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Carbohydrate Chemistry

VOLUME 25

Monosaccharides, Disaccharides, and
Specific Oligosaccharides

A Review of the Literature
Published in 1991

ROYAL SOCIETY OF CHEMISTRY

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A Review of the Recent Literature Published during 1991

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Preface

The completion of Volume 25 of this annual series, which covers the relevant literature of 1991, obviously marks a milestone at which it is perhaps worthwhile emphasizing the marked changes which the quarter century has seen in the organic chemistry of the monosaccharides and related compounds. Throughout, a fairly consistent screening policy has been used and retrieved 765 papers for abstracting in 1967 (Volume 1), 1023 in 1978 and 2022 in 1990, the increase in activity being ascribable to concurrent enhanced appreciation of the significance of sugars in biology and in general synthetic organic chemistry on the one hand, and advances in separation and analytical techniques on the other.

Much more significant than the simple number of papers cited is, in my judgement, the striking changes in the quality of content of very many publications in the field. A glance at Volume 1 shows that few papers published in 1967, for example, made penetrating or seminal advances to knowledge, and from the point of view of the Specialist Periodical Reporter all material was readily managed. Today's literature is vastly more complex, and it is rather difficult to do justice to many published papers in a few sentences. Much of their content is very complex, it may be difficult to assign to appropriate Chapters, and even the issue of relevance as a whole may be uncertain. Is a particular paper on cyclitols or antibiotics or synthesis or analysis inside our guidelines for cover? In which of perhaps six possible chapters is a complex report covered? When does nucleoside chemistry become heterocyclic or nucleic acid chemistry? How much of a 20-step synthesis which uses a sugar as key starting material for the preparation of a complex macrocyclic antibiotic is relevant? The 25th milestone has taken on millstone characteristics.

From their prejudiced point of view the reporters themselves use the Reports a great deal in their research, and have growing experience of how valuable they are for basic searches - even in these days of automated facilities. They trust others share this sense of value of the Reports and note how readily they assist the identification of growth areas and selective advances in the field. Progress is far from even.

Our writing team has been stable for several years, but now Dr Keith Clinch has joined us as a welcome colleague from private industry, and we will be expanding further for the next volume. Needless to say an enlarged team implies increased chances of one member being held up by other responsibilities and thereby delaying production, but we remain (still) of the view that we can reduce delays in publication and we continue to try.

It is probable that this volume will be the last in which Dr Neil Williams' invaluable contribution as molecular structure producer will be required. Progress dictates that computer art work be used in future, and while this will obviously be welcome in one way, loss of Neil's carbohydrate expertise in the handling of drawings will be a considerable handicap to all Reporters. I acknowledge with warmest thanks his major contributions as reporter, Senior Reporter and draughtsman over 17 years, and look forward to his continuing assistance in the first of these roles.

Warm thanks go to all reporters for their patient assistance and to Dr P.G. Gardam and Mr A.G. Cubitt of the Royal Society of Chemistry for their support.

R.J. Ferrier
April 1993

Contents

Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ad	adenin-9-yl
AIBN	2,2'-azobisisobutyronitrile
All	allyl
BBN	9-borabicyclo[3,3,1]nonane
Bn	benzyl
Boc	t-butoxycarbonyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
c.d.	circular dichroism
CI	chemical ionization
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
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
EE	1-ethoxyethyl
e.s.r.	electron spin resonance
FAB	fast-atom bombardment
GC	gas chromatography
HMPT	hexamethylphosphorous triamide
i.r.	infrared
LAH	lithium aluminium hydride
LDA	lithium di-isopropylamide
LTBH	lithium triethylborohydride
MCPBA	*m*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MOM	methoxymethyl
m.s.	mass spectrometry
Ms	methanesulphonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
n.m.r.	nuclear magnetic resonance
o.r.d.	optical rotatory dispersion
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PTC	phase transfer catalysis
Py	pyridine
SIMS	secondary-ion mass spectrometry
TASF	tris(dimethylamino)sulphonium difluorotrimethyl silicate

TBDMS	t-butyldimethylsilyl
Tf	trifluoromethanesulphonyl
Tfa	trifluoroacetyl
TFA	trifluoracetic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
TMS	trimethylsilyl
TPP	triphenylphosphine
TPS	tri-isopropylbenzenesulphonyl
Tr	triphenylmethyl
Ts	toluene *p*-sulphonyl
U	uracil-1-yl

1
Introduction and General Aspects

The steady advances reported in the 1991 literature show how well the subject connects basic aspects of organic chemistry with medical and biological science. Knowledge of the chemistry of glycosyl cations, anions, free radicals and carbenes has been taken forward on the one hand, and many syntheses have been reported that have been initiated by the needs of biologists, and biological (especially enzymic) methods as tools in synthetic carbohydrate chemistry have become overtly more accessible and useful.

Oligosaccharide syntheses and structural/conformational analyses by spectroscopic and theoretical methods have advanced appreciably and in line with the continuing increase in the recognition of these compounds as key elements of certain biological processes.

An appreciation of the life and work of the great Japanese medicinal chemist Hamao Umezawa has appeared.[1]

Many articles of general interest and reviews on specific topics have been published in 1991. One describes a method for transferring Fischer projection formulae into zig-zag alternatives which should be of interest to those teaching the subject.[2] Of more historical significance is a review of the evolution of the formulae used to depict sucrose, ranging from the earliest to those that are graphic displays which reveal the hydrophobic surfaces.[3] A symposium report covers such topics as configurational and conformational assignments, comparison of solutions and solid state conformations, the orientations of substituent groups and conformational features of oligosaccharides.[4] Related reviews have dealt with the current state of knowledge on the solution properties of low molecular weight polyhydroxy compounds including the influence of solvation on their dynamic characteristics,[5] the stereochemical aspects of hydration of carbohydrates in aqueous solution as derived from density and ultrasound measurements,[6] the role of lone-pair interactions in the chemistry of monosaccharide derivatives including unsaturated compounds,[7] the use of the "prudent ascent" method in the conformational analysis of methyl cellobioside and the sweetener "trichlorogalactosucrose",[8] and molecular dynamics simulation of carbohydrates including conformational energy mapping of mono- and oligo-saccharides.[9]

Special interest will be taken in the topic of association of resorcinol-aldehyde cyclotetramers and sugars in aqueous or non-aqueous media which has been reviewed (in Japanese).[10]

In the area of synthesis, reviews have covered the use of carbohydrate in industrial chemical manufacture,[11] the synthesis of long-chain sugars and branched compounds from furan derivatives,[12] and the preparation of sugars by different methods as synthons for asymmetric synthesis.[13]

A major review covering 203 references on the use of enzyme methods in sugar and oligosaccharide synthesis and acylations and deacylations has appeared.[14] Others have focused on enzymic synthesis of sugars, oligosaccharides and sugar nucleotides[15, 16] and on enzymic methods for bringing about *O*-substitution and deprotection.[17]

Vasella has reviewed the chemistry of glycosyl carbanions, carbocations, radicals and carbenes and related work covering his own important contributions and those of others.[18]

Specific areas to have been reviewed are carba-sugars (with ring oxygen atoms replaced by carbon),[19] the enediyne anticancer antibiotics notably calicheamycin and esperamycin (Nicolaou's synthetic work on the disaccharide component especially).[20]

Allyl sulphenates show promise as hydroxyl protecting groups. These are stable under conditions in which many types of groups are cleaved and may themselves be removed by Pd (0)-calalysed transfer (see Chapter 7).[21]

Finally, a paper has been published on the therapeutic applications of various carbohydrate-based compounds.[22]

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2
Free Sugars

1 Theoretical Aspects

An essay on the structural representation of sucrose has been published. Following an historical account of the establishment of the constitutional formula and conformational features of sucrose, the present possibilities for graphics displays of its molecular geometry, contact surfaces, and hydrophobicity potential are given.[1]

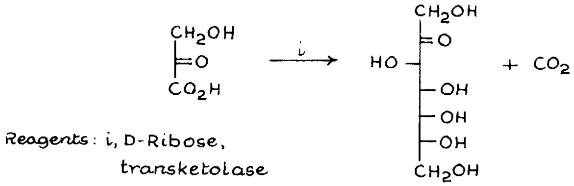
Free energy simulations of the equilibrium between the α- and β-anomers of D-glucopyranose in aqueous solution have been described.[2]

2 Synthesis

Two reviews on the use of furan-derived "naked sugars" in the synthesis of unusual carbohydrate derivatives (*e.g.*, L-hexoses, higher carbon sugars) have been published,[3,4] and recent developments in the synthesis of carbohydrates by means of microbial aldolase catalysis have been reviewed.[5]

In continuation of earlier studies on the formose reaction in aqueous DMF catalysed by triethylamine and thiamine hydrochloride (see Vol.23, Chapter 2, ref.13), the effects of changes in the concentration of either water, formaldehyde, or triethylamine on the product distribution have been examined.[6,7] Improved yields of *threo*-3-pentulose (19% by g.l.c.) were obtained when the formose reaction was carried out in DMSO in the presence of $Pb_2O(OH)$ and thiamine hydrochloride.[8]

