of two inversions of configuration at C-2' of an adenosine derivative,[64] whilst the 2'-deoxy-2'-fluoroderivatives of a wide range of purine nucleosides have been made by glycosyl transfer from 2'-deoxy-2'-fluorouridine using thymidine phosphorylase and purine nucleoside phosphorylase.[65]

A total synthesis has been developed of the racemic lactone **29**, which was then converted to the nucleoside (±)**30** and its α-anomer. The equivalent compounds of *ribo*-configuration (α-fluorine) were also described.[66]

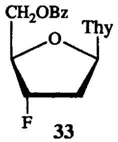
Addition of NBS and pivalic acid to the 1',2'-unsaturated nucleoside derivative gave the product **31** stereoselectively; treatment of **31** with allyl trimethylsilane and tin(IV) chloride led to the 1'-*C*-allyl derivative **32**, and a number of other carbon nucleophiles were similarly introduced.[67]



29 **30**



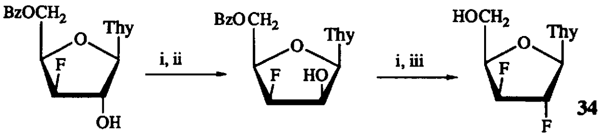
31, R = OPiv
32, R = All



33

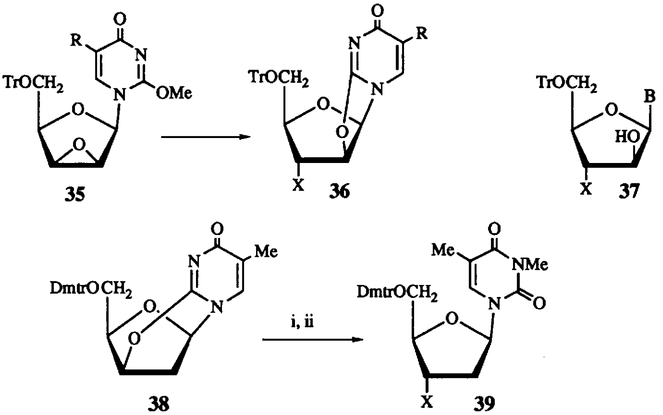
Both α- and β-isomers of 1,5-di-*O*-benzoyl-2,3-dideoxy-3-fluoro-D-*erythro*- pentofuranose were separately prepared; both coupled with bis-(TMS)thymine to give the 3'-deoxy-3'-fluorothymidine derivative **33** with β-selectivity.[68] Some 5-dialkylaminomethyl-3'-fluoro-2',3'-dideoxyuridines have also been reported by direct sugar-base coupling.[69]

Full details have been given of an earlier report (Vol. 23, p. 213) on the synthesis of 3'-deoxy-3'-fluoro-β-D-xylofuranosyl nucleosides and their 2'-deoxyanalogues. The conversion (Scheme 4) of one of these compounds into the difluoronucleoside **34** has also been reported.[70] Treatment of epoxides **35** (R=H,Me) with reagents Li_2CuX_4 (X=Cl,Br) gave the anhydronucleosides of type **36**, products of highly regioselective opening of the epoxide ring. The analogous uracil and thymine derivatives gave mostly products **37** (X=Br,Cl; B=Ura, Thy), but with some D-*xylo*-products also formed.[71] When the anhydronucleoside **38** was treated as indicated in Scheme 5, the N^3-methylated products **39** (X=Br,I) were obtained,[72] whilst the cytidine derivative **40** could be prepared from **25**.[57]



Reagents: i, DAST; ii, HCl, EtOH; iii, NH_3, MeOH

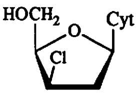
Scheme 4



Reagents: i, MeOTf, 2,6-di-*t*-butylpyridine, THF; ii, NaBr or NaI

Scheme 5

There has been a full and extended account of the synthesis of the 3'-bromoalkenes **41** (B=Ade, Ura) from the parent nucleosides *via* selenium-containing intermediates (see Vol. 25, p.251); the isomeric 2'-bromoalkenes are also available by this chemistry.[73]



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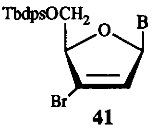

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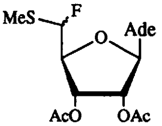

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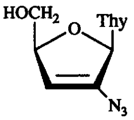

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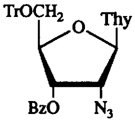

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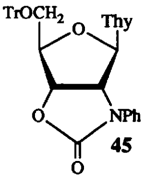


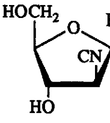
45

A solution of DAST in CH_2Cl_2, preferably but not necessarily with Sb(III) catalysis, converts thioethers into α-fluorothioethers such as **42**; fluorination of the methyl group was a competing reaction.[74] Some 5'-chloro-5'-deoxy-N^6-cycloalkyl-isoguanosines, agonists for the adenosine A_1 receptor, have been prepared by chlorination using NCS-TPP.[75]

6 Nucleosides with Nitrogen-substituted Sugars

A route to the unsaturated 2'-azidothymidine derivative **43** has been described. During this synthesis, intermediate **44** was produced by treatment of the 2,2'-anhydronucleoside with lithium azide in DMF, and in this reaction the oxazolidinone **45** was also produced in up to 19% yield. A reasonable mechanism for this rearrangement was proposed.[76] 2'-Deoxy-2'-isocyanonucleosides **46** (B=Ura, Thy, Cyt) have been prepared *via* 2'-azidointermediates. Similar chemistry was carried out in the D-*ribo*- series, but here the products tended to cyclize to give oxazolines.[77]

The aziridinonucleosides **47** (B=Ura, Thy) have been made by Vorbrüggen-type coupling of the sugar with silylated heterocycles.[78]



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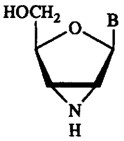

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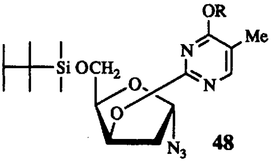
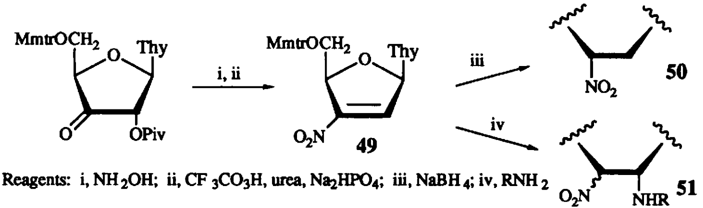


48

Some 3'-N-substituted -3'-amino-3'-deoxythymidines have been reported, synthesized either by displacement of an 'up' -mesylate by the amine or by reductive amination of 3'-amino-3'-deoxythymidine.[79] There has been a further report on simplified routes to AZT from 3'-O-mesyl-5'-O-Mmtr-thymidine,[80] and a full account of the synthesis of AZT stereospecifically deuteriated in the 2'-*pro-R* position from β-D-xylofuranosylthymine derivatives (Vol. 26, p .235) has been published, together with a route to AZT deuteriated at C-3' involving reduction of a 3'-ketointermediate with $NaBD_4$. These deuteriated materials were used in a conformational study which indicated an approximately 1:1 ratio of the C-2'-*endo*- and C-3'-*endo* species in solution.[81]

With regard to analogues of AZT, there has been an expanded account of a route to 3'-azido-2',3'-dideoxynucleosides by coupling of bases to a sugar unit made from D-mannitol (Vol. 22, p.211-212), which includes some pyrazolo[3,4-*d*]pyrimidines.[82] Use of lithium azide instead of sodium halides in the chemistry of Scheme 5 gives a route to N^3- methyl-AZT;[72] other workers have reported analogous chemistry using the 5'-O-thexyldimethylsilyl analogue of **38**, where activation of the anhydronucleoside with an O-sulfonylhydroxylamine instead of methyl triflate led to N^3-amino-AZT. However, use of higher alkyl triflates gave a mixture of N-alkylated AZT derivatives and products of type **48**, presumably as a result of initial O^4-alkylation, followed by an alternative mode of opening of the anhydronucleoside.[83] The 4-thioderivative of AZT has been made *via* a 2,3'-anhydronucleoside,[84] and 3'-azido-2',3'-dideoxynucleosides of quinazoline 2,4-diones have been similarly prepared.[85] There has been another synthesis reported of the AZT homologue 3'-azido-2',3'-dideoxy-β-D-*ribo*-hexofuranosylthymine (see Vol. 25, p .253 and Vol. 26, p .235).[86]

The 3'-nitroalkene **49** can be made as indicated in Scheme 6, and can be reduced stereoselectively to the dideoxynitro-compound **50** or by Michael addition of amines, to products **51** (R=Me,Bu^n).[87]

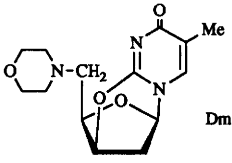


Reagents: i, NH_2OH; ii, CF_3CO_3H, urea, Na_2HPO_4; iii, $NaBH_4$; iv, RNH_2

Scheme 6

Reaction of 3',5'-di-*O*-mesylthymidine with cyclic amines give anhydronucleosides such as **52**, which could be converted to 2',3'-enes, AZT analogues and, by base hydrolysis, to the D-*threo*-systems.[88]

In order to link an FDU unit to human serum albumin, further linked to a monoclonal antibody, 5'-amino-2',5'-dideoxy-5-fluorouridine was converted to the 5'-amides with, e.g., succinic and fumaric acid, prior to linkage to the albumin.[89] 5'-Amino-5'-deoxythymidine was used to make a series of TTP mimics, such as **53**.[90]



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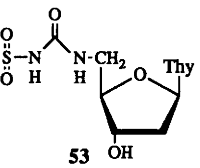

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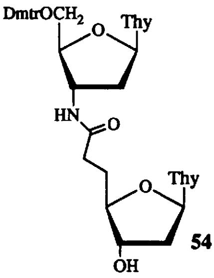

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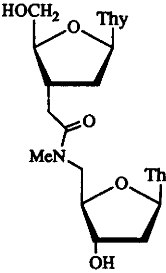
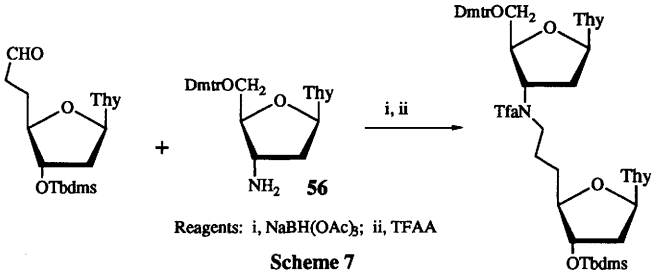


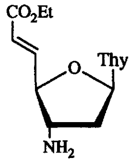
55

A number of interesting papers have described the use of aminonucleosides to assemble neutral isosteric replacements for the internucleosidic phosphodiester link (see Vols. 25 and 26 for earlier work). The thymidine dimer **54** has been prepared,[91] as has the related structure **55**.[92] The CH_2CH_2NH isostere has been assembled by reductive amination between a 5'-amino-5'-deoxycompound and a unit branched at C-3', in a manner similar to that used for the $NHCH_2CH_2$ replacement (Scheme 7), where a unit extended at C-5' was linked to a 3'-amino-3'-deoxy-compound.[93] This latter approach could also be used when unit **56** was replaced by a building block **57** which was also extended at C-5', thus leading to an iterative process used for making a 'trimer' with two identical internucleotidic links (and in principle applicable to higher oligomers).[94] Guanidine-linked nucleosides of type **58** have been assembled by sequential linkage of 5'-amino-5'-deoxythymidine and 3'-amino-3'-deoxythymidine to reagents $(MeS)_2C{=}NR$;[95,96] a thiourea linked dimer was also made by reaction of the 3'-isothiocyanate with the 5'-amine.[96]



Reagents: i, $NaBH(OAc)_3$; ii, TFAA

Scheme 7



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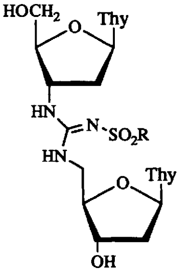


58

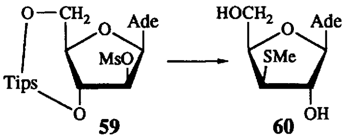
7 Thio- and Seleno-nucleosides

A review has appeared dealing with the synthesis, chemical transformations and biological properties of thio- and seleno-nucleosides, with a section on *C*-sulfonate nucleosides and oligonucleotide analogues with sulfur-based linkages.[97]

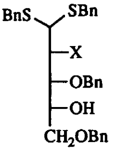
Various 2'-methylthionucleosides have been synthesised and their conformational properties studied, a high preponderance of C-2'-*endo*-pucker being indicated. It was found during this work that treatment of the mesylate **59** with NaSMe gave the 3'-methylthio-compound **60**, due presumably to deprotection under the conditions, and formation of an epoxide intermediate; the corresponding triflate, on the other hand, gave a clean inversion at C-2'.[98] The formation of some 3'-deoxy-2'-phenylthionucleosides (e.g. **23**) as precursors for 2'-deoxy- and 2',3'-didehydro-2',3'-dideoxy-nucleosides was mentioned above.[50,51]

Routes have been developed for the conversion of D-ribose into 3'-alkylthio-2'-deoxy-β-D-*erythro*-pentofuranosyl pyrimidine nucleosides[99,100] and into 3'-alkylthio-2'-deoxy-β-D-*threo*-pentopyranosyl systems.[100]

In the area of sulfur-in-ring compounds, it has been claimed that treatment of **61** (X=H) with triphenylphosphine, iodine and imidazole caused cyclization to a 4-thiofuranose of D-*erythro* (2-deoxy-D-*ribo*-) configuration, as a result of double inversion at C-4, and the thymine nucleosides (allegedly **62**) were made.^{101} Other workers have disputed this, and shown that the nucleosides so obtainable from **61** (X=H) are the L-threo-compounds **63**.^{102} The Montpellier group have similarly shown that treatment of **61** (X=OBn) with triphenylphosphine, I_2 and imidazole gives cyclization to an L-lyxofuranosyl system,^{103} whilst a Japanese group have described the synthesis of both epimers of **62** by base-sugar condensation (see Vol. 25, p. 254). An X-ray structure determination on **62**β showed that C-5' was less than 0.1Å further away from the nitrogen atoms than is the case in 5'-bromo-5'-deoxythymidine; the C-S bonds are longer, but the C-S-C angle is only ~95°; the sugar ring adopted a 'southern' conformation.^{104}



59 **60**



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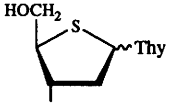

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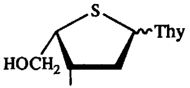

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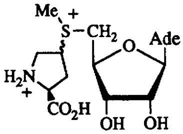

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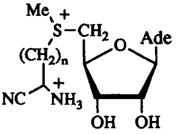
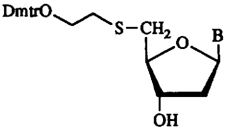


65, n = 1, 2



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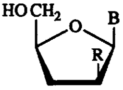
1-(5-Thio-β-D-xylopyranosyl)-lumazine and -pyrimidine nucleosides,^{105} and 1-(5-thio-β-D-glucopyranosyl)-6-azauracils substituted at C-5 (uracil numbering)^{106} have been prepared by silyl procedures.

There have been further reports (see Vols. 25 and 26) on the preparation of analogues of *S*-adenosylmethionine (SAM) as inhibitors of SAM decarboxylase, with **64**^{107} and **65**^{108} being described. Compounds **66** (B=Thy, Gua) have been made for incorporation into oligonucleotides with a 'stretched' phosphodiester backbone, designed to form triple helices.^{109} The 5'-phenylthio analogues of 8-aminoguanosine and formycin B have been reported as potential inhibitors of purine nucleoside phosphorylase.^{110}

8 Nucleosides with Branched-chain Sugars

Compounds of type **67** (R=Me, -C≡CH, B=Ura, Thy, Cyt, Ade) have been made by Grignard addition to 2'-ketones, followed by radical deoxygenation, as previously described by the same team (Vol. 25, p.256) for 3'-hydroxylated cases.^{111} The 2'-*C*-allyl compounds **68** (B=Ura, Thy) have been prepared by stereoselective free-radical coupling. The corresponding *C*-ethyl compounds were also made by modification of the allyl group, and these systems were incorporated into oligodeoxyribonucleotides.[112] There has been a fuller account of the synthesis of compounds of type **69** by deoxygenation of cyanohydrins (see Vol. 25, p. 256; also Vol. 26, p. 239 for similar work by another group),[113] and an improved route has been developed to make (*E*)-2'-deoxy-2'-(fluoromethylene)cytosine (see Vol. 25, p. 257).[114] The spiro-cyclopropyl compound **70** has been prepared by cycloaddition of diazomethane to a 2'-methylene compound;[115] the analogous adenosine and uridine compounds were reported last year (Vol. 26, p. 240).



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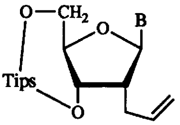

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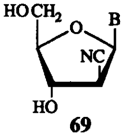

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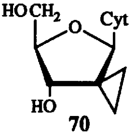

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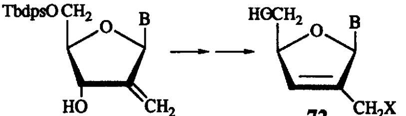
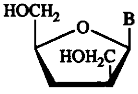
Treatment of the allylic alcohols **71** with Ph_2PCl and imidazole, followed by iodine, induces an allylic rearrangement giving access after deprotection to products **72** (X=I, B=Ura, Thy, Cyt), and substitution of the iodide gives types **72** (X = OH, N_3).[116,117] Reduction of the alkene gives products **73**.[117] Similar chemistry starting with the 3'-*C*-methylene compounds leads to the regioisomers **74** (X=I, N_3, OH; B=Ura, Thy, Cyt),[116,118] and again reduction gave the saturated products **75**. Meanwhile, another group has developed a related approach to similar targets; treatment of the 2'-*C*-methylene cyclonucleoside **76** with azide ion leads to **72** (X=N_3, B=Ura), and if 3'-methylene-2,2'-cyclonucleosides are used, then **74** (X=N_3, B=Ura, Thy) could be made.[119] The 3'-hydroxymethyl compound **75** (B=Thy) has been made by stereoselective hydroboration of the *C*-methylene system, and incorporated into oligodeoxynucleotides.[120] A detailed conformational study has been made of **75** (B=Cyt) and its 3'-epimer (which has high antiviral activity).[121]





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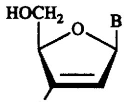

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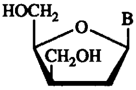

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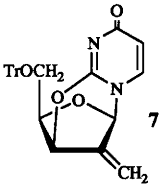

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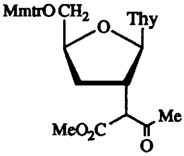

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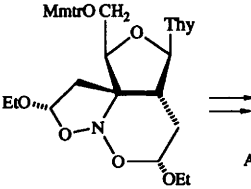
A series of papers from Chattopadhyaya's laboratory have described the use of nitroalkene **49** and its reduction product **50**[87] to make various types of structures branched at C-2', C-3', or both. Michael addition of carbon nucleophiles to **49**, followed by reductive denitration with Bu_3SnH, gave products such as **77**[87] whilst reaction of **49** with ethyl vinyl ether gave as major product **78**, formed by consecutive [4+2] and [3+2] cycloadditions, which could be hydrolysed, reduced and acetylated to give **79**.[122] Addition of electrophiles to deprotonated **50** gave products



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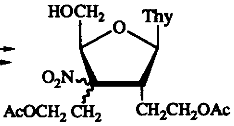

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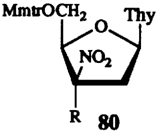

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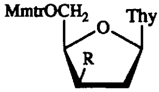

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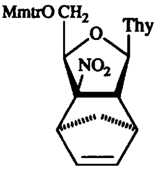

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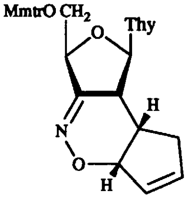
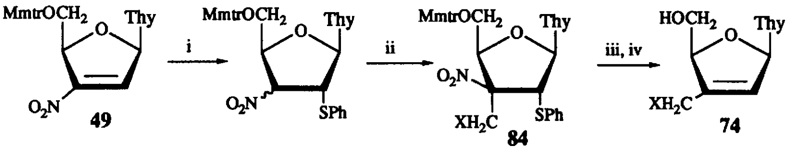


83

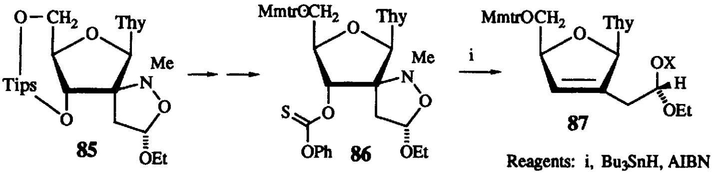
of type **80** ($R=CH_2OH$, CH_2CH_2CN, CH_2CH_2COMe) as the major diastereomers; reductive denitration also occurred with stereoselective hydrogen abstraction from the α-face, giving products of type **81**.[123] Various Diels-Alder reactions of **49** have also been studied. With cyclopentadiene, the *endo*-adduct **82** predominated, and on attempted reduction with Bu_3SnH, the rearrangement product **83** was formed, arising from addition of $Bu_3Sn^\bullet$ to the nitro group to give a nitroxide radical which interacted with the alkene. The *exo*-adduct, with which such a process is sterically impossible, underwent denitration in the normal manner.[124] When nitroalkene **49** was treated as indicated in Scheme 8, carbon-branched structures of type **74** (B=Thy) were produced; the intermediate alkylated products **84** ($X=OH$, $-CH_2CN$, $-CH_2COMe$) were predominantly the epimers formed by α-attack of the reagent on the nitronate.[125]



Reagents: i, PhSH, $(Me_2N)_2C=NH$; ii, HCHO, acrylonitrile or methyl vinyl ketone, $(Me_2N)_2C=NH$; iii, Bu_3SnH; iv, AcOH, H_2O

Scheme 8

Cycloadducts such as **85** (Scheme 9) can be obtained when the 2'-ketonucleoside is firstly converted to a nitrone and then treated wih, in this case, ethyl vinyl ether. Conversion to phenoxythiocarbonyl derivatives such as **86** and then treatment with Bu_3SnH led to alkenes of type **87** (X=NHMe or -N=CH_2). Similar chemistry was also carried out on 3'-ketonucleosides to give 3'-substituted -2',3'-enes.[126]

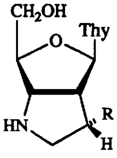


Scheme 9

Pyrrolidine-fused systems of type **88** (R=Me, Et, Pr^i, Bn) have been made by cyclization of a radical at C-2' (from reduction of a phenylselenide) onto an allylic amine at C-3'; analogous chemistry in which the positions of the amine and the PhSe group were reversed led to the systems with the pyrrolidine fused in the opposite sense. Good *endo*-selectivity was observed in the case of **88**, but the regioisomer was formed with lower (*endo*) selectivity.[127]

Use of carbon nucleophiles in the chemistry of Scheme 5 leads to N^3-methylated thymidines with α-oriented branches at C-3'; cuprous cyanide led to the isolation of **39** (X=CO_2H), due presumably to Cu^I-catalysed hydrolysis of the initial nitrile.[72] Compounds **89** (X=OH, F, N_3) have been made by base-sugar condensation; the structures with D-*arabino*-configuration (*via* 2,2'-cyclonucleosides), and those deoxygenated at C-2', were also reported.[128]

Compounds such as **90**, and its 3'-epimer, containing purine bases, have been made in similar fashion to the pyrimidine analogues reported last year (see Vol. 26, p. 243), and the *ribo*-configured compounds showed anti-HIV activity.[129]



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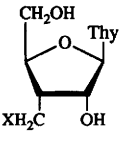

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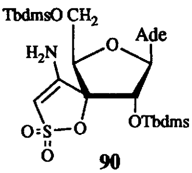

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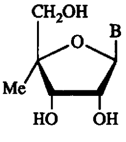
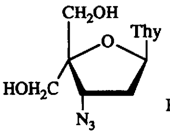


91

Some papers on deoxyapiosyl nucleosides, which can be regarded as 3'-hydroxymethyl systems, are discussed more appropriately in Section 14 below, and a report on the assembly of carbon-bridged dinucleotide analogues *via* phosphonate intermediates is covered in Section 12.

The 4'-*C*-methylated compounds **91**, with all five nucleobases, have been prepared by a sequence involving sugar-base coupling; the D-xylo-isomer with thymine as base was also made. These compounds were found to have the 3'-*exo*-configuration for the furanose ring.[130] The 4'-*C*-hydroxymethyl derivative **92** of AZT has been reported, along with the d4T analogue.[131]

An approach used earlier (Vol. 25, p.257, Scheme 16) for making *C*-3'-hydroxymethyl furanosyl nucleosides has been adapted to the synthesis of *C*-4'-hydroxymethyl hexopyranosyl systems **93** by modification of the allyl group without loss of carbon.[132]



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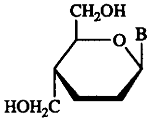

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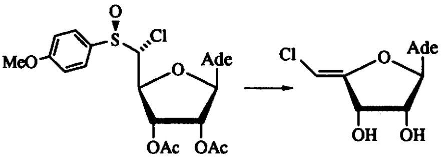


94 **95**

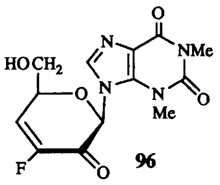
9 Nucleosides of Unsaturated Sugars, Keto-sugars and Uronic Acids

Papers dealing with 2',3'-didehydro-2',3'-dideoxy-derivatives are covered in Section 4, along with their saturated analogues.

The α-chlorosulfoxide **94**, together with the compound isomeric at both C-5' and at sulfur, and the dichlorosulfoxide (both epimers) were produced when the sulfide was treated with $PhICl_2$ and K_2CO_3 in acetonitrile. Reaction of **94** with $EtNPr_2^i$ and deacetylation gave the (*Z*)-alkene **95**, a potent mechanism-based inhibitor of *S*-adenosylhomocysteine hydrolase. The (*E*)-alkene, and the dichloroalkene could be made similarly from the appropriate precursors.[133]

There has been a report on the preparation of theophylline ketonucleosides also containing fluorine, including enone **96**, made by oxidation and elimination from a known precursor (Vol. 23, p. 214).[134]

Ozonolysis of 5'-deoxy-4',5'-enes has been used to make nucleoside lactones such as **97** (see also Vol. 26, p. 244-5 for an alternative procedure).[135] Some nucleosides of ribofuranuronic acid have been reported, with the uronic acid group being introduced by oxidation. Some 3'-deoxy-3',4'-enes were also described, having been made by elimination.[136] Glucuronides of some fluoropyrimidine drugs have been synthesized by base-sugar linkage,[137] as has an *N*-glucuronyl derivative of a nitrofurantoin.[138]



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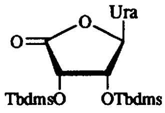

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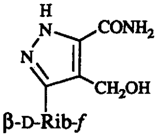
10 *C*-Nucleosides

An improved route to oxazofurin (4-carboxamido-2-β-D-ribofuranosyl-oxazole) has been described,[139] and Maeba's laboratory has reported the synthesis of 5-(β-D-ribofuranosyl)isoxazole from a furanone riboside.[140]

The pyrazofurin analogue **98** has been prepared by a sequence involving cycloaddition of an alkyne to (2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)diazomethane,[141] whilst **99** was made by oxidation of a protected ribosyl *p*-nitrophenylhydrazone and cycloaddition of the resultant nitrilimine with methyl propiolate.[142] Some 3- and 4-D-lyxofuranosyl pyrazoles have been prepared by acid-catalysed cyclization.[143]

Alderweireldt's group have described the synthesis of 2-carbamoylmethyl-6-(β-D-ribofuranosyl)pyridine by a route similar to those used earlier in the same laboratory for other pyridine *C*-nucleosides.[144] The unsaturated pyrimidine *C*-nucleoside **100** has been made by a palladium-catalysed reaction between the heterocycle and the 3-deoxyglycal.[145]



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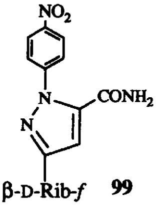

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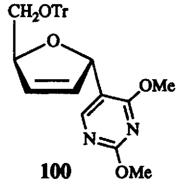

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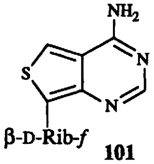
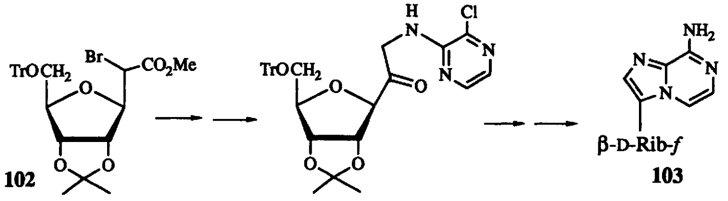


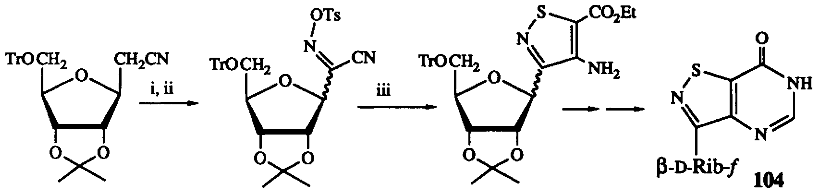
101

2'-Deoxy-9-deazaadenosine[146] and 2'-deoxy-9-deazaguanosine[147] have been prepared from the ribofuranosyl *C*-nucleosides by conventional deoxygenation, whilst the thieno[3,4-*d*]pyrimidine analogue **101** of adenosine has been prepared by a sequence involving *C*-ribosylation of a thiophene, followed by elaboration of the pyrimidine ring (see Vol. 24, p.238 for the inosine analogue).[16]

The known α-bromoester **102** has been used to make the imidazo[1,2-*a*]pyrazine analogue **103** of adenosine as outlined in Scheme 10,[148] and the isothiazolo[4,5-*d*]pyrimidine **104** and its α-anomer have been assembled as shown in Scheme 11.[149]



Scheme 10



Reagents: i, RONO, OH$^-$; ii, TsCl; iii, HSCH$_2$CO$_2$Et, Et$_3$N

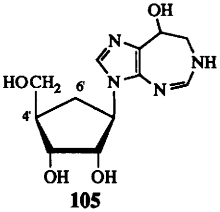
Scheme 11

There has been a further report on the formation of *C*-nucleosides by reaction of anomeric radicals (formed by decarboxylation) with heterocycles (see Vol. 25, p.260).[150]

New routes to anhydroaldonic acids of use in making *C*-nucleosides are mentioned in Chapter 16, and some carbocyclic *C*-nucleosides are referred to below.