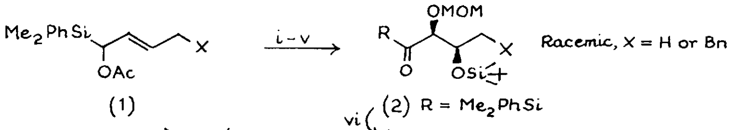
Transketolase from spinach leaves has been used in the stereospecific condensation of hydroxypyruvic acid with a variety of aldehydes, including free sugars, which gives ketoses with (*S*) configuration at the new chiral centre. An example is given in Scheme 1.[9]



Reagents: i, D-Ribose, transketolase

Scheme 1

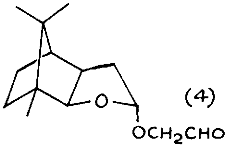
<u>1.1 Trioses - Hexoses</u>. - Full details have been published on a high yielding bulk synthesis of *O*-isopropylidene-D-glyceraldehyde from D-mannitol.[10]



Reagents: i, OsO_4 ; ii, ${}^tBuPh_2$Si-Cl (1 equiv), im ; iii, MOM-Cl, LDA ; iv, DIBAL ; v, $(COCl)_2$, DMSO ; vi, H_2, Pd/C

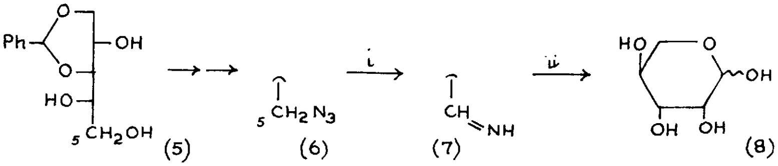
Scheme 2

Derivatives (**3**) of DL-threose and 4-deoxy-DL-threose are available from C-1 oxygenated allylic silanes (**1**) *via* α,β-dialkoxyacylsilanes (**2**) as shown in Scheme 2.[11] The di- and tri-merisation of the acetal protected glycolaldehyde (**4**) under strongly basic conditions furnished, after deacetalization, DL-threose (*ca.*10%) and a 2:1 mixture of DL-allose and -mannose (*ca.*20%), respectively.[12]



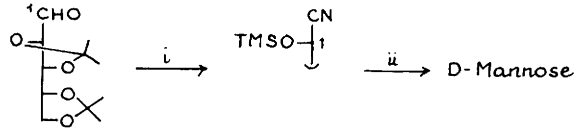
(4)

In a preparation of L-lyxose (**8**) from L-arabinitol (Scheme 3), oxidation of the free primary hydroxyl group of intermediate (**5**) was achieved by photolysis of the azide (**6**) to give the imine (**7**), and subsequent hydrolysis.[13] A rapid, stereoselective synthesis of D-mannose from D-arabinose 2,3:4,5-diacetonide is shown in Scheme 4; both reaction steps took only minutes and isolation of the intermediate (**9**) was not necessary. The procedure has been used for ^{11}C-labelling.[14] The key-steps in the conversion of D-glucose to L-glucose (Scheme 5) were the



Reagents: i, MeOH, hν ; ii, HOAc.aq

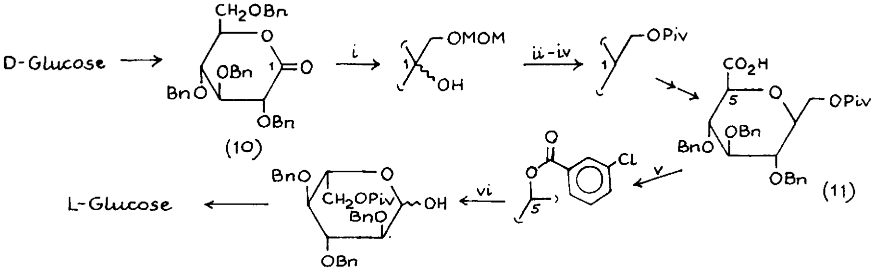
Scheme 3



Reagents : i, TMS-CN, ZnI_2 ; ii, Raney Ni, HCO_2H, EtOH

Scheme 4

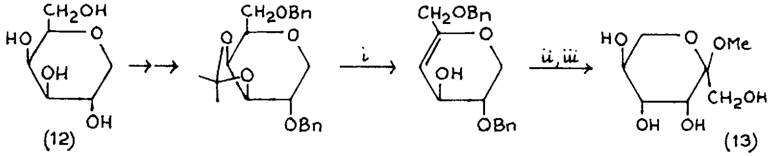
introduction of a protected hydroxymethyl branch at C-1 of the hexonolactone derivative **(10)** and the decarboxylation of the hepturonic acid derivative **(11)**.[15] D-Allose has been obtained from levoglucosenone by stereoselective reduction at C-2 followed by *cis*-hydroxylation of the double bond from the less hindered face and hydrolytic opening of the anhydro-ring.[16]



Reagents: i, Bu_3SnCH_2OMe, BuLi; ii, H_2O, H^+; iii, Piv-Cl, py; iv, Et_3SiH, $BF_3.OEt_2$; v, MCPBA; vi, NaOH aq.

Scheme 5

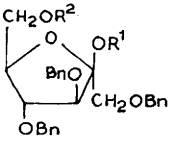
An efficient preparation of methyl α-L-tagatopyranoside **(13)** from 1,5-anhydro-D-galactitol **(12)** in which C-6 of the starting material became C-1 of the product is outlined in Scheme 6.[17] The selectively 1,3,4-protected fructofuranose derivative **(15)** is readily available by cleavage of the glycosidic bond of the perbenzylated sucrose silyl ether **(14)** with concomitant loss of the silyl group, by use of HBF_4.[18] [4-^{2}H],[6-^{3}H]-labelled glucose is referred to in Part 5 of this Chapter.



Reagents: i, Bu^tOK, DMSO; ii, MCPBA, MeOH; iii, H_2, Pd/C

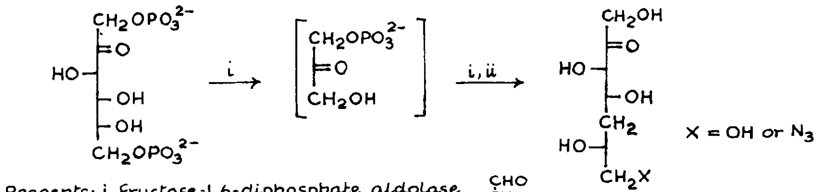
Scheme 6

Chain-extended Compounds. - Unusual hexoses and higher carbon sugars have been produced by use of fructose 1,6-diphosphate aldolase which catalysed firstly, in combination with triosephosphate isomerase, the release of dihydroxyacetone phosphate (DHAP) from fructose 1,6-diphosphate and secondly the stereospecific condensation of DHAP with a variety of simple aldehydes. Two examples are given in Scheme 7.[19]



(14) R^1 = α-D-Glc-p(OBn)$_4$, R^2 = TBDPS

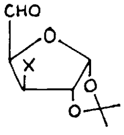
(15) R^1 = R^2 = H



Reagents: i, fructose-1,6-diphosphate aldolase, triose phosphate isomerase, $\begin{array}{l}\mathrm{CHO}\\ \mathrm{CH_2}\\ \mathrm{HO{-}}\\ \mathrm{CH_2X}\end{array}$; ii, phosphatase

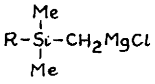
Scheme 7

A full paper on the synthesis of octoses by the "naked sugar" approach has been published (see Vol.23, Chapter 2, ref.31).[20] An improved, shorter version of this synthesis employs a Wittig Horner reaction instead of the original Mukayama cross-aldolization for chain-extension.[21] Similar work has been reported by a Japanese group.[22]



(16) X = H

(17) X = OBn

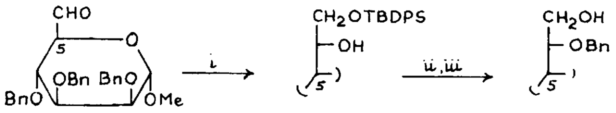


$\mathrm{R{-}\underset{Me}{\overset{Me}{Si}}{-}CH_2MgCl}$

(18) R = Ph

(19) R = Pr^{i}O

The stereochemistry of the addition of organometallics ($LiCH_2SO_2Ph$, MeMgBr) in the presence or absence of added metal salts ($ZnCl_2$, $TiCl_4$, $SnCl_4$, *etc.*) to compounds **(16)** and **(17)** (exemplifying an α-alkoxy- and an α,β-dialkoxy-aldehyde, respectively) has been examined. The product ratios were strongly influenced by the counter cations, in particular by Sn^{4+} and Zn^{2+}, which enhanced α-chelation and by Mg^{2+}, which favoured β-chelation.[23] Hydroxymethylene-extension of the α-D-*manno*-dialdehydo sugar **(20)** with the Grignard reagent **(18)** represents an improvement over earlier procedures employing **(19)**, in that the addition product **(21)** is stable, allowing, for example, benzylation and glycosylation prior to the oxidative removal of the silyl group (Scheme 8).[24] The four stereomeric octofuranose derivatives **(24)** have been produced from the dialdehydo sugars **(23)**, obtained by DIBAL reduction of the protected D-gluco- and L-ido-furanurono-6,3-lactones **(22)** by treatment with allylmagnesium bromide.[25]

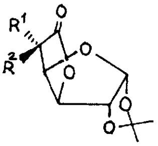


(20) (21)

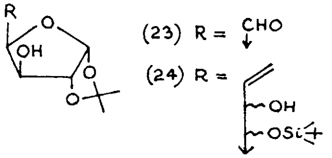
Reagents: i, (18); ii, BnBr, NaH ; iii, CF_3CO_3H

Scheme 8

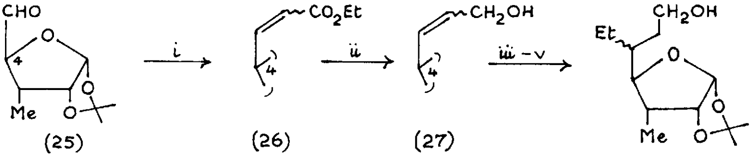
The Wittig adducts **(26)** of the branched 1,5-dialdehydopentofuranose derivative **(25)** were reduced to the allylic alcohols **(27)** which underwent a Claisen rearrangement as shown in



(22) R^1 = TBDMSO, R^2 = H ;
R^1 = H, R^2 = TBDMSO



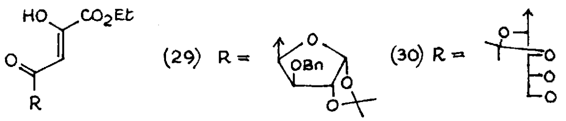
Scheme 9 to give, after selective reduction of the ester group and hydrogenation of the double bond, 3,5-dialkylated 3,5,6-trideoxy-heptose derivatives (**28**).[26]

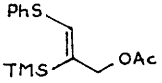


Reagents: i, $Ph_3P{=}CHCO_2Et$; ii, DIBAL ; iii, $(EtO)_3CMe$; iv, LAH ; v, Raney Ni, H_2

Scheme 9

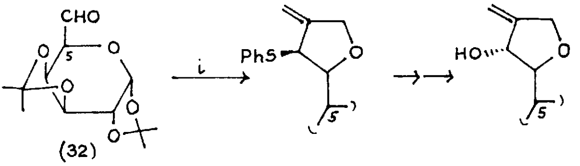
Chain-extension of aldoses or dialdoses with ethyl diazopyruvate furnished sugar 2,4-diketoesters, such as compounds (**29**) and (**30**), respectively, suitable for transformation into complex carbohydrates containing heterocyclic moieties,[27] and Pd-catalysed trimethylene cycloaddition (see Trost *et al.*, *J. Am. Chem. Soc.*, 1991, *113*, 9007) of diacetone D-*galacto*-





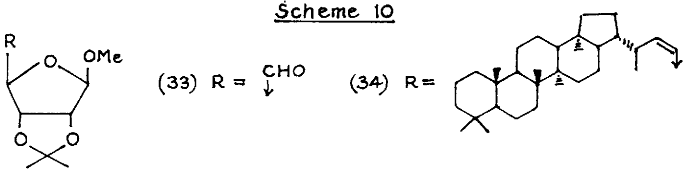
(31)

dialdose (**32**) employing the bifunctional reagent (**31**) represents a useful carbohydrate homologation for ionophore synthesis (Scheme 10).[28] The D-*ribo*-dialdose derivative (**33**) reacted with a terpene-derived phosphonium salt to give the precursor (**34**) of hopane polyols.[29]

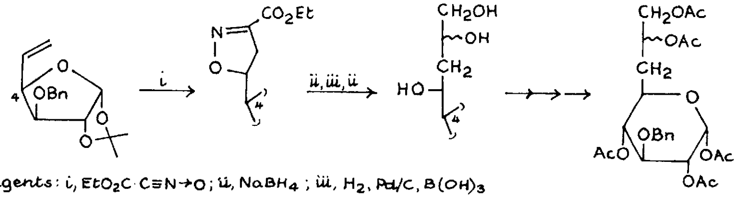


Reagents : i, (31), N,O-bis(TMS)acetamide, Me_2SnOAc

Scheme 10



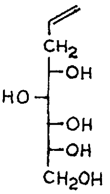
Monodeoxy-octose, -nonose, and -decose derivatives have been synthesized by cycloaddition of nitrile oxides to sugar alkenes and reductive hydrolysis of the resulting 2-isoxazolines. The method is illustrated in Scheme 11.[30]



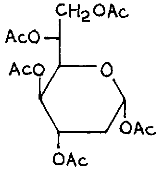
Reagents: i, $EtO_2C\cdot C\equiv N\rightarrow O$; ii, $NaBH_4$; iii, H_2, Pd/C, $B(OH)_3$

Scheme 11

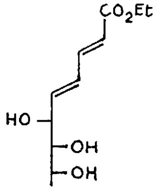
Chain-extension at the reducing end of unprotected tetroses to hexoses has been effected by reaction with allyl bromide and tin metal under the influence of ultrasound, followed by ozonolysis of the double bond. D-Arabinose, for example, was converted to the unsaturated deoxy derivative (**35**) and hence to the peracetylated methyl 2-deoxy heptoside (**36**). An overall yield of 43% indicated good *threo* selectivity in the C-C bond forming step.[31] Chain-elongation of D-arabinose at the reducing terminus with $Ph_3P=CH\text{-}CH=CH\text{-}CO_2Et$ gave the di-unsaturated product (**37**) which on catalytic hydrogenation furnished methyl 2,3,4,5-tetradeoxy-D-*arabino*-nononate.[32]



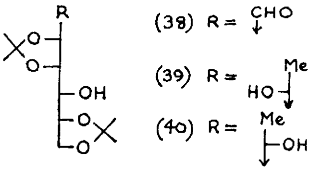
(35)



(36)



(37)



Treatment of 2,3-*O*-isopropylidene derivatives of furanoses with Grignard reagents RMgBr (R = Me, Ph, $CH_2=CH$, $CH_2=CH\text{-}CH_2$) gave consistently main products with *erythro* configuration across the new double bond, *e.g.*, compound (**39**) from di-*O*-isopropylidene-D-mannose (**38**). Use of the corresponding alkyl lithium reagents, although furnishing mainly the *threo* product (**40**) from (**38**), gave in general *erythro*/*threo* mixtures.[33]

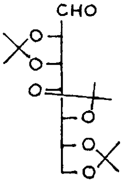
Further examples of four-carbon chain-extensions with 2-(trimethylsilyloxy)furan (see Vol.24, Chapter 2, Scheme 7) have been reported. Application of this method to *O*-isopropylidene-D-glyceraldehyde afforded D-*glycero*-D-*talo*-heptose triacetonide (**41**), and an iterative procedure gave D-*glycero*-D-*talo*-L-*talo*-undecanose pentaacetonide.[34] Similarly, a 8-*O*-benzyl-L-*threo*-D-*talo*-octose derivative was obtained from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose.[35]

Carbohydrate lactones, *e.g.*, compound (**42**), added $TMSCH_2Li$ and TMSCHClLi to form

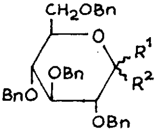
1-deoxy- and 1-chloro-1-deoxy-ketose derivatives (**43**) and (**44**), respectively, in good yields.[36] Exposure of lactone (**42**) to the aryllithium reagent (**46**) gave, after hydrolysis, the spiroketal (**45**).[37]

Spiroketals have also been produced from 1-*exo*-methylene compounds derived from aldonolactones: i) by epoxidation, the products hydrolysing and solvolysing to give ketoses and ketosides, respectively,[38] and ii) by iodoallyloxylation to give allyl 1-deoxy-1-iodo-ketosides followed by radical cyclization.[39] Otherwise, they have been made by solvolysis of [4+2]-cycloadducts of 1-*C*-(3-acetoxypropyl)glycals and bis(trichloroethyl)azodicarboxylate. From the resulting 2-deoxy-2-hydrazonon-4-ulose spiroketals, 2-amino-2-deoxy spiroketals are obtainable.[40]

The synthesis of ketose nucleosides from 1-deoxy-1-nitro-D-ribose is covered in Chapter 20.



(41)

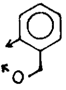


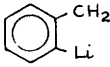
(42) $R^1,R^2 = O$

(43) $R^1 = Me, R^2 = OH$

(44) $R^1 = CH_2Cl, R^2 = OH$

(45) $R^1,R^2 =$





(46)

3 Physical Measurements

A review with 50 refs. on the melting point of sucrose and possible reasons for the discrepancies in the literature has appeared.[41]

In a theoretical study on the glass-transition behaviour of maltose/water mixtures, predicted T_g values were close to those obtained experimentally.[42]

The apparent molal volumes and compressibilities of galactose, glucose, maltose, sucrose, and dextran have been calculated from measurements of the density and ultrasound velocity of their aqueous solutions at 25°C.[43] ^{13}C- and ^1H-n.m.r. lattice relaxation times T_1 have been used to provide information on the temperature dependence of the rotational mobility of both the sugar and the water molecules in concentrated aqueous solutions of sucrose and trehalose.[44]

The kinetics of the liquid-phase heterogeneous isotopic exchange reaction between [1-^3H]monosaccharides and molecular hydrogen have been found to depend on the structure of the sugar, the catalyst (PdO/Al_2O_3 or $PdO/BaSO_4$), and the buffer used. The concentration of the acyclic sugar forms appeared to play a crucial role in determining the kinetic mechanism.[45] The acid-catalysed hydrolysis of sucrose and the oxygen exchange at the anomeric centres of various hexoses, monitored by use of the ^{18}O-isotopic shift in ^{13}C-n.m.r. spectroscopy, have been discussed in a symposium report.[46] Similar work has been reported for D-ribose and its 2-deoxy analogue. The results have been analysed in terms of the hydration kinetics of the open-chain forms.[47] The proton affinities and the deprotonation enthalpies of the primary and anomeric hydroxyl groups of D-gluco- and L-sorbo-pyranose have been calculated, as well as the proton affinities of the ring oxygen atoms of these two hexoses.[48]

The determination of the absolute configuration of monosaccharides by use of asymmetric glycosyl esters is covered in Chapter 7.