11 Carbocyclic Nucleosides

The fermentation broth of a *Saccharothrix* species has been found to contain the carbocyclic nucleoside **105**, which showed post-emergence herbicidal activity, together with its 5'-*O*-β-D-glucosyl derivative, its C-4' epimer, the corresponding 4',6'-ene (the known adecypenol), and aristeromycin.[151]



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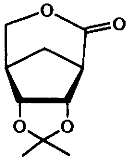

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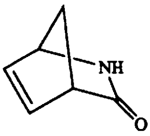

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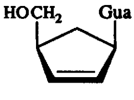

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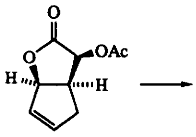

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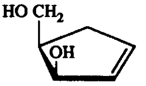

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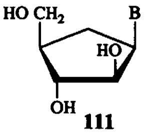

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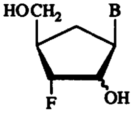


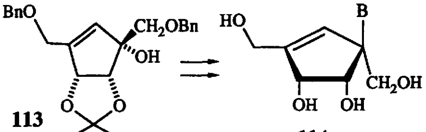
112

A new short synthesis of the Ohno lactone **106**, a useful building block for carbocyclic nucleosides, has been described, proceeding in 54% overall yield from the cycloadduct of cyclopentadiene and acrylic acid.[152] Also reported is a large-scale route to the racemic synthon **107**, which can be resolved enzymically and used for carbocyclic nucleoside synthesis.[153] Indeed, there has been a further paper reporting some improvements in the conversion of resolved **107** into (-)-carbovir (**108**),[154] whilst in another route to **108** the chiral acetate **109** was prepared by enantioselective acetylation of the racemic α-hydroxylactone using a lipase and vinyl acetate; degradation of the lactone ring then gave the diol **110**, convertible to (-)-carbovir (**108**) by π-allyl palladium chemistry similar to methods previously described (see Vol. 26, p. 246-7).[155]

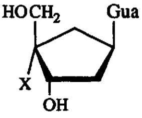
D-Arabinose has been converted (Chapter 18) into a cyclopentane which was used to prepare the *arabino*-carbocyclic nucleosides **111** [B=Ade (i.e. cyclaradine) and Ura].[156] Some 5'-substituted analogues of carbocyclic 3-deazadenosine have been made, along with the 5'-uronamide,[157] and racemic fluorinated carbanucleosides **112** (both configurations at C-2') have been synthesized by processes involving building the heterocycle (Ade, Gua, Ura, Thy) from an amino function at C-1'.[158] Some other papers dealing with analogues of aristeromycin are mentioned in Chapter 19.

The tertiary alcohol **113**, made by addition of Still's $LiCH_2OBn$ reagent to the ketone, has been converted into the first carbocyclic analogues **114** (B=Ade, Cyt) of ketose nucleosides,[159] and the compounds **115** (X=OH, F) have been prepared from aristeromycin *via* a 4',5'-ene.[160]

Two papers have reported carbocyclic nucleosides related to clitocine (see Vol. 24, p.241 for carbocyclic clitocine itself). The neplanocin-like analogue **116** has been prepared, and this was converted to 8-aza-neplanocin A and similar inosine and guanosine systems,[161] whilst other workers have described the racemic 3'-deoxycompound **117**.[162]



113 **114**



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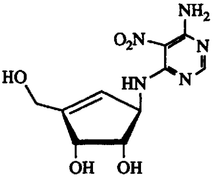

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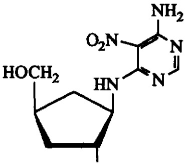

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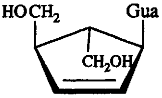

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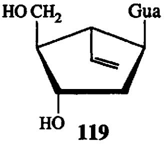

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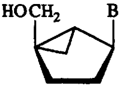

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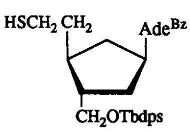
Mitsunobu reactions were used to introduce the base during syntheses of (±)-**118** (see Vol. 26, p. 248 for related work),[163] *C*-vinyl compounds of type **119**,[164] racemic cyclopropane-fused systems of type **120**,[165] and the chain-extended thiol **121**; this last unit was used to make the sulfide-linked dinucleotide analogue **122**.[166] Similar intermediates were used, without resolution, to prepare the sulfone analogue (±)-**123** of cAMP.[167]

There has been a report on the synthesis of a range of racemic cyclohexenyl nucleosides such as **124**, and various other substitution patterns were also described.[168]

The lactone **106** has been used to make the carbocyclic *C*-nucleoside **125**,[169] and carbocyclic tiazofurin (**126**) has been prepared along similar lines to a previous synthesis of tiazofurin itself (Vol. 24, p.51-2).[170]

Some references to phosphates and phosphonates of carbocyclic nucleosides are in the next Section.



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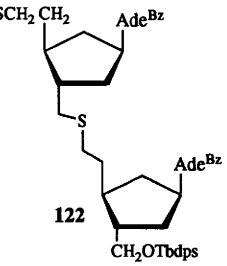

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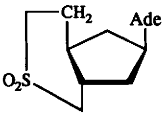

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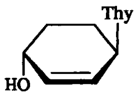

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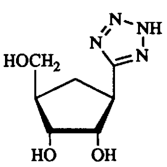

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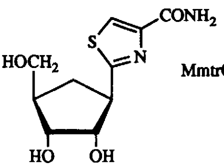

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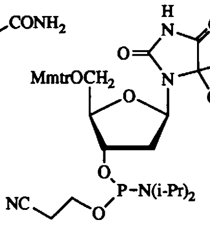

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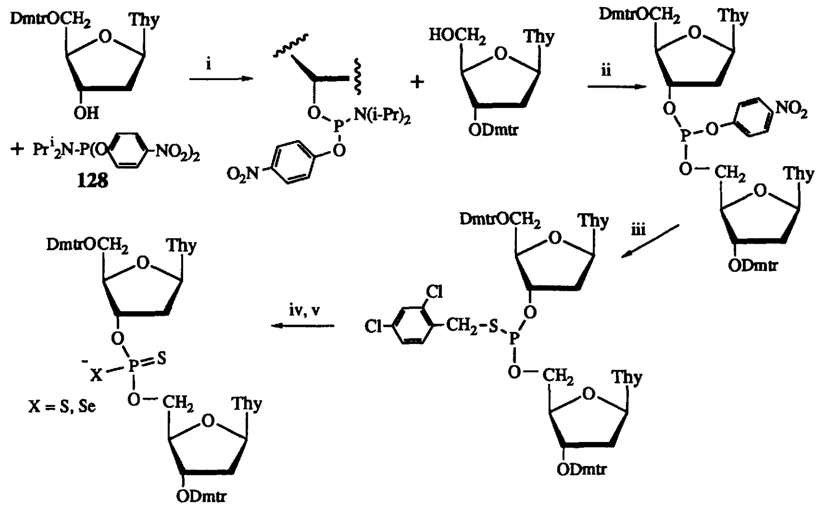
12 Nucleoside Phosphates and Phosphonates

A paper from Reese's laboratory reports a reappraisal of the phosphotriester approach to oligonucleotide synthesis, evaluating the efficacy of various combinations of activators and nucleophilic catalysts, and highlighting the advantages of the phosphotriester method.[171] An extensive review has appeared which discusses the synthesis of modified oligonucleotides by the phosphoramidite approach, with references to many phosphoramidite derivatives prepared for use in couplings.[172] The 3'-phosphoramidite **127**, containing a base modification induced by ionizing radiation, has been described and incorporated into oligodeoxynucleotides,[173] as has a similar phosphoramidite of 5-methyl-α-deoxycytidine,[174] whilst both a phosphoramidite and an H-phosphonate building block were described for 1-deaza-2'-deoxyadenosine.[175] Michalski's group have described the use of *N,N*-diisopropyl-*O*-methyl-*O*'-4-nitrophenyl phosphoramidite as a flexible phosphitylating reagent in the synthesis of thio- and seleno-oligonucleotides,[176] and also have developed the related reagent **128** (Scheme 12); the use of this reagent to make dinucleotidyl dithiophosphates and selenothiophosphates is outlined, the *p*-nitrophenoxy group being displaced rapidly in the presence of DBU, whilst the diisopropylamino unit is displaced in the presence of tetrazole.[177] A new reagent, bis(*O,O*-diisopropoxy-phosphinothioyl)disulfide ('*S*-tetra') has been advocated for sulfurizing internucleotidic phosphites,[178] and *S*-benzyl phosphorochloridothioate ($BnSPOCl_2$) has been employed for making internucleotidic phosphorothioates by a phosphotriester-like process.[179] There has been an expanded account of the use of *N,N*-dialkylphosphonamidates in oligodeoxynucleotide synthesis (see Vol. 24, p.242).[180]

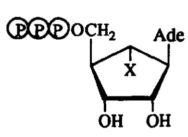


Reagents: i, DBU; ii, tetrazole; iii, ArCH $_2$SH, DBU; iv, S $_n$ or Se$_n$, DBU; v, PhSH, DBU

Scheme 12

Routes have been described for the synthesis of 2'-deoxy-5'-*O*-thymidylyl-6-thioinosine and -6-thioguanosine.[181]

If a nucleoside has just one unprotected alcohol group, but with the base unit unprotected, it is possible to effect efficient phosphorylation on oxygen by treatment with a strong base (RLi, KOBu^t, etc.) followed by a phosphorochloridate.[182]



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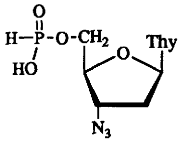

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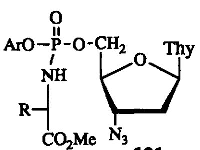

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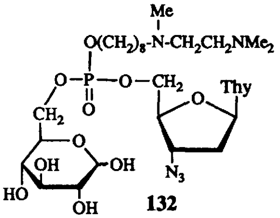
Aristeromycin and its 6'-α-fluoroanalogue (Vol. 25, p.263) have been converted to their 5'-monophosphates and hence enzymically to the triphosphates **129** (X=H, F), which were able to act as mimics of ATP for hexokinase and glycerol kinase.[183] Multigram syntheses have been described for the 5'-*H*-phosphonates of AZT (**130**) and of 3'-deoxy-3'-fluorothymidine, and the equivalent 5'-phosphorofluoridates,[184] whilst **130** has also been made by decarboxylation of a phosphonoformate intermediate.[185] Aryl phosphoramidates of type **131** have been made in order to provide intracellular delivery of AZT phosphate, and some proved to be active in TK$^-$ cells,[186] whilst mono- and bis-(4-acyloxybenzyl) esters of AZT monophosphate have also been reported.[187] Glucosyl phospholipid-type derivatives of AZT (Vol. 23, p.223) have now been made which incorporate a trimethyl ethylenediamine (**132**) or N-methylpiperazine unit; it was hoped that Cu^{II} complexes of these compounds would combine reverse transcriptase inhibition with ribonuclease activity.[188] There have also been reports on 5'-phosphotriesters and phosphoramidates[189] and 5'-phosphodiesters with lipophilic alcohols[190] as prodrugs of d4T and its monophosphate. Conjugates of ara-C, linked *via* a 5'-diphosphate to thioether lipids, have also been described, and show superior antitumour activity.[191]

The potent carcinogen *N*-nitrosopyrrolidine has been linked to deoxynucleotides as in structure **133**; u.v. irradiation in the presence of DNA caused chain-scission to occur.[192]

The 5'-*O*-(1-thiotriphosphates) of 8-bromo- and 8-azido-2'-deoxyadenosine have been prepared, and both could be incorporated into plasmid DNA.[193]

Two chemical synthesis of CMP-NeuNAc have been reported. In one of these, a 5'-phosphoramidite of cytidine was coupled with a NeuNAc derivative with only the anomeric hydroxyl group unprotected,[194] whilst in the other, CMP, activated at O-2', O-3' and N-4, reacted with β-specificity with a glycosyl phosphite of NeuNAc.[195]

Four analogues **134** (X = OH, F; Y = O, CF_2) of tiazofurin adenine dinucleotide (TAD) have been synthesized,[64] and both 2-(β-D-ribofuranosyl)-pyridine-6-carboxamide and 3(β-D-ribofuranosyl)-pyridine-5-carboxamide have been converted into their NAD analogues, the latter one proving to be a good inhibitor of IMP dehydrogenase.[196]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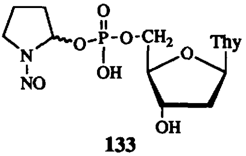
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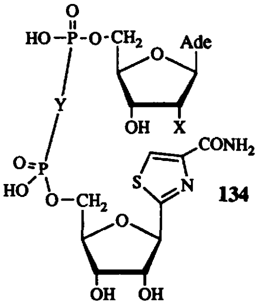
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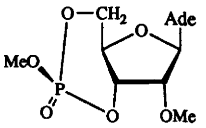
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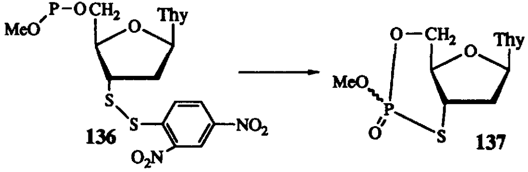
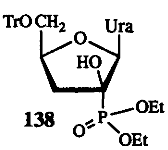

136 **137**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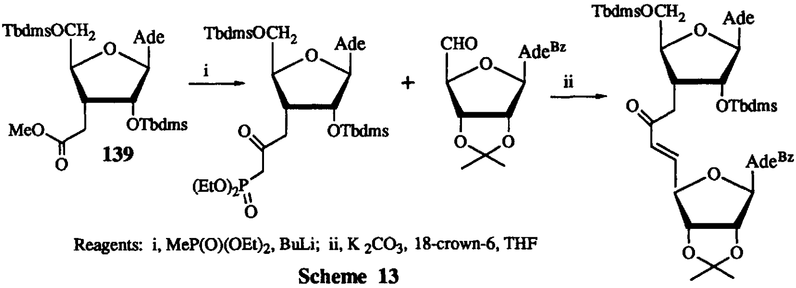
In the area of cyclic nucleosides, a new route to derivatives of cAMP has been described, proceeding *via* a 3'-,5'-cyclic phosphite,[197] and treatment of cAMP with benzyl bromide and Ag_2O in MeCN-DMSO gives the *O*-benzyl cyclic triester as an epimeric mixture in good yield.[198]

The 2'-*O*-methylated cyclic triester **135** has been made by stereospecific oxidation of the cyclic phosphite; the required epimer of the phosphite is thermodynamically preferred, and pyramidal inversion occurs fairly rapidly on heating in the presence of tetrazole. Base hydrolysis of **135** gave only the products of ring-opening, with no cyclic phosphate.[199] The cyclic phosphorothiolate **137** could be made by warming a solution of the phosphite **136**, prepared *in situ* at low temperature, and similar D-*threo*-cyclic phosphorothiolates were also made in a similar way.[200]

A study has been reported on the rates of cleavage of UpU to give uridine and uridine 2',3'-cyclic phosphate and the simultaneous isomerisation of the substrate to 2',5"-UpU, the results giving insights into the mechanism of ribonuclease A.[201]

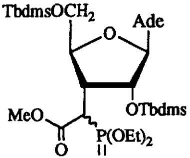
As regards phosphonates, protected α-hydroxyphosphonates such as **138** have been made by addition of diethyl phosphite to the ketonucleoside, and similar adducts were obtained with 3'-keto-substrates.[202] In a route to carbon-linked dinucleotide analogues, the branched adenosine derivative **139**, made from the 3'-ketonucleoside by Wittig reaction and hydrogenation, was manipulated as outlined in Scheme 13. The branched phosphonate **140** was also reported.[203]



Reagents: i, $MeP(O)(OEt)_2$, BuLi; ii, K_2CO_3, 18-crown-6, THF

Scheme 13

In further work on compounds of potential use in boron neutron capture therapy, the carboranyl dinucleotide **141** has been prepared as a lipophilic nucleotide analogue resistant to cleavage by phosphodiesterases.[204] The dinucleoside phosphonate **142** has been synthesised and incorporated into thymidine oligonucleotides by automated procedures.[205]



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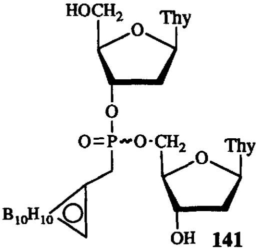

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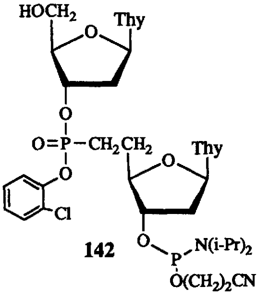

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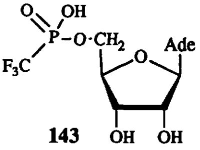
The AMP analogue **143** has been described, along with the similar analogues of thymidine 5'- and 3'-monophosphates.[206] Another paper describes a range of 5'-*O*-phosphonates of ribonucleosides and deoxyribonucleosides, and also the 5'-*O*-phosphonomethyl compounds **145** (B=Thy, Ade), prepared from **144** by treatment with Bu^{t}OK.[207] The carbocyclic phosphonate analogue **146** of ddA monophosphate has also been prepared in racemic form.[208]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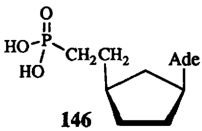
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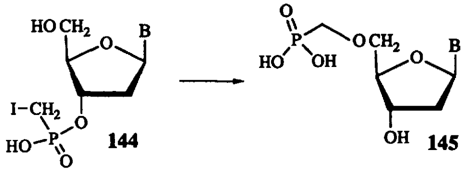

144 **145**

A number of papers mentioned in the next section discuss protecting groups of relevance in the synthesis of oligonucleotides and their analogues.

13 Ethers, Esters and Acetals of Nucleosides

A synthesis of 2'-*O*,5-dimethyluridine relies on reasonable discrimination between the 2'- and 3'-hydroxyl groups in methylation with NaH and MeI.[209] *N*^{4}-Isobutyryl-2'-*O*-methylcytidine has been made *via* the 3',5'-*O*-Tips derivative, and incorporated into oligonucleotides,[210] as have 5-(1-propynyl)-2'-*O*-allyl-uridine and -cytidine, the presence of which in oligonucleotides enhances double-helix formation with single-stranded RNA.[211] The ether **147** has been prepared, again by regioselective *O*-alkylation, and incorporated into oligonucleotides where the thiol offers the opportunity of attaching ligands that will bind in the minor groove of DNA.[212] In another approach to 2'-*O*-modified nucleosides, compounds of type **148** were prepared by β-selective base-sugar condensation and various groups could then be linked by amide bonds to the 2'-position.[213]

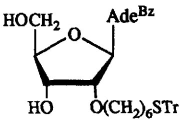
The reaction of AMP and UMP with epichlorohydrin has been shown to lead to products derived by attack of O-3' on the epoxide, as well as products of reaction on the base unit.[214]

There has been a further report on porphyrin-nucleoside conjugates, describing the linkage of FDU to a water-soluble porphyrin *via* an ether at O-5'.[215]

Trityl ethers have been cleaved from nucleosides very rapidly by treatment with trifluoroacetic acid and its anhydride in dichloromethane, followed by methanolysis of the resultant trifluoroacetate (Et_3N/MeOH). The acid-sensitive trimethylsilylethoxymethyl (SEM) group was not affected under these conditions.[216]

A modified dimethoxytrityl group has been developed which, when present at O-5' of a nucleoside 3'-phosphate, as in **149**, can catalyse the formation of an internucleotidic link with 3'-

O-benzoylthymidine, reaction occurring much more rapidly than in the case of the 5'-*O*-tritylated analogue of **149** with *N*-methylimidazole as an external catalyst.[217]



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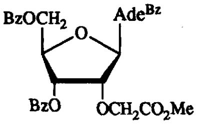

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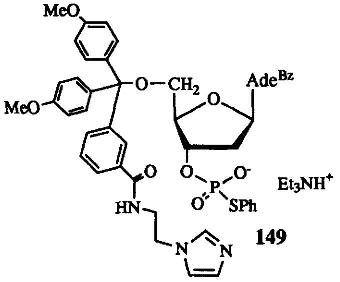

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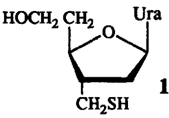
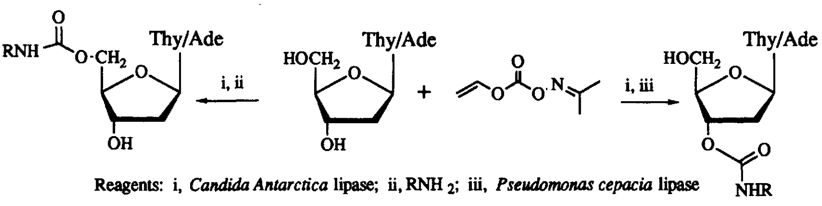


150

In work connected with the synthesis of oligonucleotide analogues with dimethylene sulfide and sulfone links (see Vol. 25, p. 255), it was found that the building block **150** could be selectively dimethoxytritylated on sulfur by use of 1 equivalent of dimethoxytrityl chloride and triethylamine in 80% acetic acid. The *O*,*S*-bis-Dmtr derivative, prepared conventionally, could be selectively deprotected on oxygen using aqueous acetic acid, or on sulfur by use of $AgNO_3$ in methanol. These mono-protected materials were coupled to a dimer via the *O*-mesyl derivative.[218]

In the synthesis of a building block for the use of 7-deazaadenosine (tubercidin) in solid phase oligoribonucleotide synthesis, a tri-isopropylsilyl ether could be introduced at O-2' with good selectivity,[219] and the Tbdms group has been placed onto 5'-*O*-Dmtr-2'-deoxynucleosides using NaH and dibenzo[18]crown-6.[220] Cleavage of Tbdms ethers from nucleosides has been carried out by adsorbtion onto neutral alumina and use of a microwave oven.[221]

Interest continues in the use of enzymes for selective acylation and deacylation of nucleosides (see last three Volumes). Using oxime esters as acyl donors, the lipase from *Candida antarctica* forms esters at O-5' of ribonucleosides and deoxyribonucleosides with good regioselectivity,[222] and the same selectivity was found with the same enzyme in the butanoylation of α-thymidine, *xylo*-thymidine, arabinofuranosyl nucleosides, and 2,2'-anhydrouridine.[223] Chemo-enzymatic routes to 2'-deoxynucleoside urethanes are indicated in Scheme 14.[224] When



Reagents: i, *Candida Antarctica* lipase; ii, RNH_2; iii, *Pseudomonas cepacia* lipase

Scheme 14

tri-*O*-acetyl-ribonucleosides are treated with subtilisin in DMF-phosphate buffer, selective hydrolysis of the 5'-*O*-acetyl group occurs,[225] whilst tri-*O*-acyl derivatives of 5-bromovinyl-1-(β-D-arabinofuranosyl)uracil are deacylated at both O-5' and O-3' using pig liver esterase.[226]

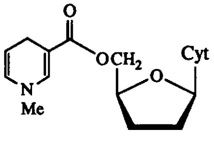
There has been a report on the deblocking of peracylated nucleosides using $NaHCO_3$ or Na_2CO_3 in methanol.[227]

In order to enhance uptake of the drug by the brain, ddC has been linked to a dihydropyridine system to give the ester **151**,[228] and 5-(2-iodovinyl)-2'-fluoro-2'-deoxyuridine (IVFDU) has been linked at O-3' to the same dihydropyridine unit for the same purpose.[229,230]

Improved routes have been developed for the synthesis of pdCpA, acylated at O-3' of the adenosine unit with non-natural aminoacids. The resultant aminoacyl compounds can be incorporated into t-RNA's by enzymic ligation, and the novel amino acid can then be inserted into a protein.[231]

Optimum procedures have been described for the preparation of 2'-*O*-*t*-butoxycarbonyl-ribonucleosides,[232] and the 2-(4-nitrophenyl)-ethoxycarbonyl (Npeoc) and 2-(2,4-dinitrophenyl)-ethoxycarbonyl (Dnpeoc) groups, removable using DBU, have been used for protection of ribo- and 2'-deoxyribonucleosides.[233]

Treatment of thymine ribonucleoside with dibutyltin oxide and R_4NCl in the presence of tosyl chloride gives selectively the 2'-*O*-tosyl derivative, whereas the presence of a substituent at C-1' gives mostly the 3'-*O*-tosyl regioisomers **152** (R=Me, CN). 2',3'-*O*-Thionocarbonates were also prepared directly from the unprotected nucleosides using stannylene activation.[234]



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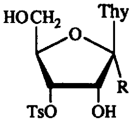

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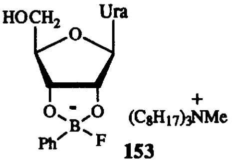


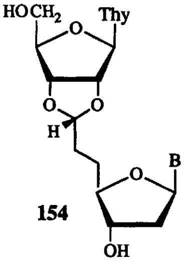
153

Cotransportation of uridine and fluoride ion through an organic liquid membrane can be achieved in the presence of phenylboronic acid, due to the formation of the salt **153**.[235]

Acetal links have been used to make dinucleotide analogues of type **154** (B=Thy, Cyt) in which the phosphodiester has been replaced by a neutral, conformationally restricted unit; the acetals were formed conventionally by condensation of a 5'-protected thymidine ribonucleoside with the dimethyl acetal of a chain-extended lower section.[236]

Acetal linkages **155** have also been employed to link the 3'-terminal ribonucleoside to long-chain alkylamino controlled pore glass during solid-phase oligoribonucleotide synthesis, this linker being compatible with the use of Fmoc and 4-methoxytetrahydropyranyl (Mthp) groups for 5'-*O*- and 2'-*O*-protection respectively.[237] The Mthp group is rather too acid-labile to be used in solid-phase oligoribonucleoside synthesis in conjunction with 5'-*O*-Dmtr or 5'-*O*-pixyl groups. Reese and coworkers have now developed the 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl group (as in the building blocks **156**), for which the rate of hydrolysis is virtually independent of pH over the range 0-2.5, since the pKa of the system is such that over this range the concentration of the conjugate acid, assumed to be hydrolysed at a negligible rate by comparison with the free base, increases in direct proportion to the acid strength.[238]

A paper concerning nucleoside-*O*-glycosides of KDN is mentioned in Chapter 3.