4 Isomerization

The steady state kinetics and thermodynamic activation constants of the heptamolybdate ion-catalised glucose-mannose epimerization, a model for metalloenzyme catalysis, have been determined for both directions of the reaction.[49,50]

A further paper, in Japanese, on the epimerization of aldohexoses catalyzed by complexes of Ni(II) with various *N*-alkylated ethylene diamines has been published (see Vol.24, Chapter 2, refs.47,48).[51] In the epimerization of D-glucose by optically active Ni(II) *N,N'*-diethylcyclohexane-1,2-diamine, 36:44 and 60:40 glucose/mannose equilibrium mixtures were obtained by use of the (*R,R*)- and (*S,S*)-enantiomer, respectively.[52]

The isomerization of lactose to lactulose by alkaline ion exchangers has been described. The heterogeneous catalyst was found not only to simplify the process but also to enhance the selectivity.[53]

5 Oxidation

The electrochemical oxidation of glucose has been reviewed (49 refs.). Special attention was given to the effect of the electrode material on the process, and to the adsorption of glucose and its oxidation products on the electrode surface.[54] The oxidation of glucose with single-crystal platinum electrodes in different orientations has been studied. Pronounced structural sensitivity of the reaction was discovered, the Pt(111) and its vicinal surfaces being the most active.[55]

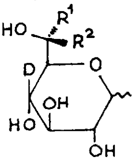
In an investigation of the transition metal-catalysed oxidation of sucrose by oxygen, high selectivity for OH-6 and OH-6' was observed with platinum on carbon at 100°C and neutral pH, with no evidence of reaction at OH-1'.[56]

Papers have been published on the kinetics of oxidation of D-mannose and D-rhamnose by Ce(IV) sulfate,[57] and of D-galactose, L-sorbose, L-arabinose, and D-xylose by OsO_4 in alkaline aqueous media.[58] A mechanism involving free radicals has been proposed in the former case, and formation of an activated OsO_4 - enediol complex in the latter. A kinetic study of the reactions related to the Mn(II)-catalysed bromate/aldose oscillating system has been reported.[59]

The oxidation of D-glucose with iodine or with H_2O_2 and traces of iodine, in the presence of $CaCO_3$, gave calcium gluconate in 60 and 19% yield, respectively. Fructose was inert under these conditions.[60] A reaction mechanism for the highly selective oxidative degradation of carbohydrates in the presence of Na anthraquinone-2-sulfonate and H_2O_2 (Spengler Pfannenstiel oxidation) has been proposed. D-Glucose was converted to D-arabinonate and lactose to β-D-Gal*p*-(1→3)-D-arabinonate with >90% selectivity.[61]

Irradiation of aqueous solutions of D-glucose with ultrasound and γ-rays in air led to the formation of gluconic acid and hexulosonic acids. When performed under argon, the irradiation produced gluconic and 2-deoxy-*arabino*-hexonic acid.[62]

Stereochemical and mechanistic studies on the isomerization of glucose to 6-deoxyglucos-4-ulose by CDP-glucose oxidoreductase have been carried out with labelled substrates (**47**); intramolecular H-migration from C-4 to C-6 with inversion of configuration at C-6 was observed.[63] A rate determining step involving enzyme-substrate interaction has been suggested for the oxidation of D-[1-^{3}H] glucose with glucose oxidase on the basis of very similar kinetic isotope effects (3.0 and 3.1, respectively) when reactant or product monitoring was applied.[64]

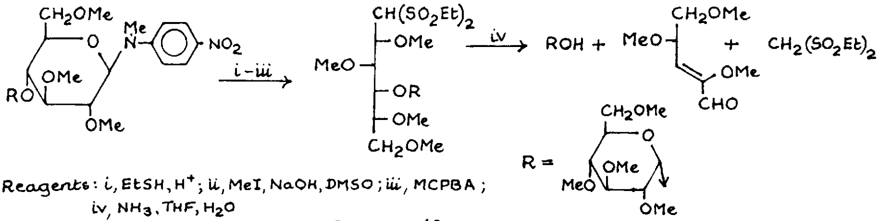


(47)

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

6 Other Aspects

The mechanism of the alkaline degradation of monosaccharides in aqueous solution has been reviewed in a symposium report.[65] A method for the stepwise degradation of glycosylated aldoses, outlined in Scheme 12, has been developed with a view to its application to the sequencing of branched oligosaccharides.[66]

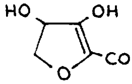


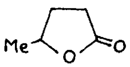
Reagents: i, EtSH, H^+; ii, MeI, NaOH, DMSO; iii, MCPBA; iv, NH_3, THF, H_2O

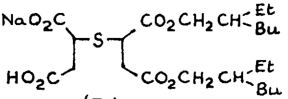
Scheme 12

New studies on the formation of furfural from D-xylose, an old reaction of economical importance, favour a mechanism through 2,5-anhydro-intermediates formed early in the process, rather than a series of reactions *via* open-chain forms and subsequent cyclization.[67]

The formation of 2,3-dihydro-3,4-dihydroxy-5-acetylfuran (**48**), a flavour component in baking, in the reaction between D-fructose and β-alanine has been reported.[68] Anionic ruthenium iodocarbonyl complexes acted as dehydroxylation catalysts of C_3 - C_5 polyols and C_6 sugars in aqueous solution, due to their bifunctional nature (acidity and hydrogenation ability). By exposure to $[Ru(CO)_3I_3]^-$ in the presence of CO and H_2, glucose, fructose, and xylitol have been transformed to γ-valerolactone (**49**), in up to 40% yield, *via* levulinic acid (formed by well known acid-catalysed dehydration and internal oxidation-reduction reactions).[69]


(48)


(49)


(50)

The surfactant (**50**) aggregates in 1:1 chloroform/cyclohexane to form reverse micelles which can bind and solubilize monosaccharides, *e.g.*, glucose, in non-polar organic solvents.[70] The extraction of saccharides into $CDCl_3$ by phenylboronic acid derivatives is covered in Chapter 7.

Four chiral cryptands, derived form D-glucose, D-galactose, D-mannose, and L-tartaric acid, have been prepared by short reaction sequences by application of a new, high pressure method.[71] The cryoprotective effect of mannitol, sorbitol, glucose, maltoologosaccharides, and dextran on the denaturation of catalase during freeze-drying has been attributed to the replacement of lost water of hydration by monomolecular saccharide layers.[72]

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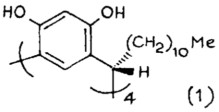
3

Glycosides

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.—Sinay has written a review on recent advances in glycosylation procedures which include one-electron transfer reactions in the synthesis of β-linked oligosaccharides, the use of 2-azido-2-deoxy-D-galactopyranosyl xanthates, and methods for synthesizing KDO- containing disaccharides.[1]

Fraser-Reid and coworkers have noted that various glycosides of aliphatic alcohols, eg $HOCH_2CH_2(CH_2)_nCH=CH_2$ (n=1,2), can be made by use of three equivalents of the alcohols in DMSO as solvent and with triflic acid as catalyst.[2] The same group have reported on the synthesis and use of 1-*O*-pent-4-enoylglycoses in glycosidations. They are less prone to being "disarmed" by electron-withdrawing substituents at O-2 than are the corresponding pent-4-enyl glycosides because it is the carbonyl oxygen atom rather than O-1 that intercepts the initially formed halonium species.[2a] In the area of furanosides, conditions for making the methyl D-glucosides and -galactosides using iron(III) chloride as catalyst have been defined.[3]



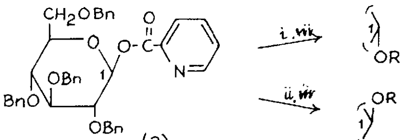
(1)

The macrocycle (**1**) complexes with free sugars (favouring 2-deoxyribose, ribose > erythrose, arabinose > glucose, mannose > xylose, lyxose) and enables them to be solubilized in carbon tetrachloride from aqueous solution and hence converted to their glycosides with the furanosides being favoured.[4] The preparation of methyl α-*D*-[$U^{14}C$]glucopyranoside (from the labelled free sugar) has been reported.[5]

Mukaiyama's group have shown that use of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-*D*-glucose and trimethylsilylated alcohols in the presence of Lewis acid catalysts leads to high yields of glycosides with remarkably high α:β ratios (9:1 or better). The preparations of simple glycosides, disaccharides and serine glycosides were reported. In one report $SnCl_4$ +20% $AgClO_4$ was used;[6] in a later note an assessment of $GaCl_3$, $InCl_3$, $SiCl_4$, $GeCl_2$ and $SnCl_4$ as catalysts indicated that the first and last of these were most effective.[7]

With 2,3,5-tri-*O*-benzyl-*D*-ribose and trimethylsilylated alcohols, furanosides with α:β ratios *ca.* 95:5 were obtained in the presence of a catechol-titanium(IV) triflate catalyst,[8] and about 99:1 in the presence of diphenyltin sulfide, triflic anhydride and base.[9] Remarkably, this ratio was inverted when the latter condensations were carried out in the presence of excess of lithium perchlorate.