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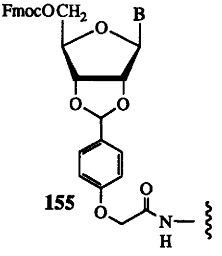

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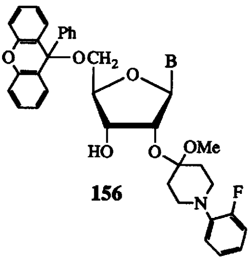
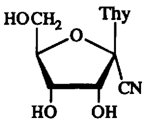


156

14 Miscellaneous Nucleoside Analogues

The 1'-*C*-cyanonucleoside **157** has been made by mercuric salt induced condensation of a *gem*-bromonitrile and silylated thymine, and was converted to the 2',3'-ene by Corey-Winter olefination.[239]

Electrophilic addition of alcohols to the 4',5'-ene gave 4'-alkoxynucleosides of type **158** (R=H, Ac, R'=alkyl), the diastereoselectivity depending on the steric bulk of the alcohol when R=Ac, but α-attack being favoured when R=H. Epoxidation of the 4',5'-ene in the presence of an alcohol gave products of type **159** (R=H, R'=alkyl).[240] Treatment of the enol ether **160** (Vol. 6, p.150) with MCPBA in the presence of alcohols gave the products **161** as the major isomers.[241]



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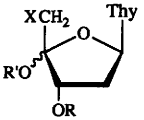
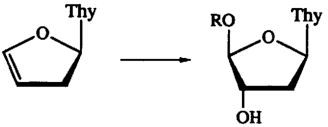


158, X = H
159, X = OH



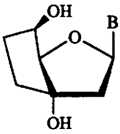
160 **161**

Adenosine-5'-carboxaldehyde and its 4'-epimer have been separately isolated and characterized for the first time.[242]

Interesting 'bicyclonucleosides' **162** have been synthesized, in which the ethylene bridge locks the molecule so as to resemble quite closely the conformation of a nucleoside unit in duplex DNA, in the hope that, when units **162** are incorporated into an oligonucleotide there will be an entropic advantage for duplex formation.[243]

Various 'double-headed' nucleosides of type **163** have been described.[244]

A full account has been given of work on the synthesis of 2,3-dideoxyapiosyl nucleosides **164** (B=Ade, Cyt), where asymmetry was introduced by a lipase-catalysed esterification. The "α"-(*cis*) products showed some anti-HIV activity.[245] Similar work by others was reported last year (Vol. 26, p. 255). The related systems **165** and their enantiomers have also been prepared.[246] The thymidine regioisomer **166**[247,248] and its adenine analogue[248] have been synthesised, and the epimer **167**, made from 1,4-anhydro-D-xylitol, was converted to the AZT analogue **168**.[247] Branched systems of type **169** have also been reported by two groups,[248,249] and the Leiden laboratory has described syntheses of 1,5-anhydrohexitol nucleosides **170**.[250,251]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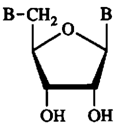
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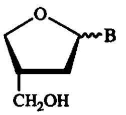
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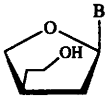
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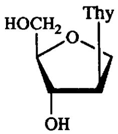
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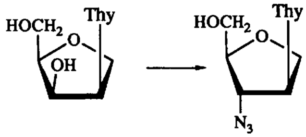
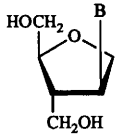

167 **168**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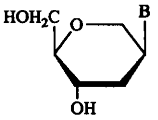
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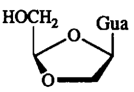
There have been several further papers concerned with dioxolanyl and oxathiolanyl nucleosides. The Georgia group has described purine dioxolanyl nucleosides such as **171** (both epimers), made by the method of Vol. 25, p. 271,[252] and has given a full account of the use of 1,6-anhydro-L-gulose to make compounds in the enantiomeric series, again including the use of purine bases.[253] There has been a paper on ways to ensure good β-(*cis*) selectivity in the synthesis of dioxolanyl nucleosides,[254] and further reports on the use of L-ascorbic acid (see Vol. 26, p. 256)[255,256] and D-mannitol[256] as precursors of dioxolanyl nucleosides in both enantiomeric series. A full account has been given of the synthesis of the (2R, 5S)-(-)-isomer of 3TC (**172**) *via* 1,6-anhydro-6-thio-L-gulose (Vol. 26, p. 256-7), which also reports on purine analogues and α-(*trans*) isomers,[257] and full details have also appeared of routes to (2S, 5R)- and (2S, 5S)- oxathiolanyl nucleosides in the purine and pyrimidine series starting from 1,6-anhydro-6-thio-D-mannose (Vol. 25, p.271) and 1,6-anhydro-6-thio-D-galactose (Vol. 26, p. 256-7),[258] and, as for the dioxolanyl series, the best conditions have been defined to ensure β-(*cis*) stereoselectivity when making oxathiolanyl nucleosides by 'sugar'-base condensations.[259] Racemic 3TC (±-**172**) can be resolved by enantioselective hydrolysis of its phosphate by 5'-nucleotidase from *Crotalus atrox* venom,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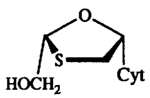
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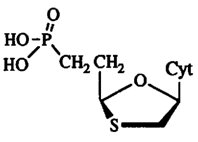
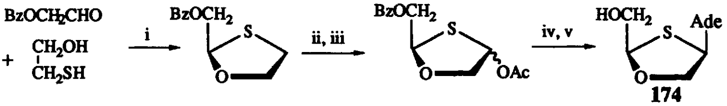

173

which produces the (+)-isomer of 3TC, leaving the (-)-isomer **172** as its phosphate.[260] The racemic phosphonate analogue **173** of 3TC phosphate has been prepared, together with the *trans*-compound, but was less potent than the nucleoside itself.[261] An interesting development in this area has been the synthesis of the isomeric oxathiolanyl nucleoside **174**, made in racemic form as indicated in Scheme 15; other bases were also used. The adenine analogue **174** showed good anti-HIV activity, and resolution by chiral h.p.l.c. or by use of adenosine deaminase showed that most activity resided in the 'natural' (-)-enantiomer shown.[262]



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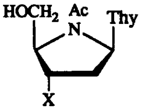
Reagents: i, TsOH; ii, Mg monoperoxyphthalate; iii, Ac$_2$O, Bu$_4$NOAc; iv, silylated 6-chloroadenine; v, NH$_3$

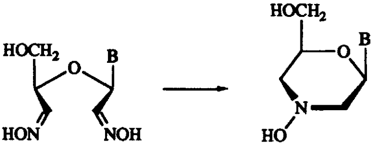
Scheme 15

The pyrrolidine nucleoside analogues **175**[263] and **176**[264] have been prepared by addition of silylated thymine to *N*-acetyliminium ion intermediates. A related *C*-nucleoside analogue is mentioned in Chapter 18.

Spin-labelled nucleoside analogues have been described, made by reduction of seconucleoside dioximes **177** with borane-pyridine to give the *N*-hydroxycompounds **178**, which spontaneously oxidize to aminoxyl radicals.[265]



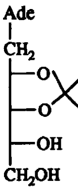
175, X = OH
176, X = H



177 **178**

15 Reactions

Reduction of 2',3'-*O*-isopropylideneadenosine with excess of DIBAL leads to the *N*-ribitylpurine **179**,[266] and this was converted to the acyclic neplanocin analogue **180**.[267]



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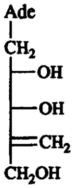

180

A paper concerning the reaction of guanosine with glucose is mentioned in Chapter 2.

The degradation of 2'-deoxyuridine was studied in aqueous solution at pH values in the range 1-12 and at different temperatures by use of an h.p.l.c. system capable of separating the α- and β-pyranose and furanose forms. The formation of the anomer and ring isomers from deoxyuridine indicates both direct *N*-glycosidic bond rupture and the formation of a Schiff base intermediate which can recyclize in different ways.[268]

Spin-trapping with Bu^{t}NO has been used to identify radicals formed from reaction of hydroxyl radicals with pyrimidine nucleosides. Although the main discussion in this paper concerned radicals in the pyrimidine ring, sugar radicals were also discussed briefly.[269] A study has been presented on the formation of radicals in the ribose units when RNA, frozen in water, was subjected to ^{60}Co γ-irradiation.[270]

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21
N.M.R. Spectroscopy and Conformational Features

1 General Aspects

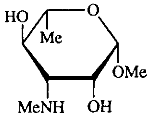
A new technique for acquiring 2D ^1H-^1H COSY spectra, using pulsed magnetic field gradients instead of phase cycling to eliminate most of the unwanted response, has been shown to reduce the measuring time by a factor of at least ten.[1] The origin of the *exo*-deoxoanomeric effect in both cyclic and acyclic systems has been studied by use of *ab initio* quantum mechanics.[2] *Ab initio* calculations for the anomeric effect in O-C-F and N-C-F systems are referred to in Chapter 8. A theoretical comparison of conformational properties of molecules, dealing with conformational probability maps and similarity indices, and using *N*-substituted sugars (*e.g.*, **1**) as examples, has been published.[3] A procedure for evaluating carbohydrate force fields has been devised from a comparison between the calculated conformation-dependence of the optical rotation of maltose and experimental polarimetric measurements.[4]

In an *ab initio* analysis of the conformers of glucopyranose, five low energy structures differing mainly in the orientation of the CH_2OH group were identified for each anomer; in each conformer, the α-form was predicted to be of lower energy than the β-form.[5] A new molecular dynamics study on conformational and anomeric equilibria of D-glucose in aqueous solution disagreed with the view that solvation favours the β-anomer.[6] Valuable information on the conformation of α-D-glucose and polysaccharides such as cellulose has been obtained by use of vibrational spectroscopy, in particular i.r., in combination with mathematical methods.[7]

Corrected structures for the cyclitol intermediates occurring in the acid-promoted degradation of pentoses and hexuronic acids to 2,3-dihydroxyacetophenone, on the basis of ^1H-n.m.r. spectrosopic evidence, are covered in Chapter 18. Structural assignments of the isomeric forms of D-*xylo*-hexos-5-ulose (see also Chapter 15) have been made on the basis of high field ^1H- and ^{13}C-n.m.r. studies.[8] The ^1H- and ^{13}C-n.m.r. resonances of a number of reduced mono- and oligosaccharides representing substructures found in *N*- and *O*-linked glycans have been assigned.[9] A review on the preferred conformations of mono-, di-, and oligo-*C*-glycosides, including palytoxin, and their parent *O*-glycosides has appeared.[10]

2 Acyclic Systems

An investigation of the structure of threitol, which includes n.m.r. studies, is referred to in Chapter 22 (section 3.9). The (*R*)-stereochemistry at C-5 of the 7-deoxy-4-heptulose **2**, obtained in an enzyme-catalysed aldol condensation (see Chapter 2) has been ascertained by extensive n.m.r. experiments, especially n.O.e. studies.[11] The structural properties of the alkali metal salts of D-gluconic acid in the crystalline state and in solution have been examined by F.t.i.r. and ^{13}C-n.m.r. spectroscopy.[12]



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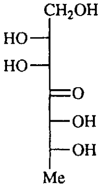

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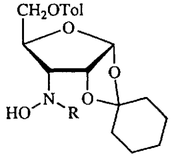

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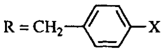


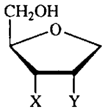
X = H, F, CN, NO$_2$, *etc.*

3 Furanose Systems

The conformational flexibilities of methyl β-D- and α-L-arabinofuranosides have been assessed through molecular mechanics computations (MM3) using the flexible-residue method.[13] Combined computational and n.m.r. spectroscopic techniques have been employed in a conformational study on 3-deoxy-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose.[14] The configurational behaviour of the sugar hydroxylamines **3** has been investigated by n.m.r. and e.s.r spectroscopy; special attention was given to configurational aspects of the C-3—N bond.[15]

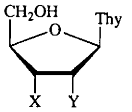
A review on the information contained in sets of vicinal ^{1}H-^{1}H coupling constants as evidence of furanose conformations in DNA has appeared.[16] The relative strengths of the various *gauche* and anomeric effects which influence the pseudorotational equilibrium in the pentofuranose moiety of nucleosides have been evaluated by an ^{1}H-n.m.r. spectroscopic investigation of the abasic nucleoside equivalents **4**.[17]

Conformational studies on deuterated AZT are referred to in Chapter 20. Molecular dynamics simulations on thymidine (**5**) and seven modified thymidines **6** have been undertaken to assess the effect of solvent (water) on the conformational properties and to examine the way electronegative substituents enhance the contribution of certain puckering modes.[18] In an extensive molecular modelling study on the four commonly occurring 2′-deoxynucleosides, an AMBER all-atom force field, rigorously parametrized for ribose and 2′-deoxyribose, was used to investigate the relationships between pseudorotation phase angle, *N*-glycosidic torsion, and puckering amplitude.[19]

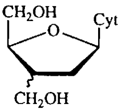


X = Y = H, or
X = Y = OH, or
X = OH, Y = H, or
X, Y = H, D

4



5 X = OH, Y = H
6 X = H, Y = OH, or
X = Y = H, or
X = Y = OH, or
X, Y = H, OMe, or
X, Y = H, Me



7

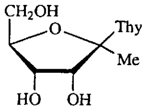
A comparison of the $^1J_{C,H}$, $^2J_{C,H}$, and $^3J_{C,H}$ coupling constants, measured at 500 MHz in D_2O, between C-1′ and several protons in the furanose and in the base moieties of [1′-^{13}C]-enriched 2′-deoxyadenosine, 2′-deoxycytidine, and thymidine with related values in corresponding ribo- and erythro-nucleosides indicated an increase in South conformations on going from ribo- to 2-deoxyribo-derivatives.[20] The steric effect of the 3′-hydoxymethyl groups in the cytosine derivatives **7** on the North ⇌ South pseudorotational equilibrium has been assessed by an examination of vicinal ^{1}H-^{1}H coupling constants at various temperatures and inspection of ΔH° values.[21]

Conformational studies by n.m.r. spectroscopy and/or computational methods have also been reported for the 1-deoxy-psicofuranosyl nucleoside **8**,[22] 2′- and 3′-substituted 2′,3′-dideoxyribonucleosides,[23] 2-substituted (F,Cl) adenosines and selected conformers of 2,3-didehydro-1,2,3-trideoxy-β-D-ribofuranosylamine,[24] and for the AMP analogue 5′-*O*-[*N*-(L-alanyl)sulfamoyl]adenosine (**9**) in solution. Compound **9** proved to be more flexible then anticipated from an X-ray structure analysis.[25]

A 500 MHz study on deuterated ribonucleotide dimers ApU, GpC, and on some 2′-deoxyribonucleotide dimers has been reported; by a comparison with data from natural abundance counterparts, the simplification of spectra in the non-deuterated areas of the molecules was assessed.[26]

4 Pyranose Systems

Unambiguous assignment of the ^{1}H-n.m.r. signals of 2-deoxy-2-amino-α- and β-D-glucose in D_2O allowed the deduction that the [Co(en)$_2$-D-glucosamine]$^{2+}$ complex with Λ-configuration at the metal atom was formed from the α-anomer.[27] The ^{1}H- and ^{13}C-n.m.r. spectra of the methylated-benzoylated derivatives of 1,5-anhydro-D-fucitol (see Chapter 7, structures **2**) have been fully assigned.[28] The anomeric configurations of aldulosonic acid ester **10** and analogues (see Chapter 16 for synthesis) have been determined by means of SFORD ^{13}C-n.m.r. spectroscopy.[29]



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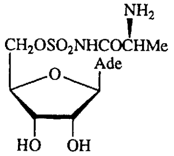

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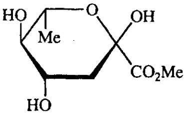
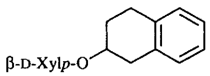


10

The β-D-xylopyranosides of cholestan-3α- and -3β-ol and of (*R*)- and (*S*)-tetralol (**11**) have been used as models to confirm the application of the ^{13}C-n.m.r. glycosylation shift rule to the determination of the absolute aglycon configurations.[30] A general, n.O.e.-based ^{1}H-n.m.r. method for the determination of the relative stereochemistry of 1-carboxyethyl sugar ethers, in which the chirality of the lactyl α-carbon is related to that of the attached sugar moiety in a conformationally rigid lactone ring has been developed. It was successfully tested on the diastereomers of methyl 3-*O*-(1-carboxyethyl)-α-L-rhamnopyranoside which were converted to lactones **12**.[31] Measurements of selective and biselective ^{1}H spin-lattice relaxation rates combined with steady-state and transient ^{1}H-^{1}H n.O.e. Data allowed calculation of intramolecular ^{1}H-^{1}H distances in methyl 2-acetamido-2-deoxy-α- and β-D-glucopyranoside and 2-acetamido-2-deoxy-α- and β-D-mannopyranose and in the respective acetates. Such interproton distance measurements permit the determination of relative configurations, including those at anomeric positions, where other methods fail.[32]



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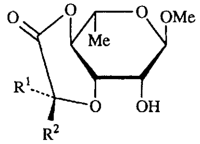
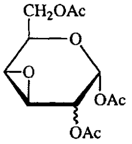


12 $R^1, R^2 = H, Me$



13

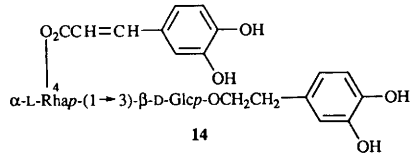
Conformational analyses by n.m.r. and computational methods have been reported for the following compounds: 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-talopyranose,[33,34] anhydro sugars **13** and similar hexopyranose derivatives,[35] methyl 3,4-*O*-isopropylidene-α- and β-D-galactopyranoside and their di-*O*-acetates and di-*O*-methyl ethers,[36] 3,4-*O*-(*R*)-benzylidene-D-ribono-1,5-lactone (see Chapter 6),[37] and 6-deoxy-6-phosphonoyl-D-fructopyranoses (see Chapter 17 for synthesis).[38] D-Glucospyranosylamine, its tetra-*O*-acetate and 4,6-*O*-benzylidene acetal and several *N*-acylated derivatives, together with D-[1-^{13}C]glucopyranosylamine, have been used in a conformational study by n.m.r. spectroscopy aimed at probing the existence of the reverse anomeric effect.[39]

The interactions between *N*-phenyl (*N*-phenyl-β-D-glucopyranosylamine)uronamide (see Vol. 24, Chapter 16, Ref. 69) and water in DMSO-d_6 have been investigated by n.m.r. methods.[40]

5 Disaccharides

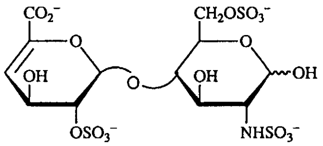
The ^1H- and ^{13}C-n.m.r. data of several 2-*O*-, 3-*O*-, and 2,3-di-*O*-glycosylated methyl α- and β-D-galactopyranosides and -glucopyranosides have been recorded.[41] Particular attention was given to connectivities between different sugar residues and between sugar and acid moieties in the 2D n.m.r. spectra of complex glycosides, such as verbascoside (**14**).[42]

The role of hydrogen bonding in carbohydrates has been examined by molecular dynamics simulations on maltose in aqueous solution.[43] Ramachandran energy surfaces have been computed for leucrose and turanose (5-*O*- and 3-*O*-α-D-glucopyranosyl-D-fructopyranose, respectively) using MM3.[44]



14

The following disaccharides and derivatives have been subjected to conformational analysis by n.m.r spectroscopy and/or computational methods: cellobiose in aqueous solution,[45] methyl β-xylobioside,[46] methyl β-cellobioside,[47] β-gentibiose,[48] all possible monomethyl ethers of methyl β-lactoside,[49] unsaturated, sulfated disaccharides, such as **15**, obtained by cleavage of glycosaminoglycans with lyases,[50] chondroitin sulfate-related compounds, such as **16**,[51] the uronic acid-containing disaccharide **17**,[52] the pectin fragment **18**,[53] β,β-trehalose and its C-linked analogue,[54] and sucralose (4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose).[55] Special attention was given to the conformation about the C5-C6 bond in similar treatments of β-gentibiose,[56] and of β-cellobioside, methyl β-maltoside and the mannobiosides **19**.[57] The conformational energies and geometries of the sucrose model tetrahydro-2-[(tetrahydro-2-furanyl)oxy]-2*H*-pyran have been studied; for this system, *ab initio* techniques have been found superior to MM3, as apparently the MM3-calculated energies for the linkage between the anomeric centres of a furanose and a pyranose ring are too high.[58]



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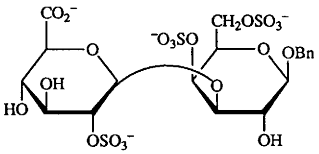
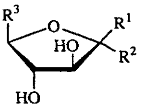


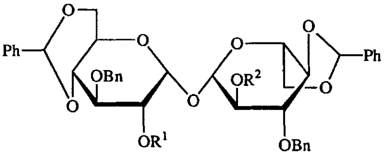
16

17 β-D-Glc*p*A-(1→3)-β-D-Glc*p*NAc-OMe
18 α-D-Gal*p*A6-*O*-Me-(1→4)-α-D-Gal*p*A6-*O*-Me-OMe
19 α-D-Man*p*-(1-n)-α-D-Man*p*-OMe (n = 1 or 2)

The ^{1}H- and ^{13}C-n.m.r. spectra of sucrose, methyl α-D-fructofuranoside (**20**) and methyl β-D-fructofuranoside (**21**) with single sites of ^{13}C-substitution at C-1, C-2, C-3-, or C-6 of the furanose moieties have been analysed to assess the conformations of the their furanose rings, and of the glycosidic linkages in aqueous solution. In addition, spin-couplings in **20** and **21** were compared with those of α-(**22**) and β-D-*threo*-pentulofuranose (**23**), respectively, to study the effect of glycosidation and hydroxymethyl substitution on the solution conformations.[59] The conformations of 2-mono- and 2,2′-di-*O*-substituted α,α-trehalose derivatives **25** have been shown by n.m.r. spectroscopy in combination with molecular mechanics calculations, to differ from that of the 2,2′-unsubstituted disaccharide **24**, both in solution and in the solid state.[60] N.O.e. experiments on the 6′-deoxy-, 6′-thio-, and 6′-*O*-THP derivatives of methyl 2-acetamido-2-deoxy-β-lactoside, potential inhibitors of (2→6)-α-sialyltransferase, proved that they adopt the same conformation as the parent compound.[61]



20 $R^1 = CH_2OH, R^2 = OMe, R^3 = CH_2OH$
21 $R^1 = OMe, R^2 = CH_2OH, R^3 = CH_2OH$
22 $R^1 = CH_2OH, R^2 = OH, R^3 = H$
23 $R^1 = OH, R^2 = CH_2OH, R^3 = H$



24 $R^1 = R^2 = H$
25 $R^1 = (CH_2)_2OH, R^2 = H$, or
$R^1 = R^2 = (CH_2)_2OH$, or
$R^1 = R^2 = CH_2O(CH_2)_2OCH_2$, *etc.*

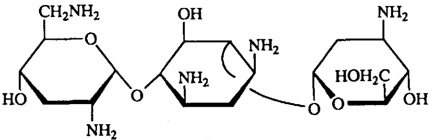
6 Oligosaccharides and Related Compounds

The application of pseudo-3D n.m.r. spectroscopic methods, such as COSY-RELAY, COSY-TOCSY, and RELAY-ROSEY, to oligo- and polysaccharides, has been reported.[62] Sequential analysis of oligosaccharides can be performed in very short times by use of a modified 3D TOCSY-ROSEY experiment; the efficacy of the method has been demonstrated by application to the glycon **26** of verbascosaponin,[63,64] and a brief explanation of the principles involved has been given.[65] The systematic use of negative nuclear Overhauser constraints in the determination of oligosaccharide conformations has been applied to sialyl Lewis X.[66]

α-L-Rha*p*-(1→4)-β-D-Glc*p*-(1→3)-[β-D-Glc*p*-(1→2)]-β-D-Fuc*p*

26

The angular dependence of one-bond ^1H-^{13}C coupling constants in β-linked oligosaccharides has been studied.[67] The conformational mobility of mono- and di-fucosyl lactoses has been investigated by use of ^{13}C spin-lattice relaxation data,[68] as well as rotating-frame n.O.e.-based distance mapping and theoretical calculations.[69]



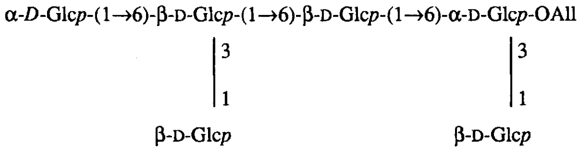
27

Protonation constants and pH dependent conformational changes of tobramycin (**27**) have been assessed on the basis of the ^1H- and ^{13}C- chemical shift changes of its three tetra-*N*-acetyl- and one tri-*N*-acetyl-derivative with pH.[70] The ^1H- and ^{13}C-n.m.r. spectra of a series of oligosaccharides derived from hyaluronic acid have been completely assigned. The observed ^{13}C chemical shifts suggested that cooperative intramolecular hydrogen bonds affect the conformation of hyaluronate in aqueous solution only in a minor way.[71]

β-D-Fru*f*-[(2→1)-β-D-Fru*f*]$_n$-(2↔1)-α-D-Glc*p*

28 n=2, **29** n=3, **30** n=1

Nystose (**28**) has been modelled with the rigid-residue PFOS program and with MM3 in an effort to determine its conformation in the crystalline state.[72] Molecular dynamics calculations have been performed on **28** in aqueous solution,[73] its ^1H-n.m.r. spectrum in D_2O has been fully assigned,[74,75] and corrections have been made to previous ^{13}C chemical shift assignments. ^1H- and ^{13}C-chemical shift values for 1,1,1-kestopentaose (**29**) have also been recorded and compared to corresponding data from nystose (**28**), 1-kestose (**30**), and inulin.[75] In addition, these compounds have been used, together with sucralose, in an n.m.r. investigation of internal motion in carbohydrates. The data collected, in particular ^1H- and ^{13}C-relaxation rates, indicated that internal motions are not slow relative to overall tumbling.[76] Selectively deuterated derivatives of the hexaglucoside **31** and several related olgosaccharides have been employed in the complete assignements of their ^1H-n.m.r. spectra.[77] The structure of the saccharide part of a *Haemophilus influenzae* lipopolysaccharide[78] and the conformation of a mucin glycoprotein-derived di-antennary octasaccharide[79] have been established by n.m.r. experiments.



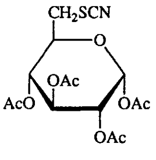
$$\begin{array}{cccc} \alpha\text{-}D\text{-Glc}p\text{-}(1\to6)\text{-} & \beta\text{-D-Glc}p\text{-}(1\to6)\text{-} & \beta\text{-D-Glc}p\text{-}(1\to6)\text{-} & \alpha\text{-D-Glc}p\text{-OAll} \\ & \big|\,3 & & \big|\,3 \\ & \big|\,1 & & \big|\,1 \\ & \beta\text{-D-Glc}p & & \beta\text{-D-Glc}p \end{array}$$

31

A ^{1}H-n.m.r. study on a 2:1 chromomycin A_3-Mg^{2+} complex in methanol has been undertaken in order to show the importance of the carbohydrate moiety in controlling the shape of the antibiotic.[80] Based on n.m.r. data and inspection of Corey-Pauling-Koltun models, the probable structure of the inclusion complex between 8-anilino-1-naphthalene sulfonate and 2,6-di-*O*-methyl-cyclomaltoheptaose has been determined.[81]

7 N.m.r. of Nuclei other than ^{1}H and ^{13}C

The thiocyanate **32** has been found the most readily prepared glucose derivative with fully resolved ^{2}H-n.m.r. spectrum, suitable for the study of natural hydrogen isotope fractionation.[82] A review on the conformation of 6-deoxy-6-fluoro-D-glucose in various solvents (methanol, acetone, DMSO, water) contains ^{1}H- and ^{19}F-n.m.r. data.[83] Nitrilium intermediates **33** have been generated at -30 °C in acetonitrile-d_3 and studied by ^{1}H-, ^{13}C-, and ^{15}N-n.m.r. spectroscopy as well as by molecular modelling to shed light on the stereoselectivity of acetonitrile-mediated glycosylations; all the evidence suggests the exclusive formation of α-configurated nitrilium derivatives.[84] ^{119}Sn-N.m.r.-spectroscopy has been applied to stannylene acetals to show that they may exist as dimers, with structures such as **34**.[85]



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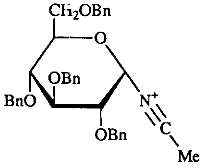

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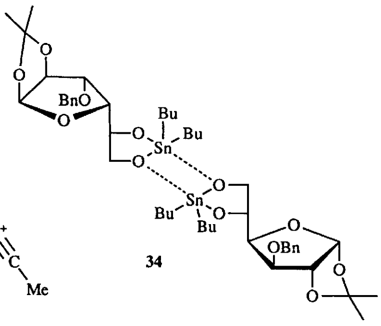

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22
Other Physical Methods

1 I.r. Spectroscopy

Activity in this aspect of carbohydrate chemistry has been limited. A comprehensive study of the spectroscopic (f.t.i.r. and ^{13}C n.m.r) and structural (X-ray powder diffraction) properties of D-gluconate salts (Li^+, Na^+, K^+, Rb^+, Cs^+ and $^+NH_4$) has been described.[1] Data obtained on aqueous solutions suggest that the metal ions are hydrated and that there are no direct sugar-metal ion interactions. Structural studies on solids then served to indicate the nature and extent of oxygen-metal ion interactions.