Thiopyridyl glycosides, and related esters with metal activators, have been used appreciably in glycoside synthesis. Now the glycosyl carboxylate (**2**) has been found to allow high yields and α:β ratios of 4:1 and 1:4 when used with unsubstituted alcohols and copper(II) triflate in ether or tin(II) triflate in acetonitrile, respectively (Scheme 1).[10] Several alcohols, including monosaccharide alcohols, were used; since the reactions did not proceed with 4-pyridyl carboxylates, chelation of the metals seems a probable component of the activation process.

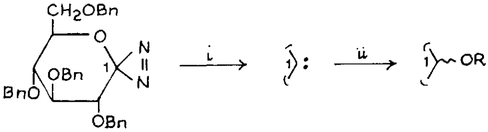


(2)

Reagents : i, Cu(OTf)$_2$, ether; ii, Sn(OTf)$_2$, MeCN; iii, RCH

Scheme 1

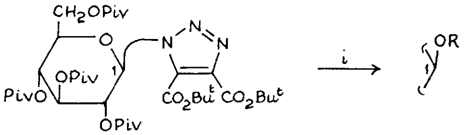
The glycosylideneaziridines (Vol. 23, p. 16), on photolysis, give glycosylidene carbenes which react with alcohols to give glycosides (Scheme 2).[11]



Reagents : i, hν; ii, ROH

Scheme 2

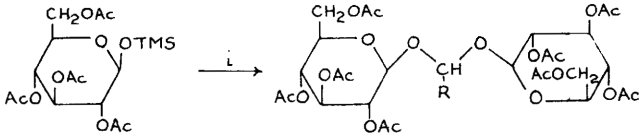
Alternatively, glycosyl triazoles, available from corresponding azides, may be used for the same purpose (Scheme 3).[12] High yields of β-products were obtained with simple and with secondary steroidal and carbohydrate alcohols.



Reagents : i, ROH, TMSOTf

Scheme 3

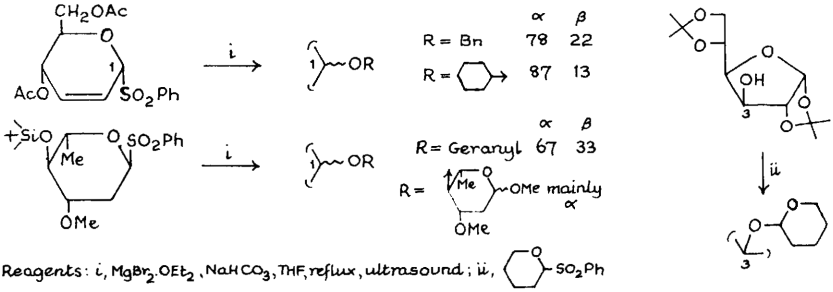
As indicated in Scheme 4, aldehydes can be converted into their diglycosyl acetals. Non-bulky alkyl aldehydes gave better yields than did aromatic or bulky aliphatic compounds. The corresponding silylated α-sugar gave poorer yields of α,α-products, and no acetals were obtained by use of ketones.[13]



Reagents: i, RCHO, TMSOTf, −70°C

Scheme 4

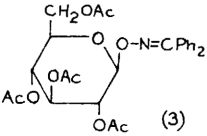
Glycosyl sulfones can be converted into glycosides under mildly basic conditions and, conversely, alcohol groups can be treated with tetrahydropyranyl sulfones to give tetrahydropyranyl acetals under these same conditions (Scheme 5).[14]



Reagents: i, MgBr2.OEt2, NaHCO3, THF, reflux, ultrasound; ii, SO2Ph

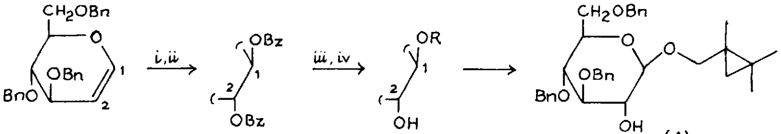
Scheme 5

1,2-*trans*-Related acetylated glycosyl fluorides, treated with *O*-trimethylsilyl derivatives of dimethylglyoxime, benzophenone oxime and acetone oxime, gave the corresponding *α-D-manno-* and *β-D-gluco-* and *galacto* derivatives, eg. compound (**3**).[15]



(3)

As always, glycal derivatives have proved to be a good source of particular glycosides. β-Linked glucopyranosides have been made by the procedure outlined in Scheme 6, and with R=allyl or substituted allyl, have been used in hydroxyl-directed stereospecific cyclopropanation reactions to give compounds such as (4) from which enantiomerically pure cyclopropane alcohols were cleaved (Chapter 24).[16, 17]

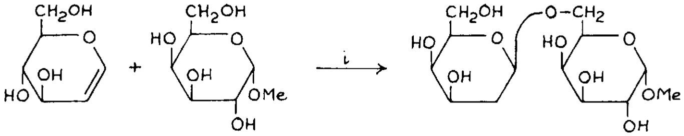


(4)

Reagents: i, OsO_4; ii, BzCl, py; reflux; iii, RO·TMS, TMS·OTf; iv, MeO^-

Scheme 6

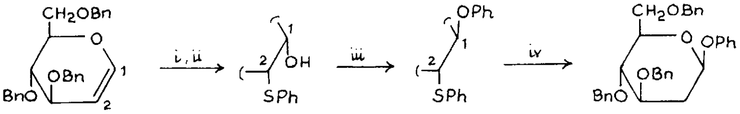
More commonly, glycals are used to give access to 2-deoxy compounds, and an interesting example concerns the enzyme-catalysed addition of alcohols to these compounds. A β-glucosidase was found to make alkyl 2-deoxy-β-*D*-*arabino*-hexopyranosides from D-glucal and simple alcohols in a buffered solution containing acetone, and a β-galactosidase was found to make disaccharides as illustrated in Scheme 7. The yield of the product shown was 50% when the reaction was carried out in a buffered solvent containing acetonitrile.[18]



Reagent: i, β-Galactosidase

Scheme 7

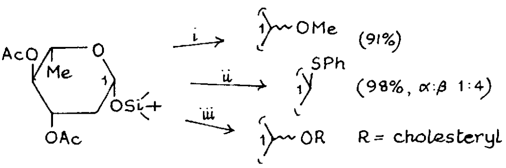
Additions of alcohols to acetylated glycals were found to give α-glycosides (from acetylated *D*-glucal, *D*-galactal, *L*-fucal and lactal) when carried out in the presence of dried sulfonic acid resins and lithium bromide. These reagents also catalysed the addition of water to give 2-deoxy sugars.[19] Aryl 2-deoxy-β-*D*-glycosides were made by the method illustrated in Scheme 8; by use of phenylselenyl chloride and tri-*O*-benzyl-*D*-galactal, 2-naphthyl and *o*-cresyl glycosides were obtained.[20]



Reagents: i, PhSCl; ii, Na_2CO_3, H_2O; iii, PhOH, Ph_3P, DEAD; iv, Bu_3SnH, AIBN

Scheme 8

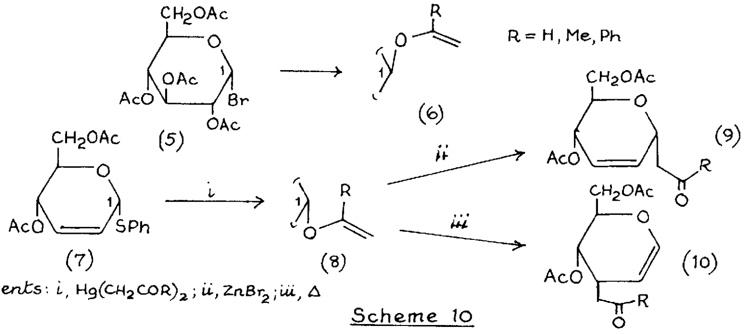
Other 2-deoxyglycosides, made from 1-*O*-silyl-2-deoxyhexoses, have been obtained as indicated in Scheme 9.[21]



Reagents: i, MeOH, HCl; ii, PhSH, $ZrCl_4$; iii, ROH, TMS·OTf

Scheme 9

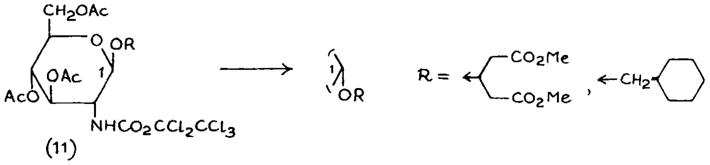
A full report (cf. *J. Chem. Soc., Chem. Commun.*, 1987, 1009) on the preparation of vinyl and 1′-substituted vinyl glycosides (**6**) from tetra-*O*-acetyl-α-*D*-glucopyranosyl bromide (**5**) and bis(acylmethyl)mercury reagents has appeared. The 2,3-unsaturated phenylthioglycoside (**7**), with these reagents, similarly gives 2,3-unsaturated products (**8**) which rearrange to *C*-glycosides (**9**) on zinc bromide treatment and to C-3-branched glycals (**10**) on heating (Scheme 10).[22]