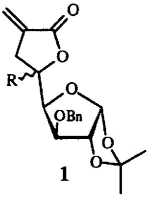
Novel and potentially important applications of vibrational Raman optical activity studies to carbohydrate structure analysis have also been reported.[2] Within the region 600-1600 cm^{-1}, this technique serves to reflect local stereochemical details (generated as a result of short-range interactions). Information relating to anomeric configuration is found at 750-950 cm^{-1}, and 950-1200 cm^{-1} provides a fingerprint characteristic of ring structure and substitution pattern. Above 1200 cm^{-1}, spectra are dominated by CH_2 and C-OH deformations which provide useful data on the conformational preference of exocyclic hydroxymethyl units.

Reference is made in Chapter 21 to the use of vibrational spectroscopy in conformational analysis of mono- and polysaccharides.

2 Mass Spectrometry

The application of field desorption, field ionization and c.i. mass spectrometry to the structural elucidation of carbohydrate-containing compounds has been reviewed (105 refs.).[3] Under "roasting" conditions, (200-210 °C), cysteine reacts with rhamnose to give a complex mixture of products. Of the (approx.) 180 compounds detected, mass spectrometry (m.s.) allowed 125 to be identified. These products are, for the most part, furan, pyrrole and thiophen derivatives.[4] The relationship between the stereochemistry of a series of stereoisomeric furanosides **1** (e.g. R=H, $CONH_2$) and their associated fragmentation mechanisms has been evaluated using m.s.[5] The configuration of partially methylated galactose derivatives using g.c.-m.s. has been reported.[6] As part of a programme to trace photosynthetic pathways, a series of ^{13}C-labelled 2-octulose phosphates has been prepared and analysed as their persilylated and aldoxime-TMS derivatives.[7] Persilylated compounds generated intense peaks having more than one origin, whereas aldoxime derivatives gave ions resulting from a single cleavage process. M.s. methods continue to find important application in natural products chemistry. The structure of the oviposition-deterring pheromone **2** has been deduced,[8] and m.s.-m.s. methods allowed assignment of structure to a series of five furostanol glycosides obtained from *Metanarthecium luteo-viride*.[9] Efforts continue towards developing m.s. methods as reliable probes for carbohydrate structure/stereochemistry.

All positional isomers of the methylated-acetylated forms of 1,5-anhydro-D-fucitol **3** have been synthesized for use as standards in the reductive cleavage method for glycosyl linkage analysis, and their c.i. and e.i. data are reported.[10]



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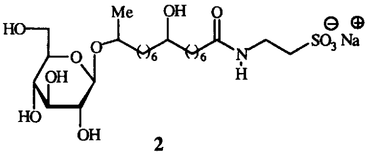

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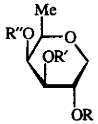


3 R=R′=R″=Me or Ac

A total of 27 oligosaccharides composed of hexopyranose, deoxyhexopyranose, deoxyfluoro hexopyranose and 2-acetamido-2-deoxy hexopyranose units have been studied by FAB-m.s.[11] Structurally significant ions were observed, and the authors suggest that this method will be important for the sequencing of oligosaccharides without prior recourse to derivatization.

Acetylated methyl 2-deoxy-D-*erythro*-pentoxides have been examined using e.i. and c.i. Anomeric pairs were studied with the conclusion that m.s. does not allow for assignment of anomeric configuration.[12]

E.i. and FAB-m.s. of tetra-*O*-acetyl-β-*ribo*-furanose and β-pyranose isomers has been reported[13] and high and low energy FAB-tandem m.s. methods have been used to characterize a series of diastereomeric 1,2-*trans*-2-deoxy-2-iodoglycopyranosyl phosphoramidates.[14] FAB has proved to be valuable in the analysis of sulfated heparin-derived oligosaccharides. Acetylation (under basic conditions) did not compromise the sulfate groups and high quality structural data are now available.[15] Sulfation sites and linkage positions have been deduced using FAB-m.s. for glycosaminoglycan-derived disaccharides.[16] FAB-m.s.-m.s. of macrolide antibiotics has demonstrated that cleavage of the glycosyl linkages is a major fragmentation pathway. The methods developed have also been applied to the identification of an *O*-phosphate of oleanolomycin (the result of enzymatic deactivation) and the site of phosphorylation was determined.[17] Boronate derivatives of carbohydrates have been examined using FAB-m.s. and, using relative abundance of characteristic ions, epimers of mono- and di-saccharides may be distinguished.[18] This is based on the selectivity and steric demands for boronate formation and is offered as a simple and effective analytical tool. Stereospecificity associated with decomposition of Ag^+-methyl glycosides ions has allowed C(1)-OMe and C(2)-OH isomers to be distinguished by FAB. If these two substituents are in a *cis* relationship, then loss of MeOH is observed, but in the *trans* situation, fragmentation with loss of AgH is preferred.[19]

The importance of instrumental parameters and sample preparation on mass-analysed ion kinetic energy (MIKE) spectra (with FAB) has been discussed within the context of peracetylated ribofuranose.[20] Isomers of perbenzylated hexonyl (Glc, Gal, Man) derivatives have been differentiated using FAB/MIKE spectra.[21] A total of 30 monosaccharides have been examined using thermospray-m.s. The value of this method for the analysis of highly polar compounds, together with the importance of several experimental variables, has been highlighted.[22]

Thermospray-m.s. (in combination with h.p.l.c.) has been used to characterize flavonoid glycosides,[23] phenolic and terpenoid glycosides[24] and saponins.[25] In the last case, information on the nature of the carbohydrate components and their sequence could be obtained.

The applications of electrospray (ion spray)-m.s. continue to broaden and have, this year, found utility for the identification of glycoprotein and glycopeptide fragments produced by enzymatic digestion.[26] Regioisomeric esters of sucrose (e.g. 6-*O*-octanoyl and 6'-*O*-octanoyl) have been characterized by electrospray tandem m.s.[27] Electrospray mass spectra for selected modified deoxynucleosides and deoxynucleoside monophosphates have been determined, and methods for intensity enhancement of MH^+ described; MH^+ may be detected with as little as 3 pmol of substrate.[28]

A quantitative study of the electrospray-m.s. of various neutral and acidic oligosaccharides has been conducted.[29] Acidic molecules undergo Na-exchange which provides information on the number of acidic residues present, and molecular mass information has been obtained on neutral, non-derivatized oligosaccharides up to 4000 Daltons. The same group have also used these methods to study the degree of methylation associated with derivatization of β-cyclodextrins and to identify oligosaccharides obtained *via* enzymatic digestion of apple and pear cell walls.[29]

An electrospray-m.s. method (using D_2O) for determining the number of exchangeable hydrogen atoms in polar compounds has been developed, and the application of this procedure to the analysis of a lactose-based contaminant in a drug formulation is described.[30] Sulfated di- and oligo-saccharides (from enzymatic digests of chondroitin sulfate and heparin) are stable towards fragmentation under electrospray-m.s. conditions. Determination of exact masses is described and the potential of m.s.-m.s. with collisionally-induced dissociation (CID) to elucidate the structure and sequence of these oligosaccharides was evaluated.[31]

Pseudo-electrochromatography (PEC), a relatively new technique, has been coupled to electrospray-m.s. (in the negative ion mode) for the detection of aryl glucuronides.[32] Further developments in the use of h.p.l.c.-thermospray-m.s. for the analysis of oligosaccharides have been reported. Malt oligosaccharides and products derived from enzymatic digestion of plant cell walls have been examined using chromatographic supports and eluents designed to minimize glycosidic cleavage at the interface, thereby allowing study of sodiated intact molecules.[33]

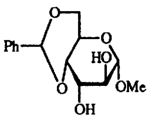
Finally, MSDCARD, a mass spectral database for carbohydrates and conjugates has been described. This system allows collection, storage, editing and retrieval of data, together with search and display facilities.[34]

3 X-ray and Neutron Diffraction Crystallography

Specific X-ray crystal structures have been reported as follows (solvent molecules of crystallization are frequently not noted):

3.1 Free Sugars and Simple Derivatives Thereof.- 3-*O*-Benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose.[35]

3.2 Glycosides, Disaccharides and Derivatives Thereof. - The D-*altro* diol **4**[36] is of interest because, while the presence of an intramolecular hydrogen bond was detected in solution, this structural feature was absent in the solid state. Other structures studied were the oxepine ester **5**[37] (derived from carbohydrate-directed epoxidation), methyl 2-*O*-methyl-α-D-glucopyranoside,[38] methyl 4,6-*O*-(S)-benzylidene-2-*O*-methyl-α-D-galactopyranoside,[38] methyl α-L-fucopyranoside,[39] the methyl 3,4-*O*-isopropylidene-α- and β-D-galactopyranosides[40] (the conformational properties of these last two systems, together with their di-*O*-acetyl and di-*O*-methyl derivatives have also been studied by ^{1}H and ^{13}C n.m.r.), methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside,[41] methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-tosyl-β-D-*arabino*-hexopyranoside,[42] 4-α-D-glucopyranosyloxy-2, 2, 6, 6-tetramethylpiperidine N-oxide **6**,[43] the steroidal derivative **7**,[44] dendranthemoside A pentaacetate (an ionol β-D-glucoside),[45] 4-(3,4-dihydroxyphenyl)-5-*O*-β-D-galactopyranosyl-7-methoxycoumarin,[46] 6-*O*-methylerythromycin A (clarothromycin),[47] xylosucrose (β-D-fructofuranosyl α-D-xylopyranoside),[48] 1,6':6,1'-dianhydro-2,3:2',3'-di-*O*-isopropylidene di-α-D-mannofuranose **8** (a by-product in the synthesis of 2,3,5-tri-*O*-acetyl-1,6-anhydro-β-D-mannofuranose)[49], β, β-trehalose[50] and the α, α-trehalose-based macrocycle **9**.[51]



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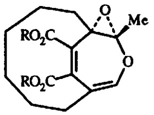
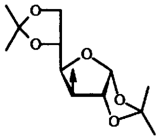
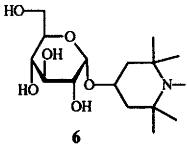


5 R=





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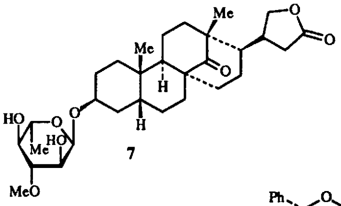

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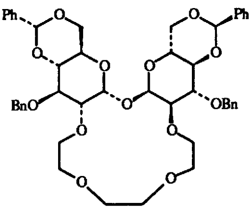

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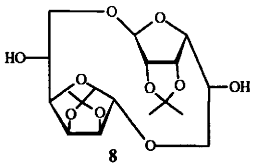
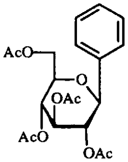


8

3.3 Higher Oligosaccharides and C-Glycosides.- Erlose [*O*-β-D-fructofuranosyl-(1→2)-*O*-α-D-glucopyranosyl-(1→4)-α-D-glucopyranoside],[52] nystose [α-D-glucopyranosyl-(1→2)-β-D-fructofuranosyl-(1→2)-β-D-fructofuranosyl-(1→2)-β-D-fructofuranoside] (which has been the subject of two independent determinations),[53] β-cyclodextrin complexes with ethylene glycerol,[54] 6-*O*-[(R)-2-hydroxypropyl] (as well as the corresponding (S)-2-hydroxypropyl) derivatives of β-cyclodextrin,[55] $6^A,6^C,6^E$-tri-*O*-methyl α-cyclodextrin,[56] (1→3)-α-D-glucan tribenzoate,[57] an extracellular α-D-glucan (based on (1→3)-α-linked maltotriose and α-maltotetrose units),[58] 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl benzene **10** (as well as the corresponding *manno* isomer),[59] the undecose derivative **11**,[60] *C*-sucrose heptaacetate **12**[61] and the two dodecose derivatives **13** and **14**.[62]



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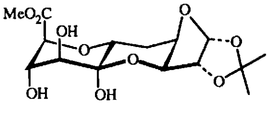

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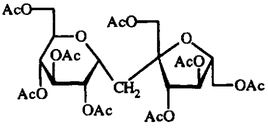

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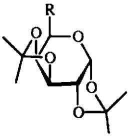
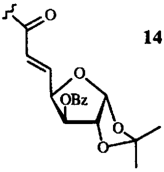
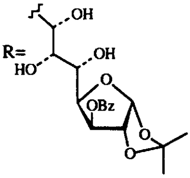


13 R=



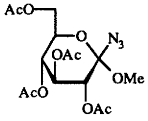
14 R=



3.4 Anhydro-sugars. - 1, 2-Anhydro-3, 4, 6-tri-*O*-benzyl-β-D-talopyranose[63] and 2, 5-anhydro-1-*O*-tosyl-D-mannitol.[64]

3.5 Nitrogen-, Sulfur- and Selenium-containing Compounds.- 2,3,4-Tri-*O*-acetyl-β-D-arabinopyranosyl azide,[65] the azido orthoester **15**,[66] the diazirine **16**,[67] episulfide **17**,[68] selenourea **18**,[69] α-D-ribopyranosylamine 1,3-(cyclic carbonate),[70] lactams **19a/b** and **20**,[71] the 6-nitro-7-methylthioheptitol **21**,[72] 2-acetamido-2-deoxy-β-D-glycopyranosyl nitromethane (3-acetamido-2,6-anhydro-1,3-dideoxy-1-nitro-D-*glycero*-D-*gluco*-heptitol),[73] the 7-nitrooctose **22**,[74] β-cellobiosylnitromethane,[75] β-maltosylnitromethane heptaacetate,[75] the nitrile oxide cycloadducts **23a/b**[76] and the sugar-related **24**,[77] 2,4:3,5-di-*O*-benzylidene-1-*C*-2'-pyridyl-D-ribitol[78] and 2-acetamido-3,4-dihydro-4-oxo 6-(D-*arabino*-tetra-*O*-acetoxybutyl)pteridine.[79] The structural aspects of hydroxylated pyrrolidines and indolizines has been an active area this year and the crystal structures of the following have been reported: 1,2,4-trideoxy-1,4-imino-3,5:6,7-di-*O*-isopropylidene-L-*glycero*-D-*gluco*-octitol,[80] the heptanoamide derivative **25**,[81] the bicyclic derivative **26**,[82] "mannonojiritetrazole" **27**,[83] the D-gluconohydroximo-1,5-lactams **28a/b**,[84] 1,3-dideoxy-3-fluoronojirimycin,[85] deoxynojirimycin,[86] castanospermine[86] and 1-

deoxycastanospermine.[87] Other structural determinations relevant to this section are: tetrahydrothiophenes **29a/b**,[88] 1-deoxy-1-(N, N-dimethyldithiocarbamoyl)-2,3:4,5-di-*O*-isopropylidene-D-xylitol,[89] methyl 2-amino-2,6-dideoxy-α-D-glucopyranoside-6-sulfonic acid,[90] and methyl α-D-galactopyranoside 2,6-bis(sodium sulfate).[91]



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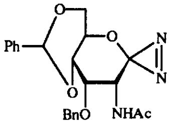

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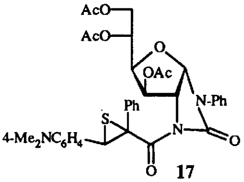

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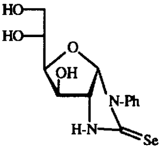

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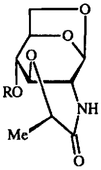
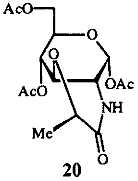


19a R=Bn
19b R=Ac



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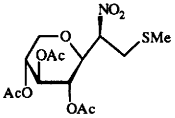

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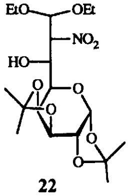

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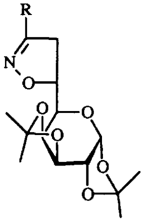
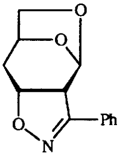
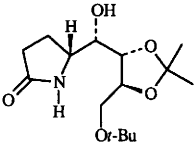


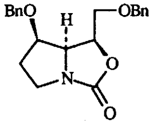
23a R=Ph
23b R=CO_2Et



24



25



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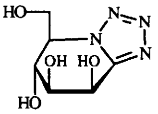
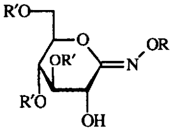
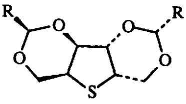


27



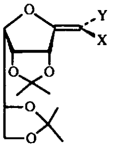
28a R=R′=H
28b R= CONH(2-ClC_6H_4), R′=H



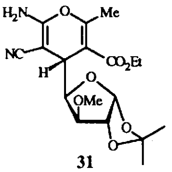
29a R=Ph
29b R=H

3.6 Unsaturated Sugars.- Ethyl 3,6-di-*O*-benzoyl-4-deoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose,[92] cyclohexyl 6-*O*-benzoyl-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranosid-2-ulose,[92] 1,5-anhydro-3,6-di-*O*-benzoyl-4-deoxy-D-*glycero*-hex-3-en-2-ulose,[92] 1,3-di-O-benzoyl-2,6-dideoxy-α-L-*glycero*-hex-2-enopyranos-4-ulose and the corresponding β-L-isomer,[92] the mono-and di-fluoroalkenes **30a**/b,[93] (E)-3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-4-enofuranose[94] and the heterocycle **31**.[95]

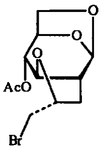
3.7 Branched-chain Sugars.- The branched-chain anhydrooctitol derivative **32**[96] (the result of NBS-mediated cyclization of the corresponding 2-*C*-allyl derivative), the levoglucosenone/nitromethane adduct **33**,[97] 1,6-anhydro-3,4-dideoxy-2-*O*-(3,5-dinitrobenzoyl)-2-*C*-methyl-β-D-*threo*-hex-3-enopyranose,[98] 1,6-anhydro-3,4-dideoxy-2-*C*-phenyl-β-D-*threo*-hex-3-enopyranose,[98] the branched decose derivative **34**[99] (an intermediate in a synthetic programme directed towards monensin), dihydrocarvone aldol adduct **35**,[100] β-lactam **36**[101] and the glycos-3-yl amino ester **37**.[102]



30a X=Y=F
30b X=H, Y=F



31



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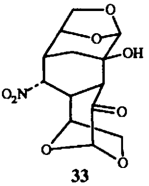

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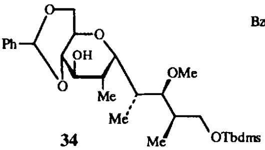

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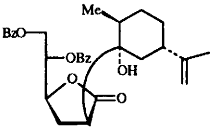

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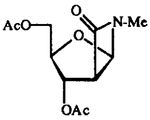

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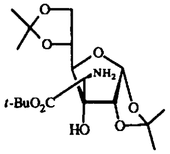
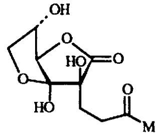


37

3.8 Sugar Acids and their Derivatives.- *N*-(1-Octyl)-D-talonamide,[103] *N*-[8-(D-gluconamido)octyl]-D-gluconamide,[104] L-mannonic acid hydrazide,[105] 3,5(R):6,7(R)-di-*O*-benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone,[106] 2-oxobutylbutyrolactone **38**[107] and derivatives **39** and **40a/b**[107] (all derived from condensation of ascorbic acid with methyl vinyl ketone and it should be noted that the structural determination of **39** served to correct an earlier assignment), 2,3,4,5-tetra-*O*-acetyl-6-amino-6-deoxy-D-allonolactam,[108] 2,6-anhydro-*N*-methyl-D-*glycero*-D-*ido*-heptonamide (in which the ring adopts a skew boat conformation both in isolation and as its complex with glycogen phosphorylase),[109] methyl (1-phenyl-1*H*-tetrazol-yl)-3-deoxy-2-thio-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate[110] and methyl 2,5-anhydro-6-deoxy-L-gluconate.[111]

3.9 Inorganic Derivatives. - The [1,7-dicarba-*closo*-dodecaboran(12)]aldose **41**,[112] 1,2:5,6-di-*O*-isopropylidene-3-*C*-(triphenylstannylmethyl)-α-D-allofuranose **42**,[113] the Cu(II) complex **43**,[114] and the *cis*-platin analogues **44**[115] and **45**[116] and galactitol (complexed to $PrCl_3$).[117]



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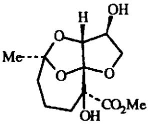

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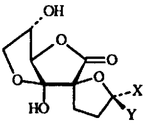
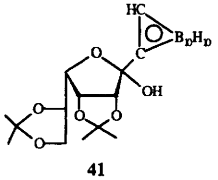


40a X=OMe, Y=Me
40b X=Me, Y=OMe



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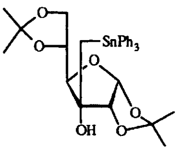

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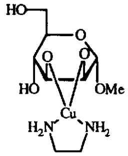

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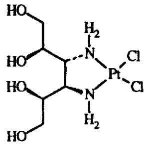

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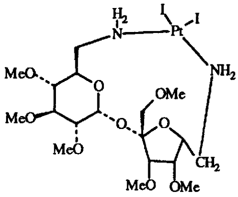
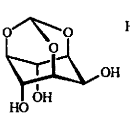


45

3.10 Alditols and Cyclitols and Derivatives Thereof.- L-Threitol,[118] 2,4:3,5-di-*O*-methylene-1-*O*-tosylxylitol,[119] 1(S)-2-C-[(R)-acetoxy(phenyl)methyl]-1,3,4,5,6-penta-*O*-acetyl-2-deoxy-1-phenyl-L-gulitol,[120] the four isomeric 1,2,3,4,5,6,7-hepta-*O*-acetates derived from D-*glycero*-D-*galacto*-heptitol and the corresponding racemate,[121] D-*glycero*-D-*manno*-heptitol[121] and meso-*glycero-gulo*-heptitol, [121] D-*glycero-L-gulo*-heptitol,[122] meso-*glycero-allo*-heptitol,[122] meso-*glycero-allo* heptitol heptaacetate,[122] the three isomeric octa-*O*-acetyl derivatives of L-*threo*-L-*altro*, L-*threo*-L-*galacto*-[123] and L-*threo*-D-*galacto*-octitol,[124] and deca-*O*-acetyl-L-*galacto*-L-*gulo*-decitol.[125] The interesting cyclitol **46**[126] shows the presence of a strong intramolecular hydrogen bond (which is reflected in solution) and this feature is discussed in terms of the ability of **46** and related molecules to act as a glycosyl acceptor towards diazirine-based donors. The structure of racemic 3,4-di-*O*-acetyl-1,2,5,6-tetra-*O*-benzyl-*myo*-inositol has been determined[127] and the thermally induced phase transitions associated with this structure are discussed.

3.11 Nucleosides and their Analogues and Derivatives Thereof. - 2'-*O*-Methyl adenosine-3',5'-cyclic methyl monophosphate,[128] the AZT-ternary zinc (II) complex **47**,[129] the 4'-alkoxythymidine analogue **48**,[130] the 2',3'-didehydro-2'3'-dideoxy variants of uridine, [131] cytidine[131] and 5-ethyluridine,[131] *N*-benzoyl-2',3'-dideoxycytidine,[132] β-cytidine,[133] the thymidine analogue **49**,[134] 2'-*O*-5-dimethyluridine,[135] 6-formyluridine,[136] the 3'-oximinouridine **50**,[137] the 2'-fluoro-3'-methyl thymidine variants **51** and **52a/b**,[138] 5-chloromercurio-2'-deoxyuridine,[139] the polycycle **53** (a 1,3-dipolar cycloaddition adduct derived from uridine),[140] the novel cyclonucleosides **54**[141] and **55**,[141] 5-fluoro-1-(2,3,6-trideoxy-α-L-*glycero*-hex-2-

enopyranos-4-ulosyl)uracil,[142] 4'-thiothymidine,[143] sangivamycin **56**[144] (a protein kinase C inhibitor) and analogues **57-60**[144] and *C*-nucleoside **61**.[145]



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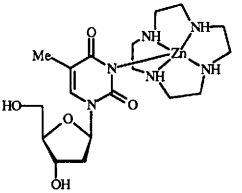

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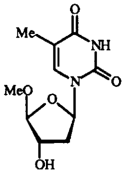

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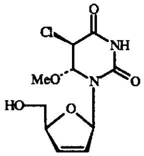

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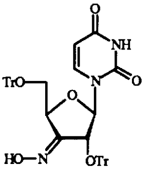

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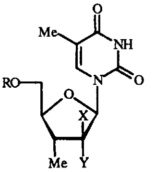
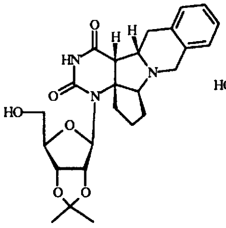


51 R=Y=H, X=F
52a R=Ac, X=H, Y=F
52b α-anomer of **52a**



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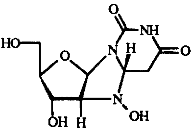

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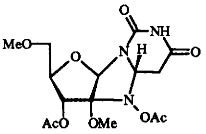

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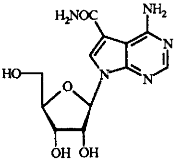

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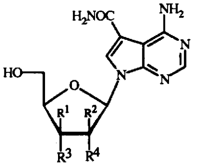
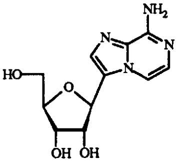


57 R^1=R^2=R^3=H, R^4=OH
58 R^2=R^3=H, R^1=R^4=OH
59 R^1=R^2=R^4=H, R^3=OH
60 R^1=R^4=H, R^2=R^3=OH



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4 E.s.r. Spectroscopy

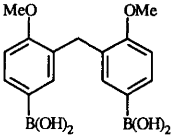
Triplet photoinitiation has been used to generate radicals from simple carbohydrates, and these species have been studied using time-resolved e.s.r.[146] E.s.r. has also been used to study cuminoxyl radicals derived from a series of 3-(*N*-arylmethyl-*N*-hydroxyamino)-1,2-*O*-cyclopentylidene-3-deoxy-5-*O*-toluoyl-α-D-ribofuranose derivatives.[147]

5 Polarimetry, Circular Dichroism, Calorimetry and Related Studies

A review (93 refs) has appeared, covering the electronic spectra and photochemical reactions of mono- and di-saccharides, which includes discussion of photocatalytic processes involving aqueous suspensions of TiO_2.[148]

An optical rotation-based method of conformational analysis has been applied to methyl β-xylobioside and a semi-empirical model of saccharide optical activity has been used to calculate the Na_D rotation of this same compound.[149] Calculated values of optical rotation based on the crystal structures of a series of 1,6-anhydro-β-D-pyranoses of galactose, talose and mannose suggest that solution conformations are very similar to those found in the solid state. However, significant differences were detected for methyl 3,6-anhydro-α- and β-pyranosides of glucose, galactose and mannose.[150]

A convenient method for determining absolute configuration has been described, based on *in situ* complexation (using a transition metal species) to generate enhanced Cotton effects. This is appropriate for optically active molecules (such as monosaccharides) that are only weakly absorbing in accessible wavelength ranges. Helicity and sector rules have been developed to correlate Cotton effects with absolute configuration and the method has also been applied to nucleoside derivatives.[151] The diphenylboronic acid **62** undergoes specific complexation with mono-and di-saccharides providing a c.d.-based method for assignment of absolute configuration.[152]



62

Reference c.d. spectra have been reported for a series of isomeric mono- and di-deoxy pentitols and hexitols (as either their anthronate or *p*-methoxycinnamate esters)[153] and spectra for a range of heptofuranose derivatives (complexed to either $Mo(OAc)_4$ or $Rh_2(OCOCF_3)_4$) have also been described.[154] A c.d. study of seven different methyl pyranosides and five disaccharides (trehalose, lactose, cellulose, melibiose and xylobioside) has been conducted in order to develop an interpretative model for dependence of chirotopical properties on conformation.[155] A study (in Japanese) of the c.d. spectra of *p*-bromobenzoates and *p*-methoxycinnamates of methyl glycopyranosides has been reported.[156] C.d. spectra of methyl 2-amino-2-deoxy-D-galactopyranoside (as either the *N*-acetyl or *N*-*p*-bromobenzamido derivative) have been examined and solvent effects, together with temperature-dependent variations, have been correlated with changes in conformation.[157]

The interaction between borate ions and a series of carbohydrates (sucrose, D-fructose and D-glucose) in aqueous solution have been examined using calorimetry,[158] and thermodynamic parameters are available for the inclusion complex of 8-anilino-1-naphthalene sulfonate with 2,6-di-*O*-methyl-cyclomaltoheptaose.[159]

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23
Separatory and Analytical Methods

1 Chromatographic Methods

1.1 Gas-Liquid Chromatography. - Capillary g.c. analyses have been reported for partially methylated alditol acetates derived from seven aldoses on a new high-polarity cross-linked stationary phase (BPX70), with m.s. identification of components,[1] a 31 component alditol mixture as either the peracetate or pertrimethylsilyl ether derivatives on high-polarity or non-polar stationary phases, respectively,[2] and trace amounts of muramic acid released from bacterial peptidoglycan by methanolysis as its pertrifluoroacetate methyl glycoside derivative, with negative ion c.i. - m.s. detection.[3] A method for determining the absolute configuration of aldoses by g.c. analysis of their peracetylated 2-octyl glycoside derivatives, obtained by use of enantiomerically pure 2-octanol, has been detailed.[4]

1.2 Thin-Layer Chromatography. - The quantitative analysis of 5-methylcytosine released from DNA has been reported by h.p.t.l.c. on primary amine modified silica.[5]

1.3 High-Pressure Liquid Chromatography. - References are grouped according to the class of sugar being analysed.

H.p.l.c. on pellicular anion exchange packings with a strongly alkaline eluant and pulsed amperometric detection is given the abbreviation HPAEC, which is used herein.