Reagents: i, $Hg(CH_2COR)_2$; ii, $ZnBr_2$; iii, Δ

Scheme 10

Glycosides of amino-sugars remain of importance, see Chapter 9, where reference is made to the use of 2-trifluoroacetamido-2-deoxy-β-*D*-galactopyranosyl fluoride as a glycosylating agent. β-Glycosides (**11**) are anomerized mainly to the α-compounds on treatment with zinc bromide and trimethylsilyl bromide with added relevant alcohol (Scheme 11).[23] Various *p*-nitrophenyl β-*D*-glucoside derivatives, including 2-amino-2-deoxy-compounds, were reduced to *p*-aminophenyl analogues and then converted into *N*-acyloyl derivatives suitable as Michael acceptors of amino-groups of proteins. In this way novel protein, carbohydrate conjugates were made.[24]

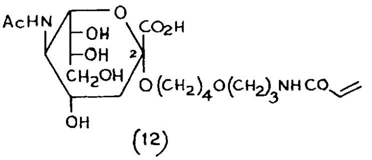


Reagents: i, ROH, ZnBr$_2$, TMS·Br

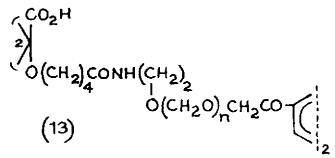
Scheme 11

In related work polyacrylamides bearing sialic acids were made from the monomer (**12**) and were found to be inhibitors of the viral membrane protein haemagglutinin.[25] Glick and Knowles have produced compounds represented by (**13**) and related materials also for use in the study of binding to viruses.[26]

A review has appeared on the synthesis of *N*-acetylneuraminic acid and its glycosides in which chemical and enzymic methods are referred to and mono- and oligo-saccharide cases are selected.[27] A new report on the synthesis of α-glycosides and α-thio-analogues of the acid utilizes the corresponding peracetylated methyl ester glycosyl chloride and treatment under Williamson conditions (alcohol or thiol together with corresponding sodium slats). No β-anomeric products or products of dehydrochlorination were reported.[28] Methanolysis of *N*-acetylneuraminic acid followed by acetylation gave the acetylated α- and β-glycosides in the ratio 3:88. These, with (methylthio)trimethylsilane in the presence of trimethylsilyl triflate, gave the corresponding methylthioglycosides in equal proportions and these, in turn, selectively afforded access to α-*O*-glycosides.[29]



(12)



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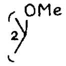
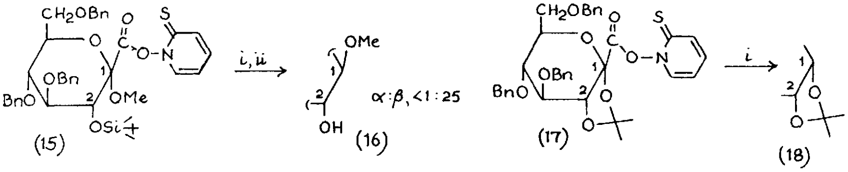


(14)

Reference is made in Chapter 9 to the synthesis of "decarboxy-*N*-acetylneuraminic acid" as its glycoside (**14**) by Wittig extension of 3,4-*O*-isopropylidene-*D*-arabinose.[30] Crich and Lim have amplified their work on the synthesis of equatorially linked glycosides by free radical decarboxylations of ulosonic acid glycosides. Thus compound (**15**) can be converted into the methyl β-glycoside (**16**) with high selectivity but, interestingly, the acetal (**17**) gave the α-1,2-*cis*-fused product (**18**). Clearly, in this case, the kinetic anomeric factor that causes radical trapping to occur from the axial direction was overcome by the relative stability and reactivity of the 1,2-*cis*-fused intermediate (Scheme 12).[31, 32]



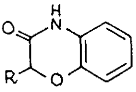
Reagents: i, hν ; ii, $Bu_4\overset{+}{N}\overset{-}{F}$

Scheme 12

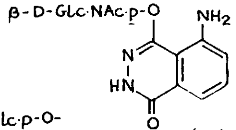
The synthesis of glycosylating agents for the preparation of α- and β-linked KDO glycosides is referred to in Chapter 16.

In the area of aromatic glycosides zinc chloride/phosphorus oxychloride have proved useful promoters of the reaction between peracetylated glucose and galactose and alcohols, phenols and thiophenols. The α-lined products predominated.[33] Tin(IV) chloride was used in the mannose case to give alkyl, alkaryl and acyl α-glycosides.[34] For the preparation of *p*-substituted aryl 2-acetamido-2-deoxy-β-*D*-glucopyranosides from the acetylated glycosyl chloride phase transfer conditions were used involving tetrabutylammonium hydrogensulphate and dichloromethane/aqueous sodium hydroxide.[35] *o*- and *p*-(difluoromethyl)phenyl β-glucosides were made via the corresponding aldehydophenyl compounds which were treated with DAST. The products were potent, time-dependent irreversible inhibitors of almond β-glucosidase.[36]

Heterocyclic compounds to have been glycosylated are benzoxazolone (ribofuranose, 2′-deoxyribofuranose, galactose and glucose derivatives were made)[37] and compound **(19)**. Use of the bromo-derivative **(20)** and 2,3,4,6-tetra-*O*-acetyl-*D*-glucose gave **(21)**, which is blepharin, a naturally occurring acetal glycoside. The X-ray structure analysis was carried out.[38] Compounds **(22)**[39] and **(23)**[40] have been prepared for use as chemiluminescent substrates for the assay of urinary *N*-acetyl-β-*D*-glucosaminidase.



	R
(19)	H
(20)	Br
(21)	β-D-Glc-p-O-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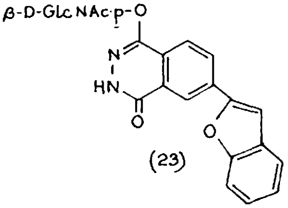
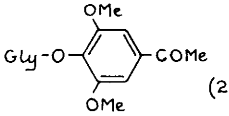

(23)

The β-maltoside, β-*D*-glucoside, β-*D*-galactoside and α-*L*-fucoside of acetosyringone [e.g. compound (24); *Carbohydr. Res.* 1990, *198*, 223] are inducers of the virulence gene of the crown gall tumour agent *Agrobacterium tumefaciens.*[41] Compound (**25**) is a new lysosomotropic fluorescent probe made to detect β-galactosidase in intact cells.[42]

The glucuronide (**26**) of the new oral antidiabetic agent CS-045 has been synthesized by use of the β-glycosyl acetate together with *p*-toluenesulfonic acid as catalyst,[43] and a report on the *O*- and *N*-linked glucosides (**27**) and (**27a**) of an aromatic amino-acid has appeared.[44]



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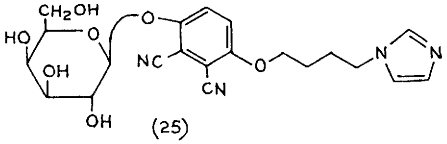

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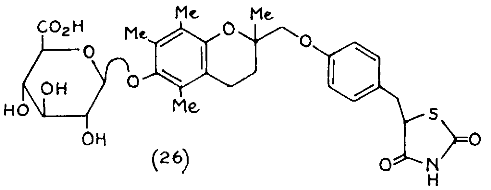

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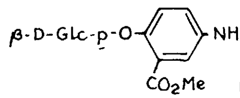

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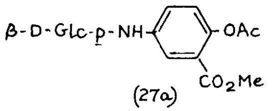
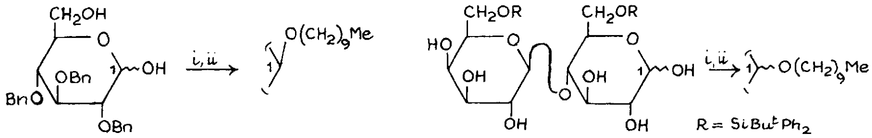


(27a)

Several papers have reported the preparation of long chain alkyl glycosides, some making use of enzyme-catalysed transfer reactions. Cellobiose has been employed as glucosyl source to make 1-heptyl and 1-octyl β-*D*-glucopyranosides (β-glucosidase from *Trichoderma viride*)[45] and β-*D*-galactosides of long chain terminal alcohols and terminal diols have been made enzymically from *o*-nitrophenyl β-*D*-galactopyranoside and lactose using an aqueous acetone medium.[46] A related paper reported glycosyl transfer from phenyl β-*D*-galactoside, lactose and phenyl β-*D*-glucoside using a crude extract of *Sulfolobus solfatarius* to racemic propane-1,2-diol and related compounds. For transfer to the primary alcohol no enantioselectivity was observed, but for transfer to the secondary site the (2S)-diol was produced with high selectivity (2S:2R, 95:5).[47] Almond β-glucosidase on a polymer support catalysed alkyl β-*D*-glucoside synthesis within a two-phase system with high concentrations of donors in the aqueous phase and water immiscible primary alcohols as the organic phase.[48] The surface-active properties of heptyl β-*D*-xylosides, made by transfers by use of a β-xylosidase, have been the subject of separate study.[49]