1.3.1 *General Reviews.* – H.p.l.c. methods for the quantitative analysis of monosaccharide residues in glycoproteins,[6] and the detection of carbohydrates by pulsed amperometric detection on Au and Pt electrodes,[7] have been reviewed.

1.3.2 *Detection Methods.* – The use of purpald (4-amino-3-hydrazino-5-mercapto-1,2,4-triazole) as a reagent for post-column derivatization of neutral monosaccharides has been reported.[8]

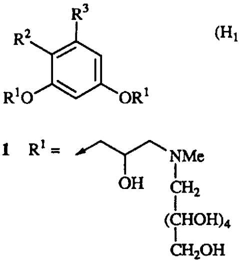
1.3.3 *Neutral sugars, amino-sugars, alditols and derivatives thereof.* – The h.p.l.c.-thermospray m.s. of thirty monosaccharides and their derivatives has been reported.[9] Trace levels of monosaccharides released by hydrolysis of glycosides from grape musts,[10] and mannitol, 3-*O*-methyl-D-glucose and lactulose (administered orally to investigate gut mucosal damage in HIV infection) in urine,[11,12] were determined by HPAEC. Analyses of the carbohydrates (e.g. maltotriose, maltose, sucrose, glucose and fructose) in wort, beer, fruit juices and carbonated beverages on cation exchange resins in the H^+-, K^+- or Ca^{2+}- form were reported; the K^+- form resin permits sucrose and maltose separation.[13]

The refractive index responses of various sugars (NeuAc, Glc, Gal, Fuc, GlcNAc, maltose, maltotriose and maltotetraose) eluted from a cation exchange resin column (H^+- form, acidic eluant) were shown to be proportional to the mass injected and their molecular mass.[14] A method to rapidly monitor glucose, fructose, sucrose and maltose in fermentation broths involved solid-phase extraction of interfering substances and h.p.l.c. on a polyamine column with refractive index detection.[15]

A polymer-coated amino-bonded phase made by exposure of silica to 1,3,5,7-tetramethylcyclotetrasiloxane showed improved stability to acid and base, and enhanced ability to separate various mono-, di- and oligo-saccharides, alditols and nucleotides, compared to aminopropylated silica.[16] Determination of glucose and 1,5-anhydro-D-glucitol in serum as a reliable test for diabetes mellitus was achieved by strong anion exchange chromatography (NaOH eluant), post column neutralization and chemiluminescence detection (immobilized glucose oxidase reactor with released H_2O_2 reacting with a luminol-potassium hexacyanoferrate(III) reagent).[17] Polyols in serum have been determined by h.p.l.c. - m.s. (negative ion, atmospheric pressure ionization) using a strong cation exchange resin column, and post-column addition of chloroform to generate $[M+Cl]^-$ base peaks. Markedly enhanced levels of erythritol, *myo*-inositol, mannitol and sorbitol, and a decreased level of 1,5-anhydroglucitol were found in serum from haemodialysis patients prior to dialysis.[18]

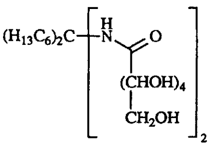
Glucosamine and muramic acid, liberated from bacterial cell walls by acid hydrolysis, were determined by reversed-phase h.p.l.c. analysis of their phenylthiocarbamate derivatives (formed by reaction with PhNCS).[19] Reversed-phase analyses of neutral and acetamido-sugars as their 9-fluorenylmethoxycarbonylhydrazone derivatives and amino-sugars as their *N*-(9-fluorenylmethoxycarbonyl) derivatives,[20] and 2-amino-2-deoxy-D-glucose and -galactose as their *N*-(4-dimethylaminoazobenzene-4′-sulphonyl) derivatives,[21] have been applied to the analysis of natural glycoproteins and synthetic glycopeptides, respectively.

Efficient separations of 2-acetamido-2-deoxy-galactitol, -glucitol and -mannitol, and of oligosaccharide-hexosaminitols released by reductive β-elimination from glycopeptides, from other materials, were achieved by h.p.l.c. with pulsed amperometric detection on a surprising combination: a cation-exchange column with dilute NaOH as eluant. Neutral and amino-sugars eluted near the void volume.[22] The cationic polyol surfactants **1** and their synthetic precursors were separated by ion-pair reversed-phase h.p.l.c., and the related non-ionic diamide polyol surfactants **2** were determined by reversed-phase h.p.l.c.[23]



1

$R^2, R^3 = H, C_6H_{13}, C_{12}H_{25}$, or $C_{15}H_{31}$



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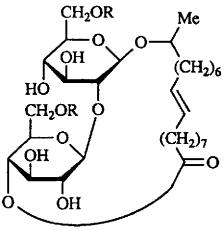


3 R = H or Ac

1.3.4 *Glycosides*. – Reversed-phase h.p.l.c. analyses have been reported for six flavone glycosides of grapefruit and sour orange juice,[24] a number of cardenolides in Digitalis leaves,[25] ginseng saponins (a C_{18}-modified porous glass column having some advantages over others),[26] and acidic (i.e. containing malonyl half esterified sugar residues) and neutral saponins from the crude drugs ginseng, bupleurum root and senega.[27] Sophorolipids **3** and the corresponding acyclic acids in fermentation products were separated by reversed-phase h.p.l.c. (with evaporative light scattering detection) and identified by chemical and m.s. analyses.[28] Phenolic and flavonoid constituents of juice beverages, such as ascorbate and the glycosides naringin and hesperidin, were detected with improved resolution in reversed-phase h.p.l.c. eluant by use of a coulometric array detector, which differentiates species on the basis of their different voltammetric properties.[29] An on-line post-column immunochemical detection system was described for use in the reversed-phase analysis of digoxin and its metabolites. Fluorescent antibodies for the aglycon digoxigenin are mixed with the eluant, excess antibody is removed on a column of immobilized aglycone, and the antibody complex with the analyte is detected fluorimetrically.[30]

Applications of reversed-phase h.p.l.c. - thermospray m.s. have been reported for flavonoids and their glycosides,[31] and phenolic and terpene glycosides[32] and saponins[33] in crude plant extracts.

1.3.5 *Oligosaccharides and Glycopeptides*. – Rapid high-resolution normal-phase separations (aq. MeCN eluant) of neutral oligosaccharides derived from starch, cellulose, pullulan, xylan, inulin and mannan were achieved on a Cyclobond I column, which has β-cyclodextrin coupled by a 10 atom spacer to silica. Separations were equivalent to those on less durable aminopropylsilica columns. Anomers of individual oligomers were not separated in this case (cf. Vol. 23, p.256 where anomer separation was achieved at 0°C).[34] (1→6)- And (1→4)-α-gluco- and (2→1)-β-fructo-oligosaccharides of DP up to 25-35 were separated by hydrophilic interaction chromatography on a diol-bonded silica column, with post-column addition of aq. NaOH and pulsed-amperometric detection.[35] The use of HPAEC to examine the precise distribution of malto-oligosaccharide chains in glycogens from different origins was reported.[36] Gram quantities of malto-heptaose and -octaose were isolated from β- and γ-cyclodextrin hydrolysis products by h.p.l.c. on a primary amine column.[37] Significantly improved methodology for anion-exchange h.p.l.c. - thermospray m.s. analysis of oligosaccharides has been demonstrated for malto-oligosaccharides and plant cell-wall enzymatic hydrolysis products (see Chapter 22).[38] The products of ozonolysis of cellulose and kraft pulp, i.e. formaldehyde, glucose, arabinose, xylose, cello-oligosaccharides and probably oxidized forms of these, were detected by HPAEC.[39] β-Cyclodextrin and its *O*-hydroxypropyl-, di-*O*-methyl- and tri-*O*-methyl-derivatives were determined by size exclusion h.p.l.c. using 1-naphthol in the eluant, detection relying upon the enhanced fluorescence of the naphthol inclusion complexes.[40]

Neutral oligosaccharide-alditols (including linkage isomers) released from human meconium glycoproteins by alkaline borohydride treatment were separated by HPAEC. Two columns connected in series were used to provide sufficient separation of weakly retained neutral alditols, but acidic alditols required an additional sodium acetate gradient for elution.[41] The use of a porous graphitized carbon column (MeCN-H_2O-CF_3CO_2H eluant) for the separation of oligosaccharides and oligosaccharide-alditols released by enzymes (*N*-linked chains) or base-borohydride (*O*-linked chains) has been examined. While a complete separation of such oligomers from standard glycoproteins was not achieved, samples recovered from the eluant by evaporation were particularly suitable for m.s. analysis.[42]

Oligosaccharides (mostly DP 2-6) released by various enzymic digestions of hyaluronic acid were derivatized with 1-(4-methoxyphenyl)-3-methyl-5-pyrazolone (to give u.v.-absorbing derivatives of an uncharacterized structure) for reversed-phase h.p.l.c. analysis.[43] Oligosaccharides from the enzymic digestion of chondroitin sulfate and heparin were examined by ion-pair reversed-phase h.p.l.c. - electrospray m.s. analyses.[44]

Applications of micro-column (350 μm i.d.) reversed-phase h.p.l.c.-electrospray m.s. and m.s.-m.s. for the identification of glycoproteins, and of glycopeptides produced by enzymic hydrolysis, have been reported.[45] The collagen metabolites *O*-galactosyl- and Glc-(1→2)-Gal-*O*-hydroxylysine were determined in urine by extraction onto a strong-acid cation exchanger and reversed-phase h.p.l.c. analysis; the ratio of these components is a possible marker for human bone collagen breakdown.[46]

1.3.6 *Sugar acids.* – *N*-Acetyl- and *N*-glycoloyl-neuraminic acids released from glycoproteins by acid hydrolysis were determined by ion-exclusion h.p.l.c. on a strong cation exchange column with an acidic eluant, using *N*-acetylglycine as internal standard with u.v. detection.[47] Free *N*-acetylneuraminic acid in body fluids was determined by reversed-phase h.p.l.c. after fluorimetric derivatization with 1,2-diamino-4,5-methylenedioxybenzene.[48]

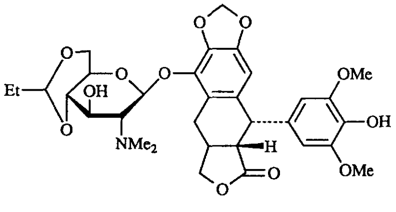
Benzodiazepine glucuronides in biological samples were determined by reversed-phase h.p.l.c. with further resolution of diastereomeric glucuronides on a β-cyclodextrin column.[49] Reversed-phase analysis and preparative isolation of the acyl and other glucuronides of desmethylindomethacin in urine have been reported,[50] as has the analysis of morphine 3- and 6-glucuronide in plasma on a diol-column.[51]. In the h.p.l.c. analysis of nicotine metabolites, including the *N*-glucuronides of cotinine and nicotine and the *O*-glucuronide of 3′-hydroxycotinine, on a C_{18}-silica column with $MeCN-H_2O$ as eluant, the less polar unglycosylated metabolites surprisingly eluted first, indicating that the separation was by normal phase chromatography.[52]

H.p.l.c. analyses of ascorbic acid have been reported as follows: a) in juice and biological samples on reversed-phase columns with variously u.v. or electrochemical detection;[53-56] b) simultaneously with sulfite in beer on an acid-form cation exchange resin;[57] and with its 2-sulphate in fish feed by an ion-pair reversed-phase method.[58] Reversed-phase h.p.l.c. analyses have also been reported for ascorbyl dipalmitate in cosmetic whitening powders,[59] and for 5,6-*O*-benzylidene-L-ascorbate diastereomers in biological fluids. The latter are prodrug forms of the antitumour substance benzaldehyde.[60]

1.3.7 *Inositol phosphates.* – Addition of urea prior to lyophilization of biological extracts containing [^{3}H]-labelled inositol phosphates has been found to prevent the formation of unidentified artifact peaks detected on strong anion-exchange h.p.l.c. analysis.[61] Di- to hexa-phosphates of *myo*-inositol were separated by anion-exchange h.p.l.c. and detected by use of a post-column iron(III) chloride-sulfosalicylic acid reagent system that relies upon decreased colour formation when the iron(III) ions are complexed by the phosphate esters.[62]

1.3.8 *Antibiotics.* – Reversed-phase h.p.l.c. analyses have been reported for the anti-arthritis drug auranofin [i.e.(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-S) (triethylphosphine) gold (I)] with post-column colorimetric detection,[63] the cytostatic podophyllotoxin derivatives etoposide and NK611 **4**,[64,65] the antileukemia agent elsamitruan **5**,[66] and a new erythromycin antibiotic EM523 (with branched-chain and *N*-ethyl-*N*-methylamino-sugar residues),[67] all in biological samples. The major components of the macrolide antibiotic tylosin, which vary both in their sugar constituents and in the macrocyclic lactone moiety, were determined by ion-pair reversed-phase h.p.l.c.[68]

Spectinomycin in pig, calf and chicken plasma was concentrated on a C_{18}-silica cartridge pretreated with sodium dioctylsulfosuccinate, derivatized with 2-naphthalenesulfonyl chloride and determined by h.p.l.c. on silica on a dual column, column switching system.[69]



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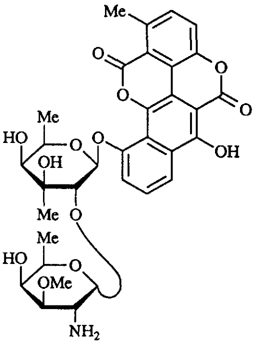

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1.3.9 *Nucleosides.* – Reversed-phase and ion-pair reversed phase h.p.l.c. analysis of nucleotides, nucleosides and bases in biological samples has been reviewed, with comparisons being made with high-performance capillary electrophoresis.[70,71] Specific analyses by reversed-phase h.p.l.c. were of the following in biological samples: adenosine A_1 antagonist *N*^{6}-cyclopentyladenosine using the *N*^{6}-cyclohexyl-analogue as internal standard;[72] 1-(β-D-arabinofuranosyl)-5-(1-propynyl)uracil;[73] 5′-deoxy-5-fluorouridine, 2′-deoxy-5-fluorourine and 5-fluorouridine after solid phase extraction onto a copper(II) strong cation exchange silica;[74] and deoxynucleosides released by enzymic hydrolysis of fish-tissue DNA, with attention being given to minimizing the loss of labile modified residues such as methylated deoxycytidine, and using either u.v. or thermospray m.s. detection.[75] The degradation of 2′-deoxyuridine in aqueous solution at pH values in the 1-12 range and different temperatures was studied by reversed-phase h.p.l.c. on a system capable of separating its anomers, ring form isomers and free base.[76] Single fluorescent components of unknown structure were produced from each of guanine and its nucleosides and nucleotides on reaction with phenylglyoxal, and determined by reversed-phase h.p.l.c.[77]. The cytotoxic AZT metabolite 3′-amino-3′-deoxythymidine was determined in plasma by ion-pair reversed-phase h.p.l.c.[78] *S*-Adenosyl-L-methionine (SAM) and its metabolites, i.e. *S*-adenosylhomocysteine, decarboxylated SAM, methylthioadenosine, adenosine and adenine, in liver and cell cultures, were determined by separation on a reversed-phase column, and rechromatography of selected fractions on a strong cation exchange silica column.[79]

1.4 Column Chromatography.

- Neutral and anionic sugar species were separated by a combination of ion exclusion and gel permeation processes on a strong cation exchange resin. Thus glucose-6-phosphate was eluted near the void volume of a Na^+- or H^+-form resin with water, whereas glucose eluted near the total column volume. Similarly 2-acetamido-2-deoxy-D-mannose, which forms an anionic borate complex, was eluted near the void volume of a Na^+-form resin with borate buffer (pH 7.8), whereas 2-acetamido-2-deoxy-D-glucose, which remains uncomplexed, was eluted later.[80] The same separation of acetamido-sugars was also achieved on Sephadex G-15 with a borate eluant. For preparative purposes, the 2-acetamido-2-deoxy-D-mannose complex could be desalted by re-elution down a Sephadex column with water, making use of the strong affinity of Sephadex for borate. Unionized boric acid in the sample can then be removed by evaporation with methanol.[81]

A new method for the separation and isolation of saccharides has been demonstrated by frontal analysis, and proposed for use with complex matrices. Mono- to tetra-saccharide alditols, hexuronic acids and amino-sugars (30-160 μmol/g) were strongly bound to a strong cation exchange resin in the Eu^{3+}-form (10-12 μm polystyrene beads in an h.p.l.c. column) using a 0.1 M aqueous NaOH eluant. Monosaccharides and especially alditols (0.3 - 7 μmol/g) were selectively retained on a Fe^{3+}-form resin. The metal ions are apparently not eluted by the alkaline eluant. The solutes could be rapidly recovered with an acidic eluant.[82]

An excellent separation of twelve mono-, di- and tri-phosphorylated purine and pyrimidine nucleosides was achieved in 50 min on a hydrophilic strong anion exchange resin in the formate form eluted with a volatile buffer (HCO_2H - HCO_2NH_4). It was applied to the purification of [U-^{14}C]adenosine-5′-diphosphate and other radiolabelled nucleotides and their analogues.[83]

2 Electrophoresis

A relatively new technique, pseudo-electrochromatography (PEC), has been coupled to electrospray m.s. for detection of aromatic glucuronides. In PEC, a high-voltage (±2-8 kV) is applied along the length of a microbore reversed-phase column. The elution of charged compounds can be accelerated or retarded depending upon the direction of the current.[84]

Capillary zone electrophoresis (c.z.e.) has been applied to the separation and determination of malto-oligosaccharides up to DP 30 after derivatization with 8-aminonaphthalene-1,3,6-trisulfonic acid and sodium cyanoborohydride, both in free solution and gel-filled capillaries,[85] D-galactonic and D-gluconic acids using indirect photometric detection with sorbic acid as electrolyte anion and chromophore,[86] ascorbic acid in fruits[87] and in biological fluids and fruit beverages using isoascorbic acid as internal standard,[88] and the anomers and ring size isomers of 2′-deoxyuridine and thymidine to aid in studies of their acidic degradation.[89]

Neutral sugars can be analysed by c.z.e. as their borate complexes through use of borate-containing electrolytes. In this way, oligogalactosyl sucroses in the raffinose family,[90] picomole quantities of constituent monosaccharides of glycoproteins released by acid hydrolysis and conversion to pyridylamino-derivatives,[91] flavonoids and their glycosides in sugar cane,[92] flavonoid 3-*O*-glycosides with the same aglycon but differing sugar residues,[93] and purine bases and nucleosides in human serum,[94] have been analysed.

C.z.e. at pH 12 with pulsed amperometric detection permitted glucose in blood to be determined at 10^{-7}M levels, and the separation of 2-amino-2-deoxy-D-glucose, its 6-phosphate and 6-sulfate, and 2-amino-2-deoxy-D-gluconic acid.[95]

Addition of a surfactant to form micelles, converts c.z.e. to micellar electrokinetic capillary chromatography (m.e.c.c.). Both c.z.e. and m.e.c.c. have been used in the detection of morphine 3-glucuronide in urine,[96] to evaluate the effects of adding various complex-forming agents to a highly alkaline electrolyte on the separation of 4-aminophenyl, 4-nitrophenyl and phenyl glycosides, their 1- and 5-thio-analogues, and six nucleosides (boric acid resulted in altered migration rates),[97] and to separate flavonoids and their 7-*O*-glycosides with or without borate in the buffer.[98]

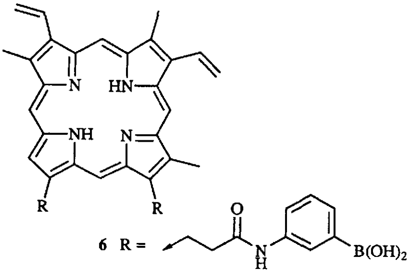
M.e.c.c. has been used for analysis of nine flavonol glycosides from *Tilia* sp.,[99] flavonoid glycosides varying in the degree of glycosylation and with or without ester moieties in the sugar part,[100] unsaturated sulfated disaccharides produced by enzymic methods from glycosaminoglycans,[101] quinoxaline derivatives formed by condensation of dicarbonyl sugars D-*arabino* - and D-*lyxo*-2-hexosulose, 7-deoxy-L-*galacto*-2-heptosulose and 5-hydroxy-2,3-dioxohexanal with *o*-phenylenediamine (applied to fermentation products and Maillard reaction products),[102] and nucleosides and nucleotides with a preliminary evaluation of the problems associated with using collected fractions for FAB-m.s.[103] Cardiac glycosides can be analysed by m.e.c.c. if cyclodextrin, urea or sodium cholate is added to alter the equilibrium between the micellar and aqueous phase, otherwise these hydrophobic molecules migrate with the micellar front. Separations were achieved that cannot be attained by reversed-phase h.p.l.c.[104]

The separation of polyols (hexoses, hexitols and disaccharides) as their borate complexes by isotachophoresis has been investigated,[105] although the model for the theoretical analysis of the separations has been challenged.[106,107] Capillary isotachophoresis has been used for the determination of ascorbic acid in biological systems.[108]

3 Other Analytical Methods

Amperometric determinations of glucose on an easily constructed graphite electrode containing ferrocene-mediated glucose oxidase,[109] and of glucose and xylose on a graphite electrode containing *Gluconobacter oxydans* aldose dehydrogenase bound to a PQQ-dependent membrane,[110] have been reported.

Deaggregation of the porphyrin-diboronic acid **6** occurred when it complexed with a sugar, particularly D-fructose, due to increased hydrophilicity. This resulted in a marked increase in absorbance at 400 nm or fluorescence intensity.[111] Complexation of the diphenylboronic acid derivative **7** with mono- and di-saccharides was studied by c.d., resulting in a method for predicting the absolute configuration of saccharides.[112]



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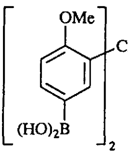

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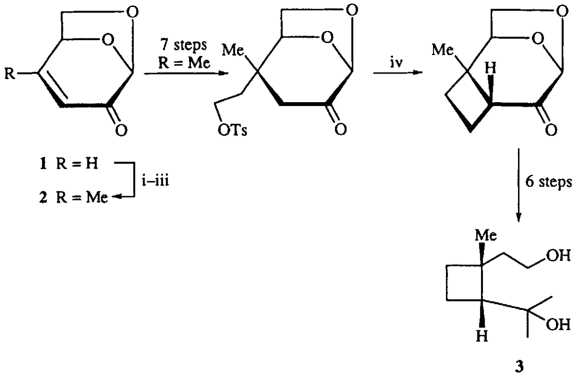
24

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

A review (207 refs.) has appeared on the application of enantiomerically pure carbohydrate-derived building blocks in natural product synthesis.[1]

1 Carbocyclic Compounds

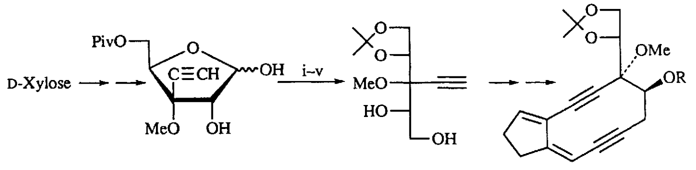
Levoglucosenone **1** has provided a starting point for the synthesis of cyclobutane **3** which constitutes a formal total synthesis of the boll weevil pheromone, (+)-grandisol.[2] Methylation of **1** to give **2** was achieved as shown in Scheme 1 and the cyclobutane unit was established *via* intramolecular enolate alkylation.



Reagents: i, PhSH, Et_3N; ii, NCS; iii, Me_2CuLi; iv, NaH, DMSO

Scheme 1

The novel 10-membered ring dienediynes **6**, which are related to neocarzinostatin, have been synthesized (see also Vol. 26, p.302) starting from D-xylose, *via* furanose **4** and the acetylenic diol **5** (Scheme 2).[3] Interestingly, direct reduction of **4** using sodium borohydride failed because of formation of a stable cyclic boronic ester $[H_2B(OR)_2^-]$. This problem was overcome by silylation to give a mixture of 1- and 2-*O*-Tbdms ethers which then underwent rapid equilibration during the reduction step.

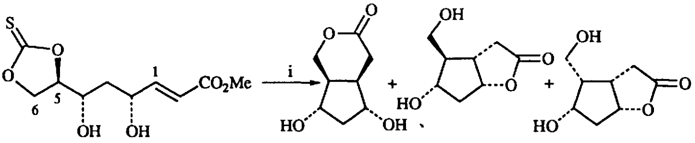


4 **5** **6** R = H or Ac

Reagents: i, TbdmsOTf, 2, 6-lutidine; ii, $NaBH_4$; iii, NaOMe, MeOH; iv, Me_2CO, $CuSO_4$; v, Bu_4NF

Scheme 2

Free radical cyclization reactions have seen further developments this year. A mixture of cyclopentanes **8**-**10** (precursors of isoprostaglandins) have been obtained *via* fragmentation of thionocarbonate **7** derived from D-glucose (sugar numbering shown) (Scheme 3).[4]



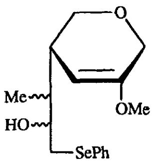
7 **8** (23%) **9** (20%) **10** (57%)

Reagents: i, Bu_3SnH, AIBN, PhH, heat

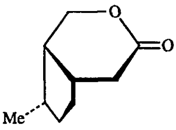
Scheme 3

(+)-Boschnia lactone **12** and (+)-isoiridomyrmecin **13** (enantiomers of naturally-occurring monoterpene lactones) have been obtained from L-arabinose with a key step being tri-*n*-butyltin hydride-induced cyclization of selenides **11** to establish the cyclopentanyl moieties.[5]

A series of complex polyhydroxylated cyclopentane amino acids **15**-**19** have been prepared by Fleet's group as analogues of the potent trehalase inhibitor, trehazolin **14**.[6] A central feature of this chemistry was the use of either an azide- or fluoride-mediated intramolecular aldol reaction of the carbohydrate-derived lactones carrying a 2-azido (or 2-iodo) substituent as illustrated in Scheme 4.



11 (from L-arabinose)



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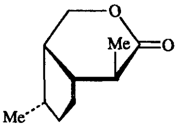

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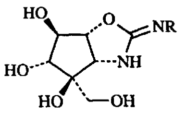
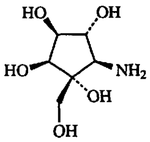


14 R = α-glucopyranosyl



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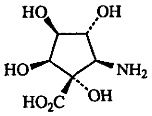

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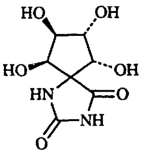

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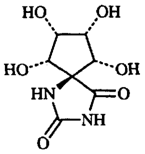

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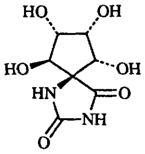

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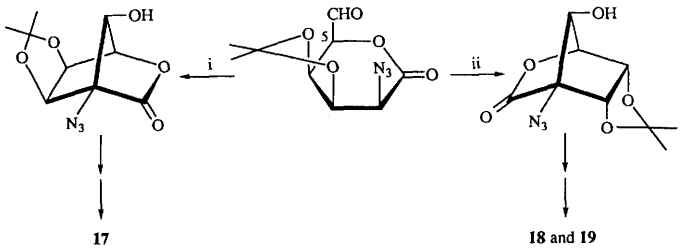
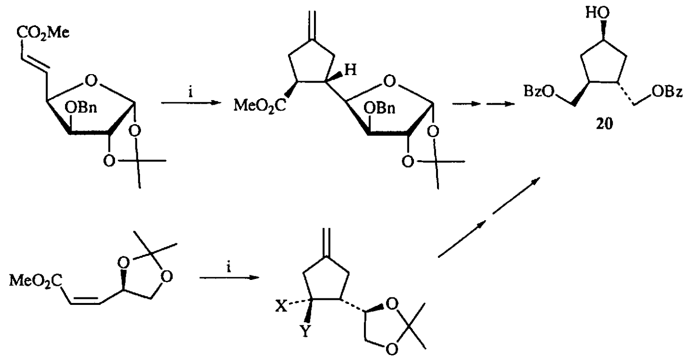


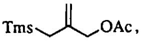
Reagents: i, KF, MeCN, 18-Cr-6; ii, NaN_3, MeCN, 18-Cr-6 (induces epimerization at C-5)

Scheme 4

Two stereospecific approaches to the synthetically useful cyclopentanol **20** have been developed, based on a palladium-mediated [3+2] cycloaddition of trimethylenemethane.[7] In the case of cycloadducts **21a/b**, **21a** is the kinetically favoured product, but equilibration (using NaOMe) to give predominantly **21b** is straightforward (Scheme 5).

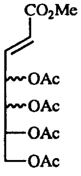


21a (X = CO_2Me, Y = H)
21b (X = H, Y = CO_2Me)

Reagents: i,  OAc, $Pd(OAc)_2$, $P(OPr^i)_3$

Scheme 5

Diels-Alder cycloadditions of cyclopentadiene to a variety of carbohydrate-based acrylates, such as **22** and **23**, provide, after oxidative degradation of the carbohydrate portion, access to a series of enantiomerically pure bicyclo[2.2.1]hept-2-enes exemplified by **24-26**.[8]



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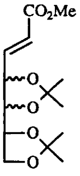

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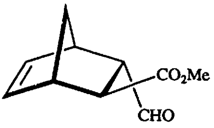
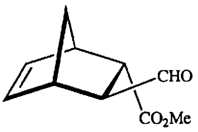


24



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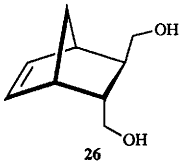
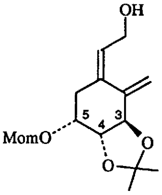


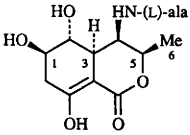
26

A series of the above dienophiles corresponding to D-*ribo*, D-*xylo*, D-*lyxo* and D-*arabino* and incorporating an (E)-acrylate unit were evaluated in terms of the *exo*/*endo* and *re*/*si* selectivity available. In the *arabino* series, the L-isomer was also prepared, as were the corresponding D- and L-series (Z)-dieneophiles.

A synthesis of the A-ring unit **27** (sugar numbering shown) of 1α, 2β, 25-trihydroxy vitamin D_3 has been achieved using D-mannitol as the starting point with the key ring-forming step being a Pd(0)-mediated Heck-type reaction.[9] D-Glucose has been utilized in a synthesis (29 steps) of (+)-actinobolin **28** (sugar numbering shown).[10] Tri-*O*-acetyl-D-glucal has provided a direct entry to dienes **29** and **30**, and the Diels-Alder reactivity of these electron-rich 4π-components towards a variety of dienophiles and heterodienophiles was examined. The diastereofacial selectivity associated with **29** and **30** was determined and compared directly with that available from the corresponding carboyclic dienes.[11]



27



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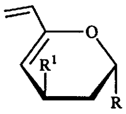
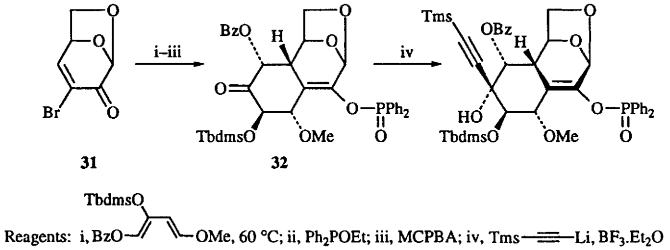


29 R^1 = OMe, R = H
30 R^1 = H, R = OMe

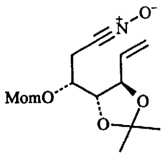
Bromo-levoglucosenone **31** provides a functionalized dienophile which undergoes cycloaddition to give, after straightforward manipulation, ketone **32**. The hindered ketone unit of **32** underwent nucleophilic attack using an alkynylborate complex in a synthetic approach directed towards tetrodotoxin (Scheme 6). Ketone **32** was found to be extremely sensitive and the precise nature of the alkynyl nucleophile was crucial to the success of the key addition step.[12]



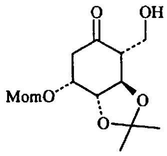
Reagents: i, BzO–C(OTbdms)=CH–CH=CH–OMe, 60 °C; ii, Ph_2POEt; iii, MCPBA; iv, Tms—≡—Li, $BF_3.Et_2O$

Scheme 6

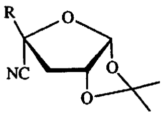
An intramolecular cycloaddition involving nitrile oxide **33** (generated *in situ*) has been utilized in a synthesis of **34**, an intermediate in an approach to the synthesis of the A-ring unit of 1α, 2β, 25-trihydroxy vitamin D_3; D-mannitol provided the starting point for the synthesis of **33**.[13] 2,3:5,6-Di-*O*-isopropylidene-D-glucose provides access to enantiomerically pure 4-cyanofuranoses **35**, (R = alkyl and MeCH(OH) *via* alkylation of **35**, R = H). 9-Methyl anthracyclinone **36** (as a 4:1 mixture of epimers at C(7)) was prepared from **35**, R = Me).[14] D-Glucose provided the three stereocentres (sugar numbering shown) required for the synthesis of **37**, in an approach to (+)-pancratistatin, with the cyclization step being effected by the quinone methide approach (*J. Am. Chem. Soc.*, 1989, **111**, 1136).[15]



33



34



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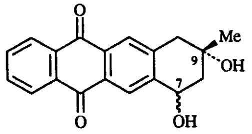

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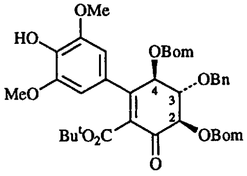
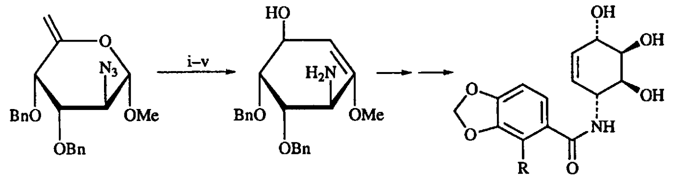


37 Bom = benzyloxymethyl

Ferrier carbocyclization of **38** (also prepared from D-glucose) has been utilized in the synthesis of **39** and **40** (Scheme 7), molecules which can be viewed as 'seco' analogues of the Amaryllidaceae alkaloids, lycorocidine and narciclasine.[16]



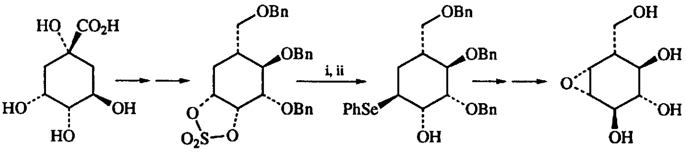
38

39 R = H
40 R = OH

Reagents: i, $Hg(OCOCF_3)_2$, H_2O; ii, MsCl, Py; iii, $NaBH_4$, $CeCl_3$; iv, Ph_3P, DEAD, $PhCO_2H$; v, $LiAlH_4$

Scheme 7

Shing has described the synthesis of the β-glucosidase inhibitor, cyclophellitol **42** (together with the corresponding (1R, 6S)-, (1R, 2S, 6S) and (2S)-isomers), starting from (-)-quinic acid with regiospecific ring opening of cyclic sulfate **41** using selenophenate anion being a key step (Scheme 8).[17]



41

42

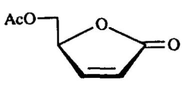
Reagents: i, $(PhSe)_2$, $NaBH_4$; ii, H_3O^+

Scheme 8

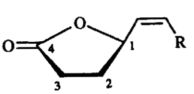
2 γ and δ-Lactones

D-Glucose provides access to the useful and enantiomerically pure butenolide building block **43**,[18] and this year has also seen further advances in the synthesis of γ-lactone natural products from sugars. 2,3-*O*-Isopropylidene-D-ribose forms the basis of the lactone rings of **44** and **45**, sex pheromones of the Japanese beetle and the cupreus chafer beetle respectively.[19] The carbohydrate carbon atoms are indicated and a key step involved alkyne reduction (using Lipschutz's hydridohalocuprate procedure: Bu_3SnH; TMSCl; LiCl.CuI) to establish the required (Z)-alkene geometry for **44** and **45**.

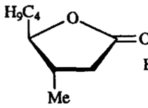
The same group have also described the synthesis of (+)-*trans*-whisky lactone **46**, (-)-*cis*-whisky lactone **47**, (+)-cognac lactone **48**, and the male corn borer pheromone, (+)-eldanolide **49**, all starting from levoglucosenone (see Vol. 24, p.305).[20] (+)-Roccellaric acid **50** (sugar numbering shown) has been synthesized starting from 2,3:5,6-di-*O*-isopropylidene-D-glucose.[21]



43



44 R = n-C_8H_{17}
45 R = n-C_6H_{13}



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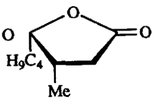

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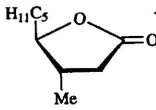

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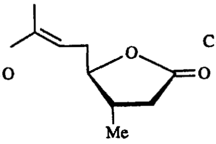

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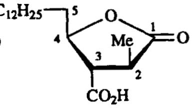
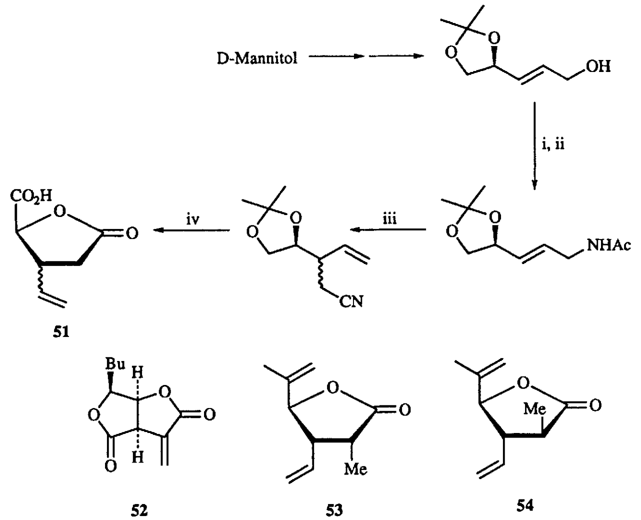


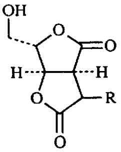
50

An imino-Claisen rearrangement allows access to lactone **51** (as a 1:1 mixture of epimers) which, following isomer separation, was converted to (+)-canadensolide **52**, (-)-santolinolide A **53** and (+)-santolinolide B **54** (Scheme 9).[22] Lee *et al* have described the synthesis of additional rigid bicyclic analogues of diacylglycerol (see Vol. 26, p.307). Bislactones **55** and **56** were obtained from L-arabinose[23] and the positional isomers **57** and **58** were synthesized from D-glucose.[24] Of these, **58** was found to inhibit the binding of phorbol ester to protein kinase C.



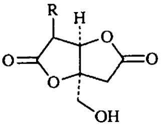
Reagents: i, DEAD, PPh_3, phthalimide, then H_2NNH_2; ii, Ac_2O, Pr^i_2NEt; iii, PPh_3, CCl_4; iv; H_3O^+

Scheme 9



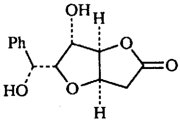
55 R = ------$C_{11}H_{23}$

56 R = ▬$C_{11}H_{23}$

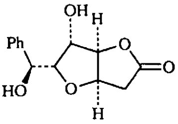


57 R = ------$C_{12}H_{25}$

58 R = ▬$C_{12}H_{25}$



59



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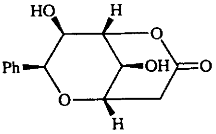

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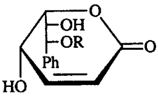
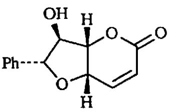
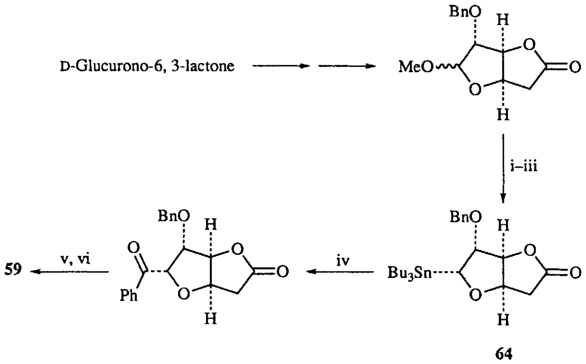


62a R = H
62b R = Ac



63

The synthesis of (+)-goniofufurone **59**, its 8-*epi* isomer **60** and the structurally related δ-lactones (+)-goniopypyrone **61**, (+)-goniotriol **62a**, the 8-acetyl variant **62b** and (+)-altholactone **63** have, as last year, been popular synthetic targets. Full details of Murphy's synthesis of **59** (from D-glucose and utilising an intramolecular Wittig olefination as a key step) have appeared.[25] Falck has described a synthesis of **59** starting from D-glucurono-6,3-lactone,[26] the key feature of this chemistry being introduction of the phenyl ketone unit *via* palladium-mediated acylation of an "anomeric" stannane **64**, a reaction that proceeds with retention of configuration (Scheme 10).

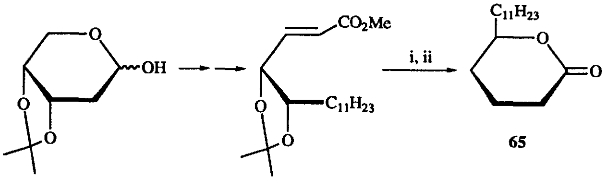


Reagents: i, H_3O^+; ii, Ph_3P, CCl_4; iii, $Bu_3SnSiMe_3$, Bu_4NF, DMF; iv, PhCOCl, $(PPh_3)_2PdCl_2$, CuCN, PhMe, 95 °C, 18 h, then DCC, DMAP (to ensure lactonization of open hydroxy acid); v, $LiAlH(OBu^t)_3$; vi, H_2, Pd/C

Scheme 10

Both **59**[27] and **60**[28] have been prepared efficiently from 2,3:5,6-di-*O*-isopropylidene-D-glucose using a Wittig olefination/conjugate addition/lactonisation (reminiscent of the strategy described last year by Shing; Vol. 26, pp.306-307) to construct the bicyclic ring system.

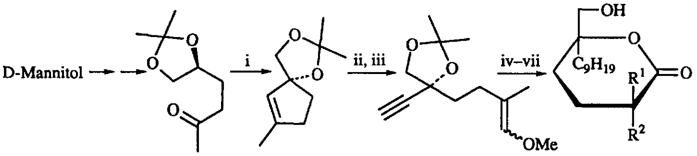
The synthesis of the δ-lactone, (+)-goniopypyrone **61**, has been reported independently by Shing[29] and Honda[30], starting from D-*glycero*-D-*gulo*-heptono-γ-lactone and D-mannitol respectively. The Japanese group also applied their chemistry to the synthesis of **62a/b** and **63**. Reductive elimination of an acetonide has been exploited in a synthesis of γ-lactone **65**, a pheromone of the oriental hornet *Vespa orientalis* (Scheme 11).[31]



Reagents: i, Mg, MeOH; ii, CF_3CO_2H

Scheme 11

(-)-Malynogolide **66** has been prepared starting from D-mannitol *via* an ingenious route that utilises alkylidene carbene reactivity at three separate stages (Scheme 12).[32] This route suffers from lack of stereocontrol in that malynogolide **66** is obtained, together with its C-3 epimer **67**.



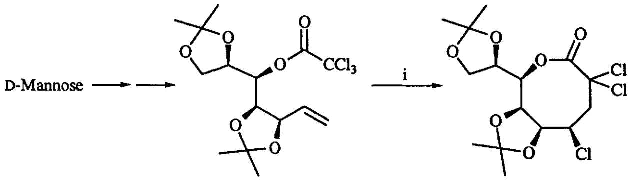
66 $R^1 = H, R^2 = Me$
67 $R^1 = Me, R^2 = H$

Reagents: i, $(MeO)_2P(O)CHN_2$, $KOBu^t$; ii, OsO_4,NMMO, then $NaIO_4$; iii, $(MeO)_2P(O)CHN_2$ (5 equiv.), K_2CO_3 (5 equiv.), MeOH; iv, BuLi, $C_7H_{15}Br$; v, $HClO_4$, MeOH, then H_2, PtO_2; vi, Ac_2O, Py, then CrO_3, H_2SO_4; vii, KOH, H_2O, then H_3O^+

Scheme 12

3 Macrolides, Macrocyclic Lactams and Their Constituent Segments.

Copper(I)-mediated cyclization of 1,2-dideoxyhept-1-enitol 5-trichloroacetate proceeds in an *endo* sense and *via* chlorine atom transfer to give 8- and 9-membered ring lactones.[33] An illustration based on the D-mannose-derived substrate **68** is shown in Scheme 13.



68

Reagents: i, CubpyCl (30 mol %), 

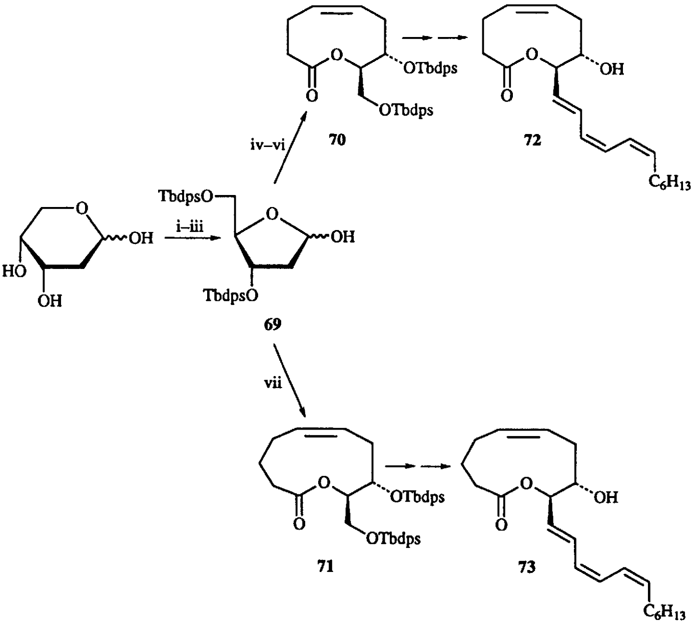
Scheme 13

A carbohydrate-based synthetic approach has provided unambiguous evidence for the structure of ascidiatrienolide A **73** (Scheme 14). When first isolated (in 1989), this macrocyclic lactone was originally assigned structure **72** containing a 9-membered ring. Holmes has used key intermediate **69** to prepare both of the macrocyclic components **70** and **71** which have been carried through to **72** and **73** respectively.[34]

D-Arabinose provides the backbone of the highly functionalized acyclic unit **74** (sugar carbons are numbered) which has been used by Kende in the first synthesis (34 steps) of (-)-lankacidin C **75**, an anti-tumour macrolide antibiotic.[35]

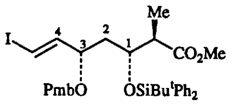
Thioacetal **79**, corresponding to the C(11)-C(16) portion of the polyene antibiotic pentamycin, has been synthesized from D-glucose *via* furanoside **76**. A key step was the use of fructose 1,6-diphosphate aldolase to couple aldehyde **77** to dihydroxyacetone phosphate to give ketose **78** (Scheme 15). A synthesis of **78** from D-mannitol has also been described.[36]

The pursuit of the synthesis of FK506 and rapamycin continues to draw contributions from the carbohydrate area. The C(21)-C(34) fragment **82** of FK506 has been prepared as shown in Scheme 16.[37] Use of a tantalum-alkyne complex to couple aldehyde **80** with alkyne **81** is an especially interesting step. The requisite low valent tantalum species is generated *in situ* and the Ta-alkyne complex shows reasonable levels of Cram selectivity towards aldehydes. Alkyne **81** was, in turn, prepared from D-quinic acid.



Reagents: i, HCl, MeOH; ii, Ph$_2$Bu^{t}SiCl (TbdpsCl), Py; iii, BCl$_3$.Me$_2$S; iv, $\diagup\!\!\!=\!\diagdown$MgBr; PhSe$\diagdown\!\diagup$(OEt)OEt, H$^+$; vi, NaIO$_4$, then DBU, PhMe, heat; vii, Ph$_3$P=CH(CH$_2$)$_3$CO$_2$$^-$, then 2, 4, 6-trichlorobenzoyl chloride, Et$_3$N, DMAP

Scheme 14



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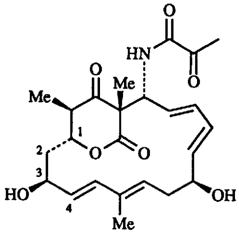
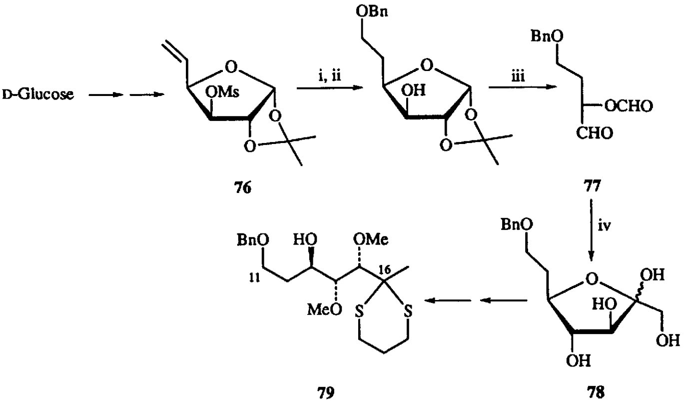
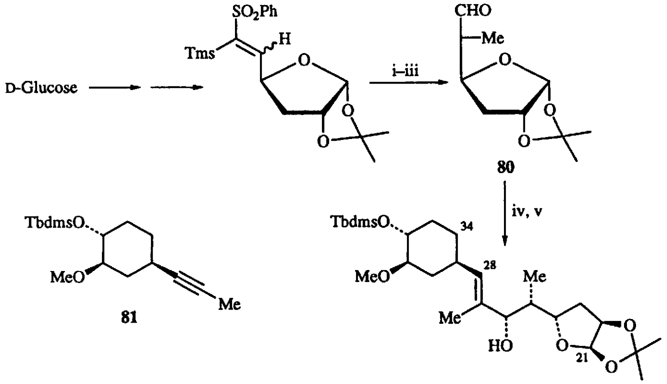


75



Reagents: i, $BH_3.SMe_2$, then H_2O_2, ^-OH; ii, $BnOC(NH)CCl_3$, CF_3SO_3H, then NaOH, EtOH; iii, AcOH, then $NaIO_4$; iv, FDP-aldolase, $\mathrm{HO}\smile\overset{O}{\parallel}\smile\mathrm{OPO_3H_2}$, then acid phosphatase

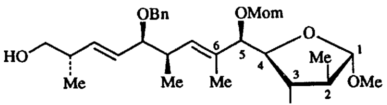
Scheme 15



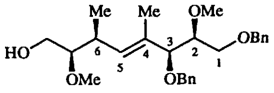
Reagents: i, MeLi, then HCHO; ii, LDA, then H_2, Lindlar's catalyst; iii, O_3, then Me_2S; iv, $TaCl_5$, Zn, pyridine, **81**; v, NaOH

Scheme 16

The advanced rapamycin intermediate **83** (sugar numbering is shown) has been synthesized in a multistep sequence from D-glucose[38], and this sugar also provides the basis of the synthesis of **84** (sugar numbering shown) which is the C(11)-C(18) unit of the macrocyclic lactam, herbimycin.[39]

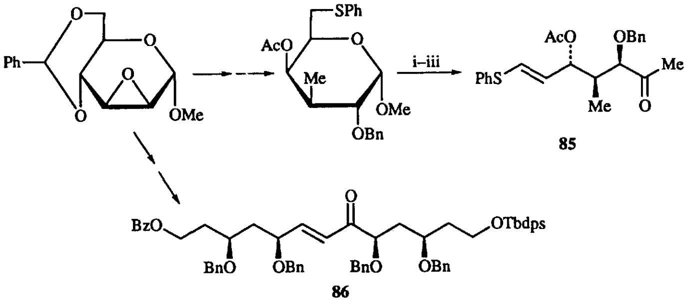


83



84

Finally, reductive cleavage of an α-chloroether provides access to vinyl sulfide **85** which corresponds to the C(9)-C(14) fragment of the macrocyclic lactams trienomycin and mycostrienin (Scheme 17). The same group have used related reductive cleavage methodology to generate the C(1)-C(13) fragment **86** of amphoteronolide B.[40]

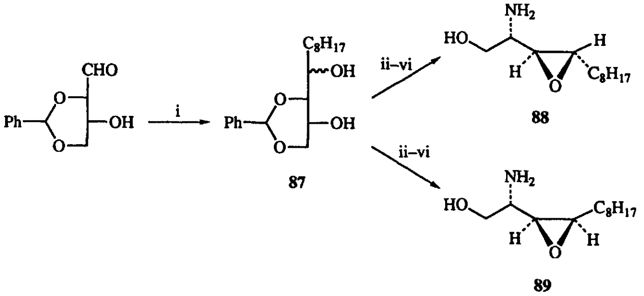


Reagents: i, N-Chlorosuccinimide; ii, Zn/Ag–graphite; iii, MeTi(OPr^i)$_3$, then PCC

Scheme 17

4 Other Oxygen Heterocycles, Including Polyether Ionophores

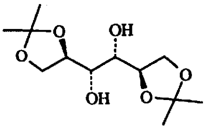
Epoxides **88** and **89** related to phytosphingosine (which is a potent inhibitor of sphingosine delivery) have been synthesized from D-threose (Scheme 18).[41] Grignard addition to give **87** is non-selective and the resulting two isomers were separated and carried through to **88** and **89**, a process that involved selective mesylation of the axial hydroxyl function. In addition, epoxide formation (*step v*, Scheme 18) was accompanied by formation of the corresponding tetrahydrofuran as a by-product.



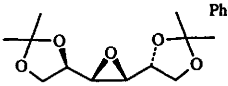
Reagents: i, $C_8H_{17}MgBr$, separate isomers; ii, MsCl, Py; iii, NaN_3, DMF; iv, MsCl, Py, then H_3O^+; v, NaH; vi, H_2S, H_2O, Py.