Fucosides of 1-octanol and 1-dodecanol have been made from the glycopyranosyl acetate. The deacetylated products were considered to represent a novel organisational type of liquid crystal compounds for which the concept of "monolayers with frustrated chain ends" (arising from the hydrophobic nature of the *C*-methyl groups) was suggested.[50] These workers independently reported on columnar liquid crystal discotic phases shown by peracetylated glycosides.[51] Other work has dealt with deuterium n.m.r. studies of *n*-octyl α- and β-*D*-glucopyranoside liquid crystalline systems.[52]

A very interesting observation relates to the preferential reactivity of the anomeric β-hydroxyl group which may be activated as a nucleophile in the presence of other hydroxyl groups (Scheme 13). When 3,4,6-tri-*O*-benzylglucose was used in THF the products consisted of 25% decyl glycosides and 75% of 4′-*O*-(decyloxy)butyl glycosides formed by incorporation of a molecule of the solvent.[53]



Reagents: i, NaH (1 equiv.), toluene ; ii, TfO(CH$_2$)$_9$Me

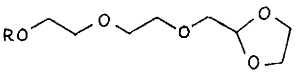
Scheme 13

The Koenigs-Knorr and orthoester methods were used to make fluoroalkyl glycosides of type (**28**). In the former case, glycosylation was assessed before and after fluoroalkylation, the second approach being the more suitable.[54]

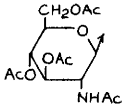
$$\text{Gly-O-(CH}_2)_n\text{OR} \qquad \text{R} = \text{fluoroalkyl}$$

(28)

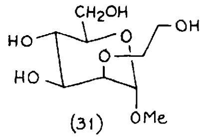
Other long chain alkyl glycosides to have been reported are those of 9,11-octadecadien-1-ol (products used as stabilisers of polymeric liposomes)[55] and the alcohol (**29**). After deprotection, the acetal products (eg **30**) can be linked to proteins.[56]



(29) R = H (30) R =



An interesting cyclic glycoside (**32**) was formed when the 2-(2′-hydroxyethyl)mannoside (**31**) (made from methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-*D*-mannopyranoside) was treated with aqueous acid, and was isolated by way of its tri-*O*-acetate and found to adopt the $^4C_1$ conformation.[57]



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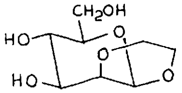
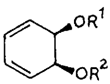


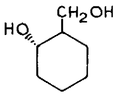
(32)

Glycosylation of several carbocyclic compounds has been reported. Thus diastereomeric β-galactosides of *cis*-cyclohexa-3,5-diene-1,2-diol (**33**) were made by *E. coli*-β-galactosidase promoted substitution using lactose as source. Initially one isomer was strongly favoured, but it also hydrolysed faster and the eventual equilibrium contained similar amounts of each, (**34**) and (**35**) being obtained in 13 and 8% yield, respectively.[58]



	R^1	R^2
(33)	H	H
(34)	β-D-Gal-*p*	H
(35)	H	β-D-Gal-*p*

Glucosylation of racemic (**36**) with tetrabenzyl thiopyridyl glucoside gave mixed products including the isomaltose analogue (**37**), and the 4-deoxy-compound was made by glycosylation of methyl 2,3-di-*O*-benzoyl-4-deoxy-α-*D*-*xylo*-hexopyranose.[59]



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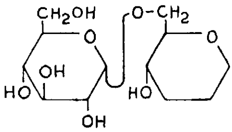
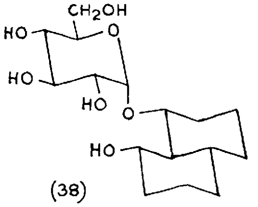


(37)

The further, conformationally restricted isomaltose analogues (**38**) and (**39**) were prepared by glucosylation using 2,3,4,6-tetra-*O*-benzyl-*D*-glucosyl acetate and TMS triflate as catalyst, and the *trans*-decalin *cis*-diol. The products were obtained in the proportions 83:5 with 12% of β-linked products.[60]



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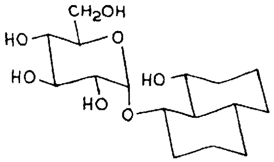
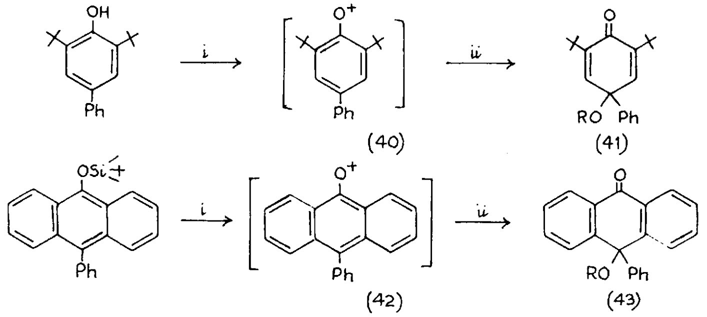


(39)

The electrochemically-produced phenoxonium ions (**40**), (**42**), with free sugar derivatives give cyclohexadienone glycosides (**41**) and (**43**) which can be deprotected by either electrochemical or chemical methods (Scheme 14).[61]



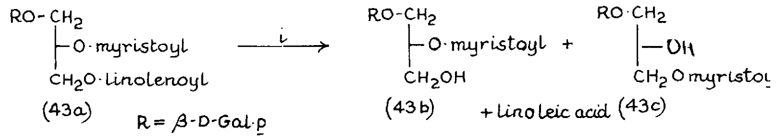
R = tetra-O-benzoyl-β-D-glucopyranosyl

Reagents: i, Anodic oxidation (+600 → +1200 mV, Et_4NBr, 2,6-lutidine, CH_2Cl_2);
ii, tetra-O-benzoyl-β-D-glucose

Scheme 14

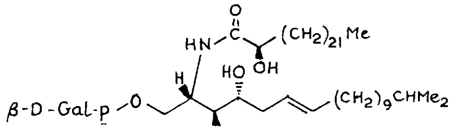
1.2 Synthesis of Glycosylated Natural Products.-A simple method for the synthesis of glycosyl diglycerides uses sugar peracetates and isopropylidene-(±)-glycerol in the presence of Lewis acids in the initial step. For example, 1-*O*-β-*D*-galactopyranosylglycerol was made in this way and hence the dipalmitoyl product.[62] In related work (R)- and (S)-2,3-di-*O*-palmitoyl-1-*O*-galactosyl and glucosyl-glycerols were separately made as mimics of bacterial cell wall compounds. The glucosyl pair showed stronger anti-inflammatory properties. Glycosylations were carried out using acetylglycosyl bromides with iodine, silver oxide as catalysts.[63] Lipase action on the diester (**43a**) resulted in loss of linoleic acid and production of the two myristoyl glycerides (**43b**) and (**43c**) (Scheme 15).[64] Also in the field of glycosylated polyols, 1,3,4-tri-*O*-benzyl-5-*O*-pivaloyl-*D*-ribitol was glycosylated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-*D*-ribose in the eventual synthesis of the spacer-containing trimer unit of *E. coli* K100 polymer.[65] A reference to the synthesis of an *L*-rhamnosylribitol derivative is given in Chapter 18, as also are references to a report on the *O*-(2-acetamido-2-deoxy-α-*D*-galactosyl)-*myo*-inositol of human pregnancy urine and on glycosylated phosphatidyl inositols.

The cerebroside (**43d**) was elaborated following synthesis of the aglycone from 1,2-anhydro-3-*O*-benzyl-*L*-glycerol,[66] and in related work the sphingenine derivative (**44**)[67] and the ovi-position deterring pheromone (**45**) of a fruit fly[68] have been prepared.