Scheme 18

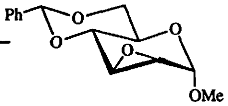
Diols may be converted to epoxides in one step: treatment of **90** with sodium hydride (2 equivalents) followed by tosyl chloride gave epoxide **91** and using the same procedure, epoxides **92** and **93** were also prepared.[42] Full details have appeared of the synthesis of the two epimeric 3-hydroxymuscarines **94** and **95**, starting from L-rhamnose.[43]



90



91



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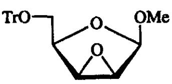

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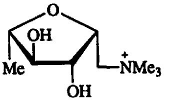
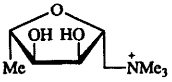
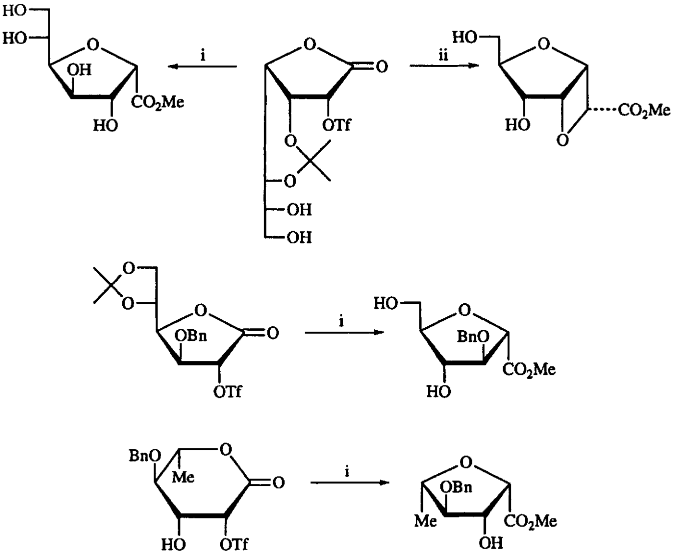


94 (as tosylate salt)



95 (as tosylate salt)

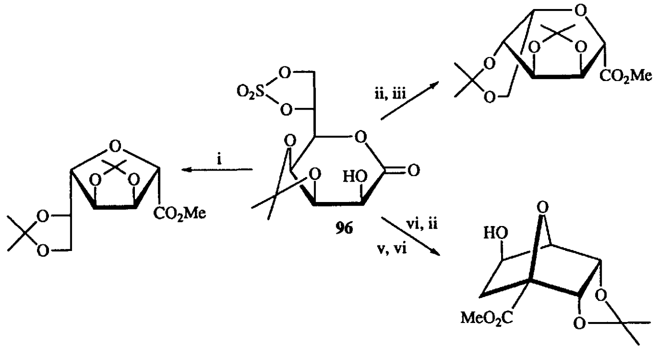
Aldonolactone 2-*O*-triflates play a key role in these sequences and Fleet has reported further developments of the chemistry of this and other, related good leaving groups. Scheme 19 illustrates the synthetic utility of 2-*O*-triflates of 1,4- and 1,5-lactones under both acidic and basic conditions.[44]



Reagents: i, HCl, MeOH; ii, K_2CO_3, MeOH

Scheme 19

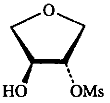
Cyclic sulfates, a comparatively new class of reactive leaving group, are also valuable in the manipulation of carbohydrates. Fleet has exemplified this potential with cyclic sulfate **96** which provides an entry into a series of oxygen-based heterocycles (Scheme 20).[45]



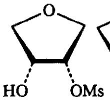
Reagents: i, K_2CO_3, MeOH, then Me_2CO, H^+; ii, NaH, DMF; iii, MeOH, then Me_2CO, H^+; iv, MsCl, Py; v, H_3O^+; vi, K_2CO_3, MeOH

Scheme 20

The novel tetrahydrofuran building blocks **97** and **98** have been prepared from L-ascorbic acid and D-isoascorbic acid respectively,[46] and 1,4:3,6-dianhydro-D-mannitol provides access to the ring and/or side chain-functionalized tetrahydrofurans **99**-**101**.[47] All of these units have obvious potential in synthesis and the value of dihydrofuran **100** has been illustrated by its conversion (in 6 steps) to (-)-*endo*-brevicomin.[47] The synthesis of (-)-acetomycin **102** (starting from D-glucose) was reported in the last volume (Vol. 26, p.306) and modification of this route has allowed the synthesis of analogues **103**.[48]



97



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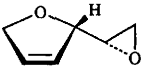
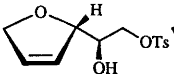
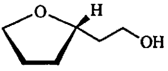


99



100



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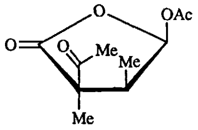
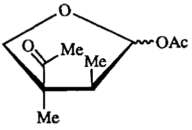
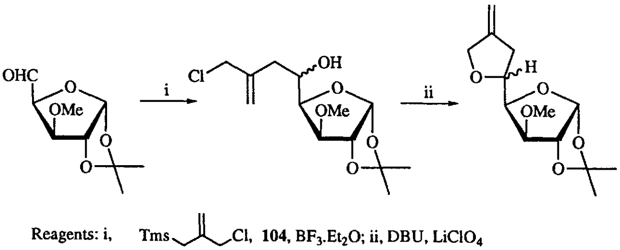


102



103

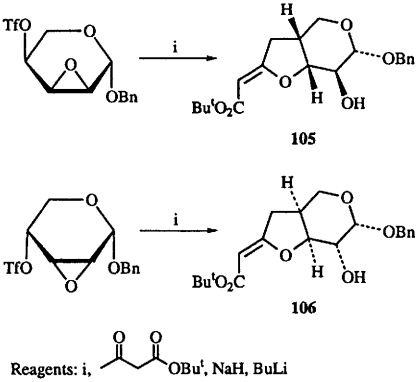
2-(Chloromethyl)-3-(trimethylsilyl)prop-1-ene **104** is a useful unit for the stepwise synthesis of methylene tetrahydrofurans and an application of this methodology to a carbohydrate substrate has been reported (Scheme 21).[49]



Reagents: i, Tms Cl, 104, $BF_3.Et_2O$; ii, DBU, $LiClO_4$

Scheme 21

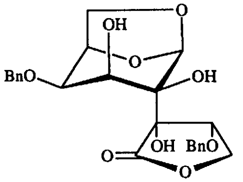
Furanose annelation, as illustrated in Scheme 22, provides efficient access to chiral furanoids such as **105** and **106**. A variety of stabilised carbon nucleophiles has been employed, including dianions derived from β-diketones and other β-ketoesters, and it is noteworthy that nucleophilic displacement of triflate is faster than epoxide ring opening.[50]



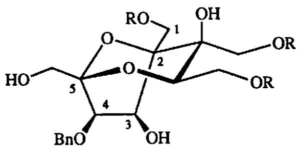
Reagents: i, OBu^t, NaH, BuLi

Scheme 22

The squalestatin (or zaragozic acid) class of squalene synthase inhibitors presents an interesting challenge to the synthetic chemist and studies directed towards this goal have been reported. 1,6-Anhydro-D-galactose has formed the basis of the synthesis of **107** and the more advanced intermediate **108** (sugar numbering is shown).[51]

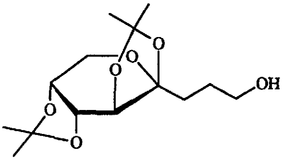


107



108 R = $COBu^t$

The D-fructose derivative **109** has been converted to (R)-1,6-dioxaspiro[4.5]decane **110** using standard deoxygenation procedures,[52] and a new synthesis of δ-multistriatin **111** has been achieved from D-glucose.[53]



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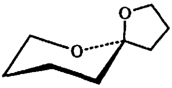
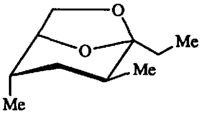
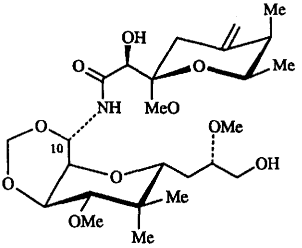


110

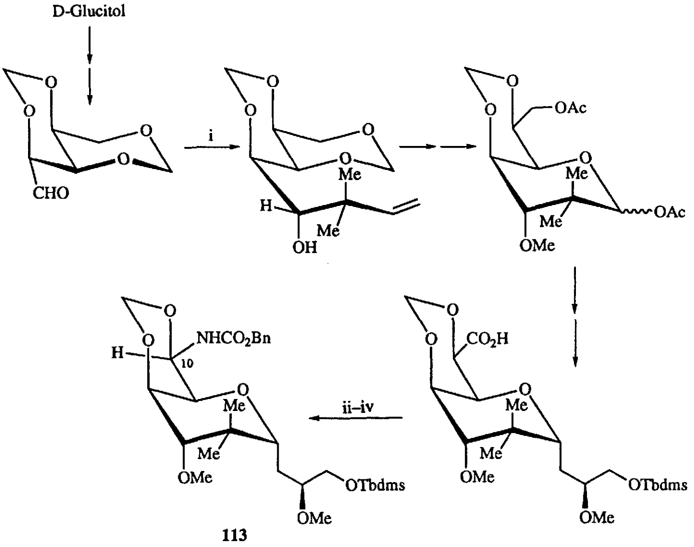


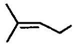
111

The trioxadecalin core **113** of mycalamide B **112** (which is structurally related to pederin) has been synthesized from D-mannitol (by Roush[54a]) and D-sorbitol (by Hoffmann[54b]). Hoffmann's approach is outlined in Scheme 23 (*see next page*), but both pieces of work incorporate interesting points. The unusual (and unstable) C(10) aminal unit of **112** has the opposite stereochemistry to that required by the natural product, but prior work has shown that equilibration at this centre is feasible. Also, both groups found that **112** exists as the ring-flipped *cis*-decalin conformer in contrast to the conformational preference expressed by mycalamide B itself.



112

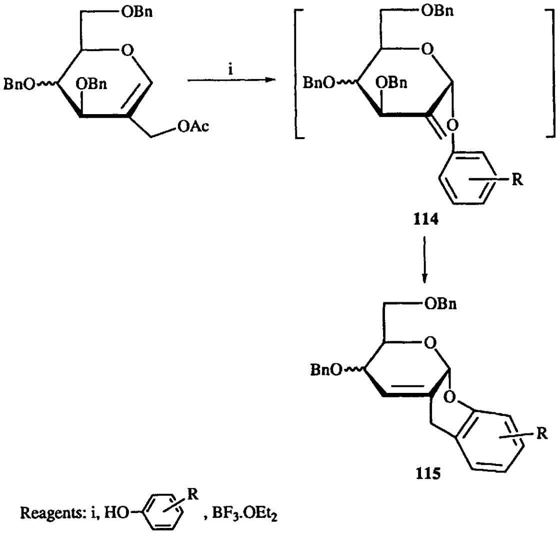


Reagents: i,  SnBu$_3$, TiCl$_4$ >95% d.e.; ii, (PhO)$_2$PON$_3$; iii, NEt$_3$, PhH, 80 °C; iv, BnOH

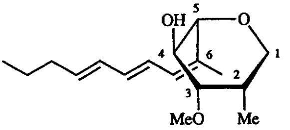
Scheme 23

A series of pyrano[2,3-*b*][1]-benzopyrans **115** has been prepared under Lewis acid mediated reaction conditions, *via* glycoside **114** suggested as a key intermediate (Scheme 24).[55]

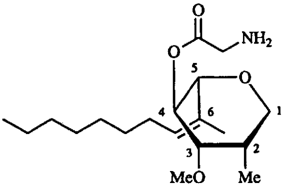
Two groups have reported success in the synthesis of the restriction class of polyene antibiotics starting from L-sugars. Restrictinol **116** and analogue **117** (sugar numbering is shown in both cases) were prepared from L-glucose,[56] and restricticin **118** (also known as scopularin) was obtained from L-mannose.[57] In both studies the carbohydrate unit forms the heterocyclic core with the polyene side chain being introduced by Wittig methodology.



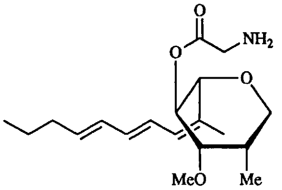
Scheme 24



116

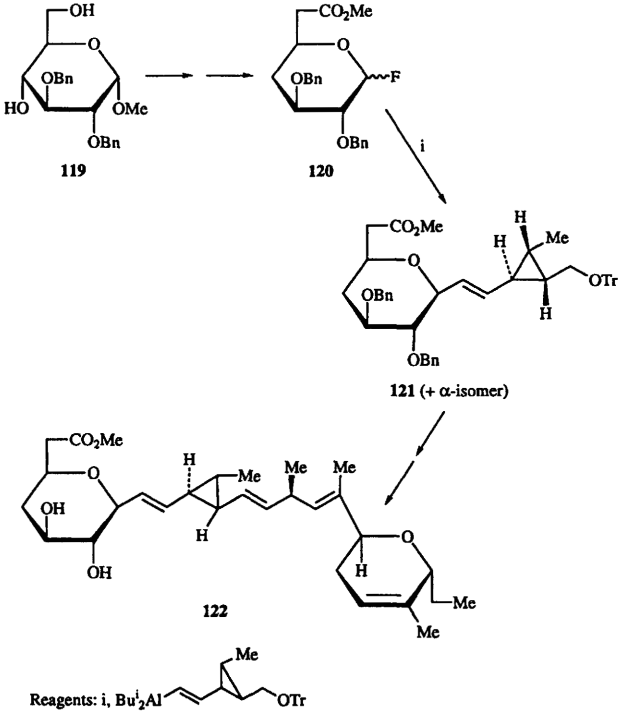


117



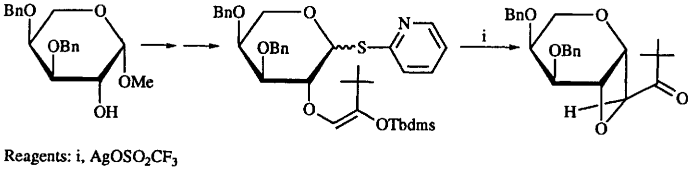
118

(+)-Ambruticin **122** has been synthesized from the known methyl glycoside ***119***. Deoxygenation at C(4) of **119** was carried out under Barton conditions and a photochemical Arndt-Eistert sequence was used to prepare fluoride **120** (11 steps from **119**) (Scheme 25). The key *C*-glycosidation step required for the synthesis of **122** involved coupling of a vinyl alane with glycosyl fluoride **120** to give **121**, with the β-anomer predominating.[58]



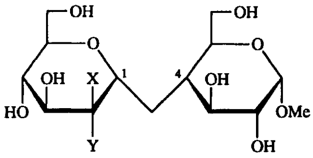
Scheme 25

A number of other important developments in the area of *C*-glycoside synthesis have been reported this year. In a process coined "template directed *C*-glycosidation", Craig has achieved intramolecular C-C bond formation based on use of a silyl enol ether to trap a conventional glycosyl donor (Scheme 26).[59]



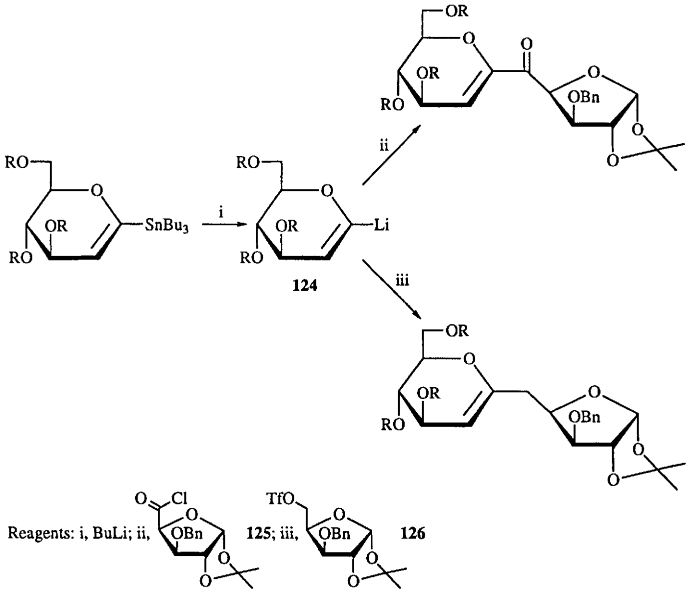
Scheme 26

A related process, based on use of a removable tether to link the "donor" and "acceptor", has been exploited by Sinaÿ, who has synthesised (1→4)-linked *C*-glycosides **123a/b** *via* 9-*endo-trig* radical mediated cyclization (see Chap. 3).[60] A series of both α– and β-(1→6)-linked *C*-disaccharides, prepared *via* $S_{RN}1$ coupling of glycosylmethyl radicals,[61] is also reported in Chap. 3.

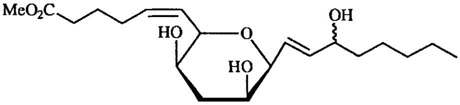


123a X = OH, Y = H
123b X = H, Y = OH

Other complex sugars continue to attract interest and Whiting has described an approach to the undecose component of the herbicidins based on a C-C bond forming reaction involving a 1-lithioglucal (Scheme 27).[62] Lithioglucal **124** has been coupled to acid chloride **125** and, more interestingly, to an alkyl triflate **126**. Tri-*O*-acetyl-D-glucal has been used to generate the C(15)-OH diastereomers of tetrahydropyran **127**, a metabolite of arachidonic acid.[63]



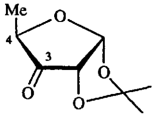
Scheme 27



127

The challenges associated with the synthesis of complex polyether ionophores continue to stimulate much effort. Carbohydrates provide a potent combination of stereochemical information and useful functionality, but the complexity of the chemistry involved limits our discussion to highlighting only the key features. The total synthesis of isolasalocid A has been achieved.[64] The C-ring unit **129** (corresponding to C(18)-C(24) of isolasalocid A, and sugar carbons are indicated) was obtained from the D-glucose-derived ketone **128**. Addition of ethyl magnesium bromide to **128** led only to ketone reduction, and the required two-carbon unit had to be introduced using vinyl magnesium bromide followed by hydrogenation.[64a]

Maintaining their impressive record (Vol. 26, p.312), Kishi's group have described an alternative synthesis of **130** (sugar numbering is shown), the C(1)-C(12) unit of the halichondrins starting from L-mannonolactone.[65] Salomon, also active in this field, has described routes to the functionalized F-ring unit **131** and the KLMN-ring unit **132** of halichondrin B, starting from D-glucose and D-mannitol respectively.[66]



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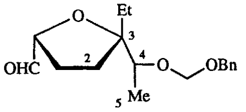

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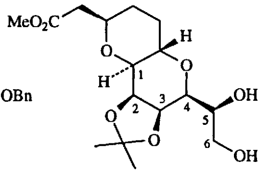

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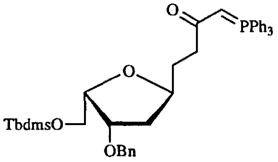

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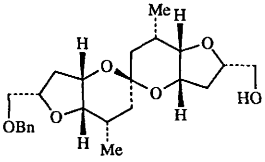
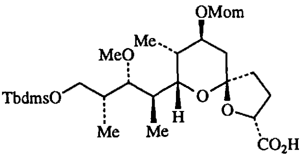


132

Intermediates **133** and **134**, to be used for the synthesis of monensin, have both been synthesized in multi-step sequences from carbohydrate precursors.[67]



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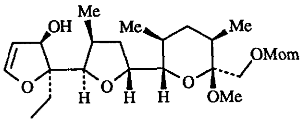
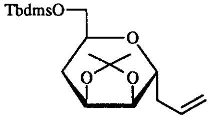


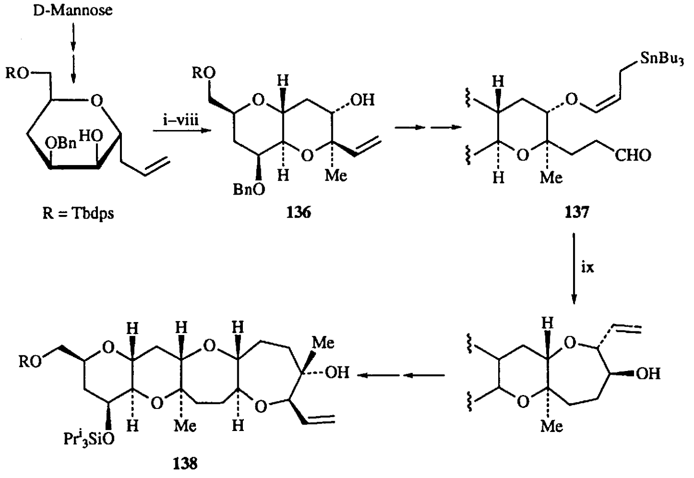
134

Nicolaou's pursuit of the brevetoxins (Vol. 26, p.312) continues to require contributions from the carbohydrate pool with the D-mannose derivative being used to synthesize **135**, a key fragment in both the total synthesis of (7aα)-*epi*-hemibrevetoxin B and of hemibrevetoxin B itself.[68]



135

Finally, a synthesis of the 7,7,6,6-tetracyclic skeleton of hemibrevetoxin **138** has been accomplished (Scheme 28).[69] Manipulation of D-mannose provided the [4.4.0]bicycle **136** and a Lewis acid-mediated intramolecular addition of an allyl stannane to a carbonyl unit (aldehyde or ketone) provided the vehicle for 7-membered ring formation. This is illustrated with aldehyde **137**, although establishing the second of the two adjacent 7-membered rings involved addition of the allyl stannane nucleophile to a ketone moiety.

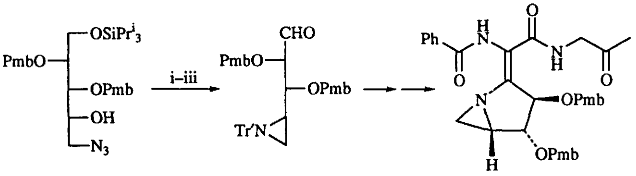


Reagents: i, Et_3SiCl, imidazole; ii, O_3, then PPh_3; iii, $Ph_3P{=}C(Me)CO_2Et$, then Bu^i_2AlH; iv, (+)-DET, $Ti(OPr^i)_4$, Bu^tOOH; v, $SO_3.Py$; vi, $Ph_3P{=}CH_2$; vii, Bu_4NF; viii, H^+; ix, $BF_3.Et_2O$

Scheme 28

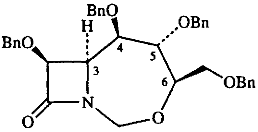
5 Nitrogen Heterocycles

Armstrong has reported an alternative approach to the aziridinyl-based core of the azinomycin class of antitumour antibiotics (Scheme 29) (see Vol. 26, p.313).[70] Glycals, based on D-ribose and D-glucose, provide a series of key stereocentres in novel β-lactam-based derivatives **139** (sugar numbering is shown),[71] and further uses (see Vol. 24, p.316) of D-glucosamine in β-lactam synthesis have been described.[72]



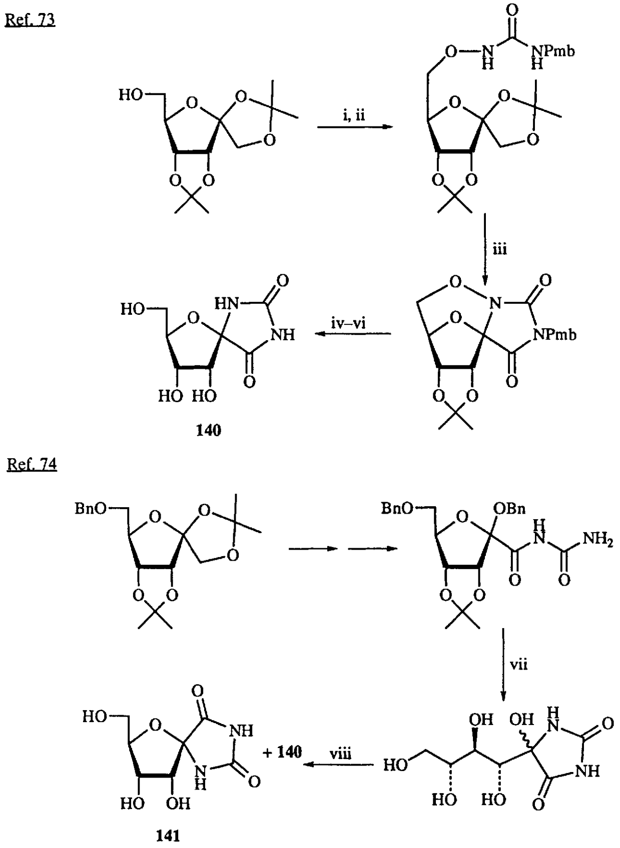
Reagents: i, PPh_3; ii, MeOTrCl (Tr'Cl), Et_3N; iii, Bu_4NF then $(COCl)_2$, DMSO, Et_3N

Scheme 29



139

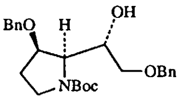
Two successful synthetic approaches to (+)-hydrantocidin **140** have appeared this year.[73,74] Both are based on D-fructose and key features of each approach are shown in Scheme 30. The route described by Chemla[73] is stereoselective, but that of Tersahima[74] leads to both **140** and *epi*-hydrantocidin **141**.



Reagents: i, *N*-Hydroxyphthalimide, PPh_3, DEAD, then H_2NNH_2; ii, $MeOC_6H_4CH_2NCO$; iii, TMSOTf then $Na_2Cr_2O_7$; iv, CAN; v, $Mo(CO)_6$; vi, CF_3CO_2H, H_2O; vii, H_2, Pd/C; viii, Dowex 50X (H^+)

Scheme 30

Carbohydrates continue to provide efficient precursors of functionalized pyrrolidines. The 2,3-disubstituted pyrrolidine **142** (sugar numbering shown), a precursor to the pyrrolidizidine class of alkaloids, has been prepared from D-galactose[75] and the 3,6-imino-derivative **143** (from D-glucose) has been utilized in the synthesis of (-)-detoxin D_1 **144** and (+)-valydetoxinine **145** (see Vol. 26, p.313)[76] Jouillé has also published a review of synthetic work carried out in the detoxin field, some of which is carbohydrate based.[77]



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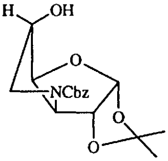

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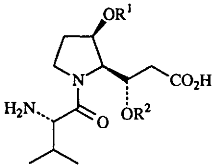
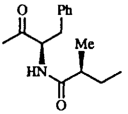


144 R^1 = Ac, R^2 =

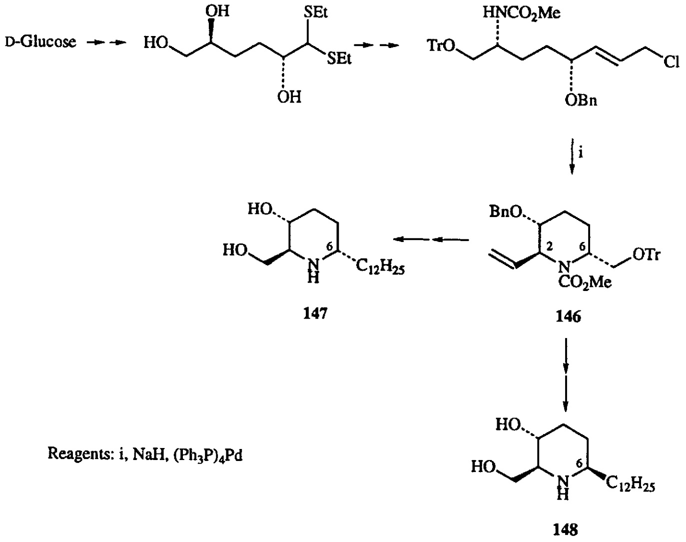


145 $R^1 = R^2 = H$

Piperidine synthesis has also been pursued this year. Shown in outline in Scheme 31 is a D-glucose-based approach to (-)-desoxoprosopinine **147** and its C(6) epimer (-)-desoxoprosophylline **148**.[78] The key heterocyclization involves a Pd(0)-mediated intramolecular N-alkylation leading to **146**, the major component of a 10:1 mixture of diastereomers.

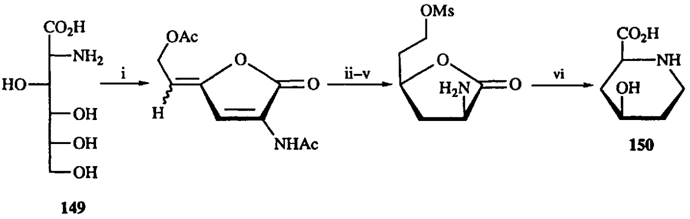
D-Glucosamine provides (*via* known procedures) access to the highly functionalized amino acid **149** which has been converted into *cis*-4-hydroxypipecolic acid **150** (Scheme 32).[79]

This year has also seen continuing high level of activity in the synthesis of deoxyiminoaldols and polyhydroxylated indolizidines based on castanospermine and swainsonine (see also Chap. 18, section 3). Vogel has reviewed (68 refs.) the use of furan-based "naked sugars" in the synthesis of castanospermine and related aza sugars.[80] A series of 1,4-dideoxy-1,4-iminohexitols **151-154** *and* their enantiomers has been synthesized from 2,6-dibromo-2,6-deoxyaldonolactones.[81] The L-idofuranurono-6,3-lactone derivative **155** has been converted to both castanospermine **156** and 1-*epi*castanospermine.[82] The L-threose derivative **157** has been converted, in two independent studies, to 1-deoxycastanospermine[83] and 8-*epi*-1-deoxycastanospermine[84].



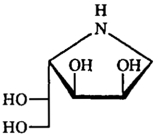
Reagents: i, NaH, $(Ph_3P)_4Pd$

Scheme 31



Reagents: i, Ac_2O, NaOAc, 100 °C, 1 mmHg; ii, H_2, Pd/C; iii, H_3O^+; iv, BnOCOCl, Et_3N; v, MsCl, Py; vi, KOH, H_2O

Scheme 32



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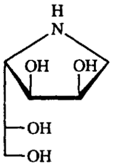

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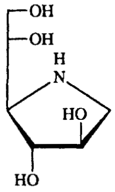

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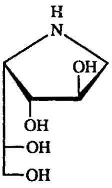

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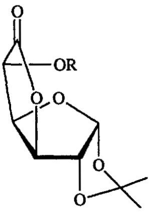
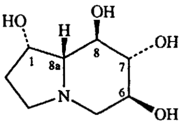


155 R = Tbdms



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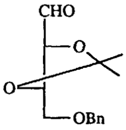
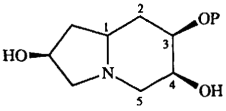
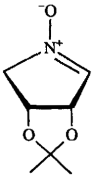


157

A potentially general route to unusual hydroxylated indolizidines, e.g. **158** (sugar numbering shown), has been developed using L-arabinose,[85] and nitrone **159** (from either D- or L-arabinose) has been applied to the synthesis of racemic hydroxylated pyrrolizidines and indolizidines.[86]

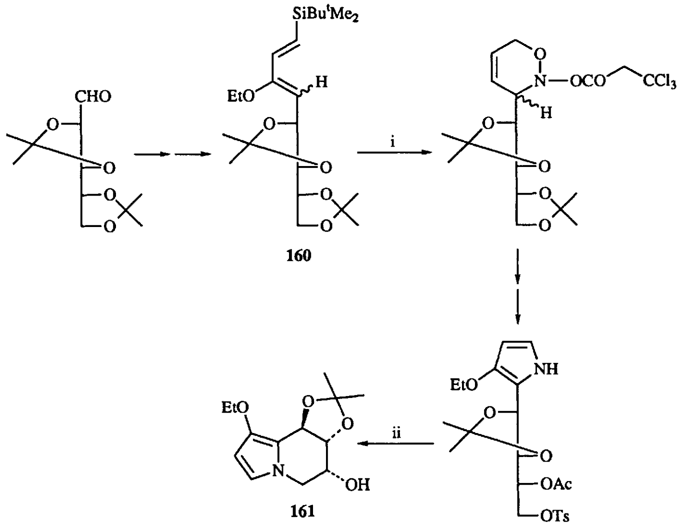


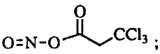
158



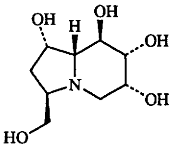
159

The synthesis of unusual variants of castanospermine and congeners has been an area of activity this year. The silylated diene **160** (from D-arabinose) undergoes a hetero Diels-Alder reaction to provide the pyrrolo-castanospermine analogue **161** (Scheme 33),[87] and the branched indolizidine variants **162**[88] and **163**[89] have been obtained from D-mannosamine (using an aldolase-mediated coupling) and D-xylose (*via* a nitrone-cycloaddition) respectively.

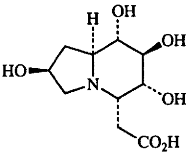


Reagents: i,  $O{=}N{-}O{-}C(O){-}CH_2CCl_3$; ii, KH, DMF

Scheme 33

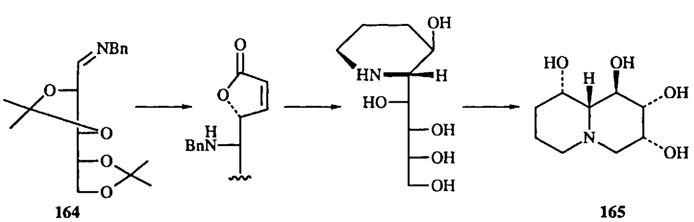


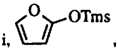
162



163

Two papers have appeared on carbohydrate approaches to polyhydroxylated quinolizidines. The key step in the synthesis of **165** was a diastereoselective Lewis acid-mediated addition to imine **164** derived from D-arabinose (Scheme 34).[90]

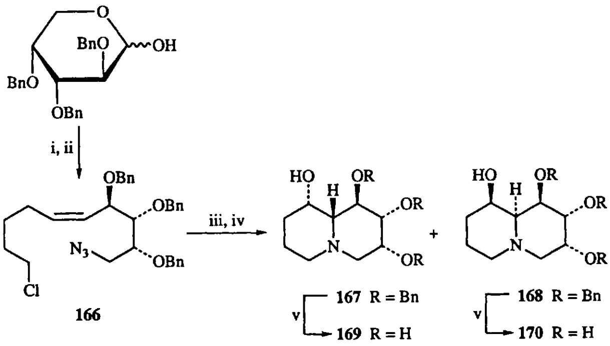




Reagents: i, , $BF_3.Et_2O$; ii, H_2, Pd/C, then DBU, xylene, 140 °C; iii, $BH_3.SMe_2$; iv, TFA, H_2O, then resin (^-OH form); v, PPh_3, CCl_4, Et_3N

Scheme 34

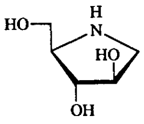
The enantiomer of **165** was also prepared *via* L-arabinose. D-Arabinose also provides the starting point for Pearson's synthesis of **169** and **170** (Scheme 35).[91] Epoxidation of **166** was modestly selective and a double displacement provided a 2.5:1 mixture of **167** and **168** which were separated and then deprotected.



Reagents: i, $Ph_3P{=}CH(CH_2)_3Cl$; ii, PPh_3, DEAD, HN_3; iii, MCPBA; iv, H_2, 10% Pd/C; v, H_2, 10% Pd/C, 2% HCl in MeOH

Scheme 35

1,4-Dideoxy-1,4-imino-D-arabinitol **171**, 1-*epi*-swainsonine **172** and 1,8-*diepi*-swainsonine have been synthesized from (S)-pyroglutamic acid and are included here for the sake of completeness.[92]



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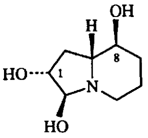
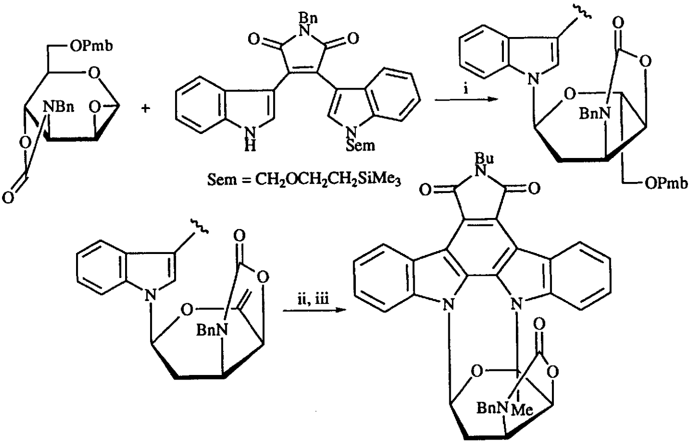


172

Danishefsky has described the synthesis of **173** which represents the fully functionalized core of staurosporine, a potent protein kinase C inhibitor.[93] Central to his strategy is incorporation and then unmasking of a double glycosyl donor by activation of (i) an endocyclic enol ether and (ii) an exocyclic enol ether, as outlined in Scheme 36.



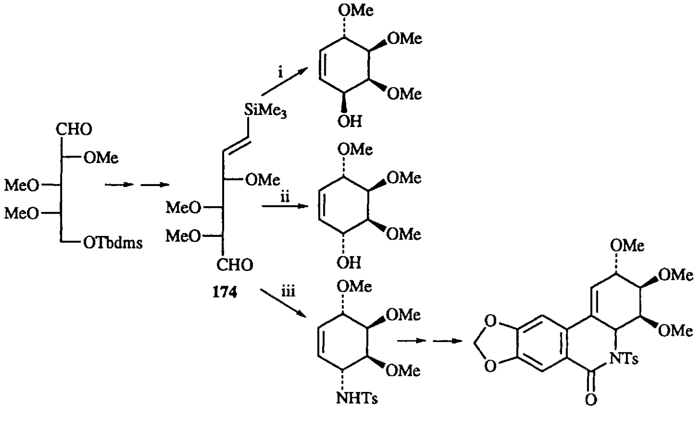
Sem = $CH_2OCH_2CH_2SiMe_3$

173

Reagents: i, NaH; ii, $KOBu^t$, then I_2; iii, Bu_3SnH

Scheme 36

Vinyl silane **174** (from L-arabinose) undergoes a series of stereoselective cyclization reactions, the outcomes of which are determined by the nature of the Lewis acid used (Scheme 37).[94] The N-tosylimine adduct **175** has been converted to the protected lycoricidine derivative **176** Full details of Ogawa's synthesis of (+)-lycoricidine have appeared (Vol. 25, p.320).[95]

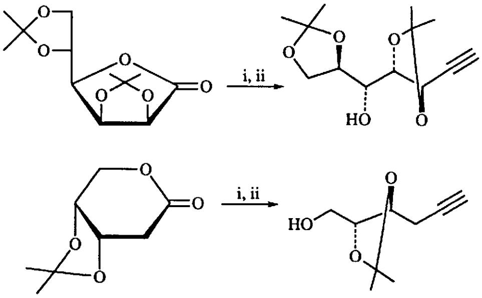


Reagents: i, $SnCl_4$ (major isomer shown in each case); ii, $BF_3.Et_2O$; iii, TsNSO, $BF_3.Et_2O$

Scheme 37

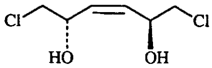
6 Acyclic Compounds

This year has seen the applications of carbohydrates in the synthesis of polyols, hydroxyesters, amino alcohols and amino acids. A new procedure has been described for the synthesis of acetylenic alditols which proceeds by way of dichloromethylene analogues of aldonolactones (Scheme 38).[96] The interesting C_2-symmetric diol **177** has been synthesized (in 8 steps) from levoglucosenone,[97] and multiple directed hydroxylations provide access to a series of long chain 1-deoxyalditols, such as **178**.[98] Iterative homologations based on 2-acetylthiazole have been exploited by Dondoni in the synthesis of polyols, with stereocontrol being exercised in the initial aldol step (which is Cram selective) and in the subsequent ketone reduction - face selective *vs.* hydroxyl directed delivery of hydride (Scheme 39).[99]



Reagents: i, PPh$_3$, CCl$_4$; ii, Li

Scheme 38



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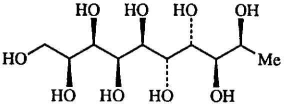
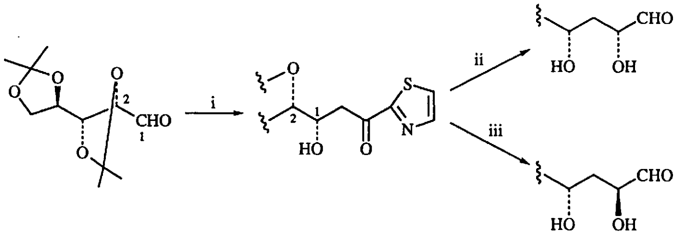


178

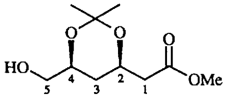


Reagents: i, 2-acetylthiazole, LiOBu^t; ii, Bu$^i_2$AlH; iii, Me$_4$NBH$_4$

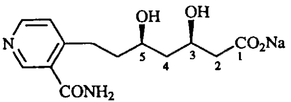
Scheme 39

A series of *O*-acetylated polyhydroxylated dienones have been prepared using cellobial peracetate as the starting point and involving opening of the "reducing ring" and Wittig-like homologations.[100] Full details (see Vol. 26, p.317) have appeared of Ogawa's route to (-)-oudemansin X from L-quebrachitol.[101]

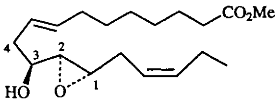
Hydroxyester **179** (sugar numbering shown) has been synthesized from ribitol, and offers potential in the synthesis of HMG-CoA reductase inhibitors.[102] Staying with this theme, levoglucosan has been used to generate **180** (sugar numbering shown). This molecule is, however, biologically inactive.[103] Arachidonic acid metabolites continue to be of interest and syntheses of, *inter alia*, hepoxilin B_3, trioxilin B_3 (both from D-mannitol)[104], and epoxide **181** (sugar numbering shown), which provides rice with protection against rice blast disease, in 10 steps from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose has been reported.[105] The two isomeric 4-azido-3-fluoro-2-hydroxybutanoic acids **182** and **183** are available from carbohydrates,[106] and D-glucitol has been exploited to provide the only stereocentre required for (S)-(-)-propanolol **184**.[107]



179



180



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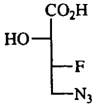

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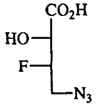

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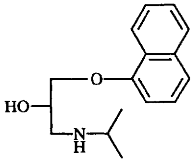
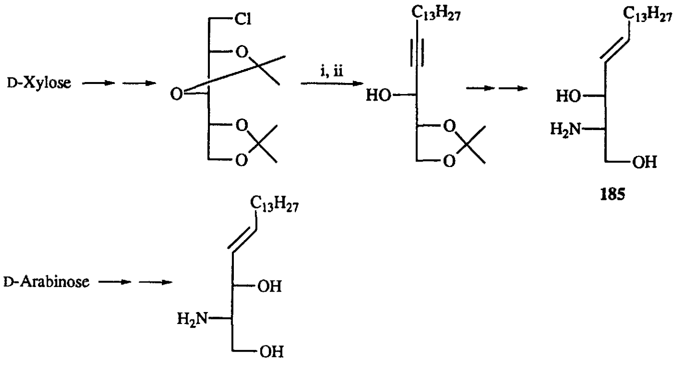


184

D-Xylose and D-arabinose have been employed (in a parallel sequence of reactions) for the synthesis of the D-(+)-*erythro* and L-(-)-*threo* sphingosines **185** and **186** respectively.[108] The key step, illustrated in Scheme 40, involved a double elimination (to generate an alkyne) followed by alkylation.



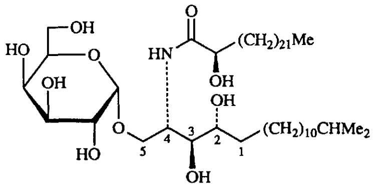
185

186

Reagents: i, $LiNH_2$, NH_3; ii, BuLi, $C_{13}H_{27}Br$

Scheme 40

The structure of agelasphin-9b **187** has been established *via* synthesis of the cerebroside component from D-galactose (sugar numbering is shown).[109] Elucidating the structure of muscaridin **188**, however, continues to be a problem. All four possible diol diastereomers have been synthesized (from D-*glucono* and D- and L-*gulono* lactones) and, while **188** (as shown) is the structure favoured for the natural product, some ambiguity remains.[110]



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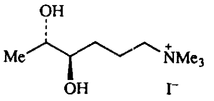
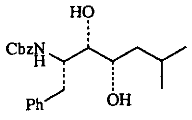


188

Amino alcohols **189** (used in the synthesis of renin inhibitors) and **190** (used in the synthesis of HIV-1 protease inhibitors) were both prepared from D-*iso*-ascorbic acid,[111] and amino diol derivatives **191** and **192** were synthesized from D-mannose.[112]



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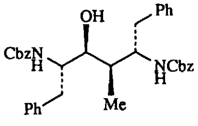

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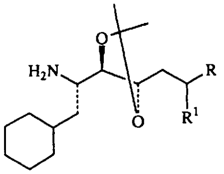
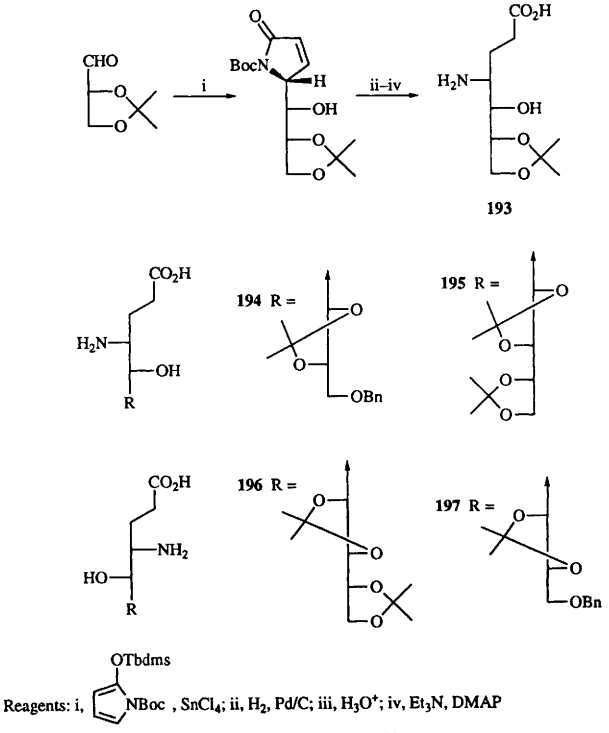


191 R = R^1 = Me
192 R = 2-pyridyl, R^1 = H

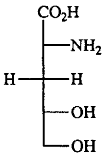
A number of papers concerning the elaboration of carbohydrates into amino acids have appeared. Synthesis of the *C*-alditol-1-yl derivatives **193-197** of GABA has involved diastereoselective addition of N-(Boc)-2-(OTbdms)pyrrole to aldehydo-sugars (Scheme 41).[113]



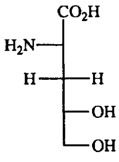
Reagents: i, NBoc , $SnCl_4$; ii, H_2, Pd/C; iii, H_3O^+; iv, Et_3N, DMAP

Scheme 41

The D-*threo* and D-*erythro* isomers **198** and **199** (which was obtained as the corresponding γ-lactones) were obtained from D-*ribono*-1,4-lactone with a key step in each case being a stereospecific reduction of an intermediate butenolide.[114]

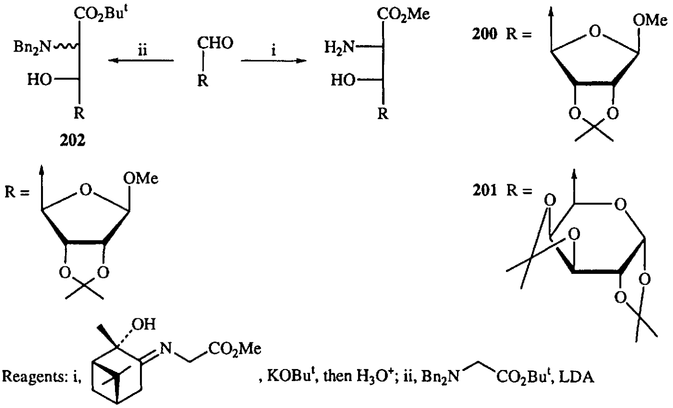


198



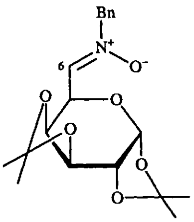
199

The diastereoselective synthesis of β-hydroxy-α-amino esters **200** and **201** has been achieved. Use of a chiral auxiliary on the enolate component leads to good *anti*-selectivity, but in the absence of this additional vehicle for stereocontrol, both *syn* and *anti* isomers **202** were produced (Scheme 42).[115]

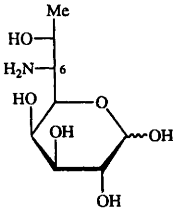


Scheme 42

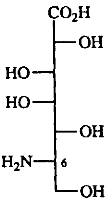
Diastereoselective Lewis acid-mediated addition of 2-lithiothiazole to nitrone **203** (derived from D-galactose) has been used by Dondoni in the formal synthesis of both lincosamine **204** and destomic acid **205** with the stereochemistry at C(6) (galactose numbering) being controlled by the nature of the Lewis acid employed.[116]



203

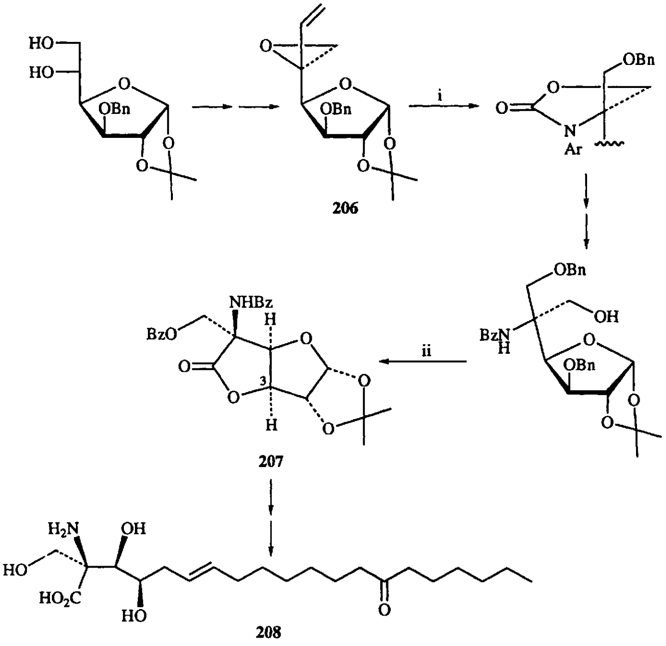


204



205

The polyfunctional immunosuppressant ISP-1 **208** has been synthesized from D-glucose (Scheme 43).[117]



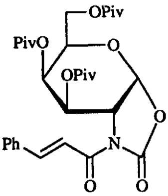
Reagents: i, ArNCO (Ar = 4-MeOC$_6$H$_4$), Pd(PPh$_3$)$_4$; ii, RuCl$_3$, NaIO$_4$, H$_2$O, CCl$_4$, MeCN

Scheme 43

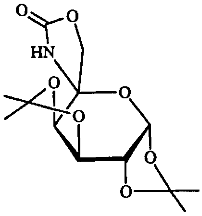
The stereochemistry of the α,α–disubstituted amino acid was cleverly controlled using a Pd(0)-catalysed *cis*-hydroxamination involving vinyl epoxide **206**, a process that has been extensively studied by Trost. Ruthenium-mediated oxidation was used to establish the lactone **207** *via* simultaneous oxidative cleavage of the benzyl ether at C(3) (glucose numbering).

7 Carbohydrates as Chiral Auxiliaries

Kunz and Rück have reviewed the use of carbohydrate-based chiral auxiliaries in stereoselective synthesis.[118] Applications in a wide range of cycloadditions, 1,4-addition, reduction, and Strecker (cyanide and ammonia) and Ugi (isocyanide and ammonia) reactions are covered. The same group have shown that the carbohydrate-based N-acyloxazolidinones **209** undergo conjugate additions with R_2AlCl to provide the corresponding β-alkylated dihydrocinnamates in 80-96 %d.e.[119] D-Galactose has also been used to generate spirooxazolidinone **210** which has been employed as an alternative to the better-known Evans' auxiliaries in aldol and Diels-Alder reactions with high diastereoselectivities being claimed.[120]



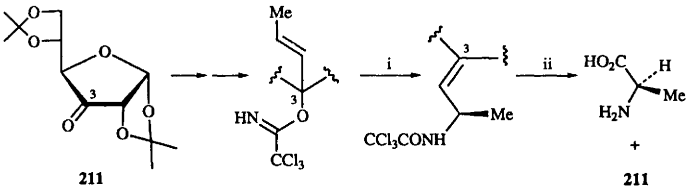
209



210

A synthesis of D-alanine has appeared using the familiar carbohydrate unit **211** as the source of the control element (Scheme 44).[121] The key step involved introduction of the amino unit *via* an Overman rearrangement, and it is worth noting that the sugar unit is a *genuine* chiral auxiliary inasmuch as the auxiliary unit may be regenerated intact, albeit under rather unusual conditions.

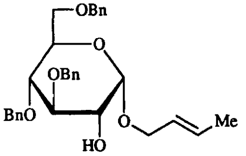
[2+2]-Cycloaddition reactions of ketenes to imines derived from glycosylamine and aldehydes provide access to β-lactams, although the level of selectivity observed with these N-linked auxiliaries is modest.[122] The alkenyl moiety of glycoside **212** undergoes diastereoselective epoxidation using peracid in 80 %d.e.; Simmons-Smith cyclopropanation of **212** was reported earlier (Vol. 25, p.335).



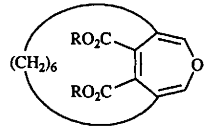
Reagents: i, xylene, reflux; ii, $RuCl_3$, $NaIO_4$, then H_3O^+

Scheme 44

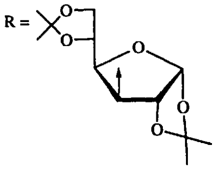
Oxepine diester **213** is convertible in two steps (epoxidation, followed by photolysis) to tetracycle **214**. This sequence was also carried using the starting material derived from L-glucose.[124]

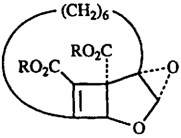


212



213 R =

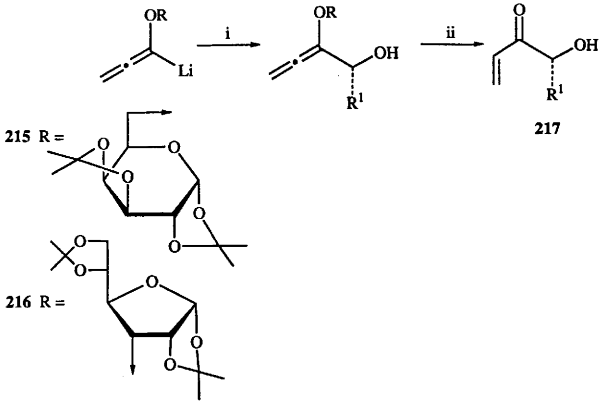




214

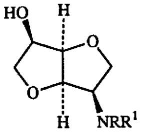
1-Lithio-1-alkoxyallenes provide α,β-unsaturated acyl anion equivalents (Scheme 45). A series of chiral auxiliaries may be utilized for stereochemical control and the carbohydrate-based lithio species **215** and **216** provide α-hydroxyalkyl enones **217** in up to 88 %e.e.[125]

A variety of new chiral auxiliaries **218** have been synthesized from 1,4:3,6-dianhydro-D-glucitol[126] and the enolate derived from **219** (with the auxiliary connected to the enolate precursor *via* an amide linkage) undergoes methylation (to give the (R)-isomer) in 83 %d.e.[127]

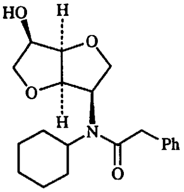


Reagents: i, R^1CHO; ii, H_3O^+

Scheme 45

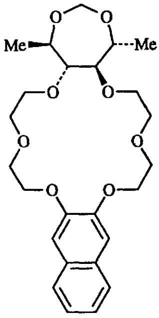


218 $R = R^1$ = H, alkyl, or Ph

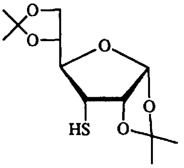


219

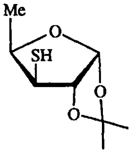
A series of chiral crown ethers, such as **220**, which offer potential as ligands for Lewis acids, have been derived from D-mannitol,[128] and 3-thiosugars, for example **221** and **222**, have been utilized as ligands to control the additions of cuprates to prochiral enones which proceed in up to 58 %e.e.[129]



220



221



222

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