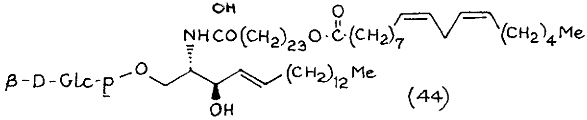


Reagent : i, Lipase

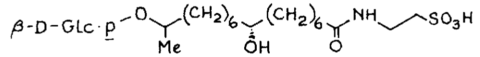
Scheme 15



(43d)



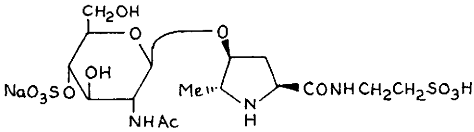
(44)

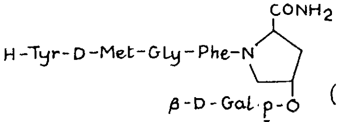


(45)

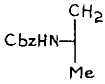
Continuing interest in glycopeptides has led to further preparations of glycosylated amino acids and peptides. 3-*O*-β-*D*-Galactosyl-*L*-serine has been made by enzyme-catalysed transfer from lactose. The *N*-butoxycarbony methyl ester was the best serine-drived substrate.[69, 70] Similar work led to the *O*-β-*D*-glucoside and -xyloside of the *N*-acetyl methyl ester.[71] *N*-Fmoc-protected hydroxyl-containing amino acids condensed with penta-*O*-acetyl-β-*D*-galactopyranose in the presence of boron trifluoride resulted in satisfactory β-glycosylation.[72] Another approach involved the use of the Schiff base formed between benzophenone and serine methylester which was effectively condensed with tetra-*O*-acetyl-α-*D*-glucosyl bromide using silver triflate as activator. Threonine could be glycosylated similarly. It was considered that the hydroxyl groups were activated by hydrogen bonding changes caused by the imine group.[73] For making 2-deoxyglycosyl serine and serine-containing peptides the *N*-iodosuccinimide method, involving acetylated glycals, has been successfully employed with *N*-Fmoc-protected benzyl esters.[74]

Deoxybulgecin A (**46**) has been synthesized[75] as have the glycosyl enkephalin derivatives (**47**) and glycosylamine analgues.[76]


(46)

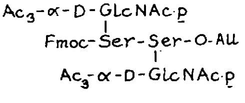

(47)

Other glycosylated peptides to have been prepared are: 3,4-di-*O*-methyl-α-***D***-rhamnose bonded to the alaninol derivative (**48**) *en route* to ***D***-Phe-***D***-*allo*-Thr-***D***-Ala-***L***-Alaninol-*O*-(3,4-di-*O*-Me-Rha*p*), a structural component of glycopeptidolipids of some *Mycobacteria*;[77] two new tuftsin derivatives containing GalNAc*p* residues α- or β-linked to the threonine hydroxyl group, and the glycosylated undecapeptide corresponding to the tuftsin regions of the heavy chains of IgG;[78] glycosylated insulins produced by reaction with glucose in non-aqueous solvents (and, thereby, conceivably *N*-linked compounds),[79] and the antifreeze glycopeptides (**49**) produced by solid-phase procedures.[80]

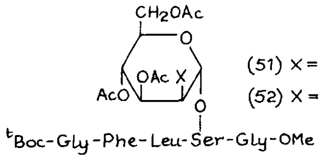

$\mathrm{CbzHN}-\underset{\mathrm{Me}}{\overset{\mathrm{CH_2OH}}{|}}$ (48)

$\mathrm{H{-}[Tyr{-}(\beta{-}D{-}Gal\text{-}\underline{p}){-}Ala{-}Ala]_{n}{-}OH}$ (49) $n = 2\text{-}4, 7$

The acetylated *O*-linked glycopeptide component (**50**) of glycophorin A was prepared by coupling glycosylated serine units, these being made by use of 2-azidoglycosyl bromide and partly protected amino acids.[81] Compounds (**51**) and hence (**52**) and related galactose and disaccharide derivatives were made by the glycal-*N*-iodosuccinimide method as part of a study of glycosylated peptides and cyclopeptides.[82]


$\mathrm{Fmoc{-}\overset{Ac_3{-}\alpha{-}D{-}GlcNAc\text{-}\underline{p}}{\overset{|}{Ser}}{-}\underset{Ac_3{-}\alpha{-}D{-}GlcNAc\text{-}\underline{p}}{\underset{|}{Ser}}{-}O{-}All}$

(50)


(51) X = I

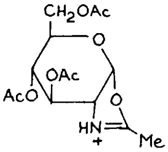
(52) X = H

Separate glucosylation and galactosylation of hydroxyproline using peracetates and boron trifluoride etherate as catalyst and solid-phase procedures led to compounds (**53**) and (**54**),[83] and a further solid-phase process involved treating resin-bonded peptides with the glycosylating ion (**55**) which was obtained from the amino sugar peracetate activated by use of TMSO triflate.[84]

$\underset{R}{\text{Tyr-Pro-Phe-Hyp-NH}_2}$

(**53**) R = D-Glc*p*

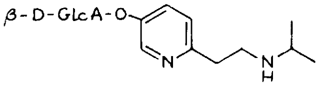
(**54**) R = D-Gal*p*



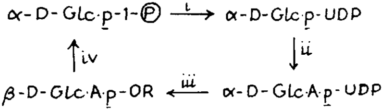
(**55**)

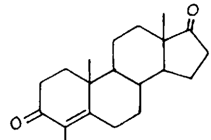
A review has been published on the glycosidation of mono-, sesqui-, di- and triterpenes and on the biological properties of the products.[85] Glycosidic members of the family to have been made are the β-*D*-glucopyranosides of citronellol, geraniol, menthol and borneol,[86] various mono- and di-saccharide glycosides of oleanolic and ursolic acids,[87]the trichothecene deoxynivalenol,[88] zearelenone,[89] and the 3-β-*D*-glucuronides of 5α-cortol-20α- and β- and 5α-cortolone-20α- and 20β.[90] A rather unusual study was made of the synthesis of the 2′-*O*-β-glycopyranosides of phloretin involving the *L*-enantiomers of fucose, 6-deoxy-β-glucose and β-glucose whose inhibitory actions on sugar transport in the rat small intestine were studied.[91]

Enzymic synthesis of the β-*D*-glucuronides (**56**) and (**57**) were completed in 65 and 28% yield, respectively, using animal liver homogenates and glucose-1-phosphate as starting material. The catalytic cycle is shown in Scheme 16.[92]



(56)





(57)

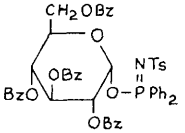
Reagents: i, UDP-pyrophosphorylase + UDP; ii, UDPG-dehydrogenase + NAD; iii, UDP-glucuronosyltransferase + ROH; iv, Pyruvate kinase + phosphoenolpyruvate

Scheme 16

A review, dealing mostly with structure and conformation, has appeared on the flavonoid glycosides of the anthocyanins.[93]

Of note is a new glycosidation method applicable to the preparation of lignan glycosides for which standard methods are not suitable. The P,P-diphenyl-(*N*-

tosyl)phosphinimidate (**58**) with the corresponding alcohol gave (**59**) in 74% yield when boron trifluoride was used as catalyst. Compound (**60**) was applicable for the production of 2-amino analogues.[94]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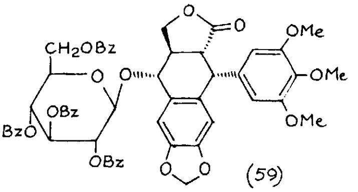
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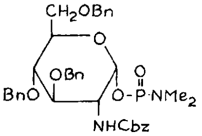
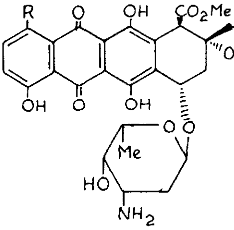
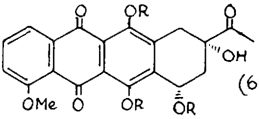

(60)

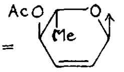
The isorhodomycins (**61**) and (**62**) were made by use of a 1-*O*-TMS sugar derivative as glycosylating agent,[95] and the daunomycinone derivatives (**63**) and (**64**) were prepared from acetylated glycals using boron trifluoride as catalyst. Iodoglycosylations of β-rhodomycinone and related compounds were assessed, being satisfactory in some cases (eg rhodomycinone) but not in others (eg ε-isorhodomycinone).[96] Glycosylated derivatives of other anthracyclins are noted in Chapters 11 and 19. In the latter a stereoselective synthesis of (+)-daunomycinone is referred to in which a butadiene glycoside is used as a chiral auxiliary in a Diels Alder process.


(61) R = H

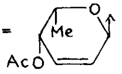
(62) R = OH



(63) R =

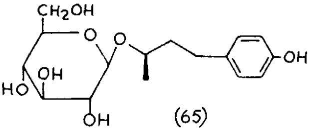


(64) R =

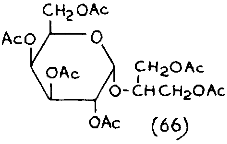


1.3 O-Glycosides Isolated from Natural Products.—This section should not be considered to be comprehensive; only a few compounds showing interesting features are referred to.

A review has appeared on cyanogenic glycosides,[97] and (S)-2-methylbut-1-yl β-*D*-glucopyranoside[98] and compound (**65**)[99] have been isolated from the leaves of *B. plumosus* and from rhododendrin plants, respectively. An X-ray analysis of the latter determined the configuration at C-2′, and the compound showed hepatoprotective activity against two hepatotoxins in rats. The absolute configurations of the previously known (+)- and (-)-rhododendrol follow. Likewise, the X-ray structure of hexa-acetate (**66**), isolated from the plant *R. brittoniana*, has been reported.[100]

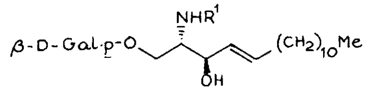


(65)

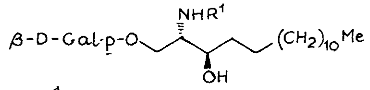


(66)

The galactosyl cerebrosides (**67, a-f**) and (**68, a-f**) have been isolated from bullfrog brain tissue;[101] likewise compounds (**69, a-c**) and (**70, a-c**) from a starfish.[102]



(67)



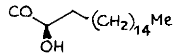
(68)

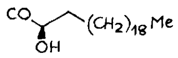
R^1

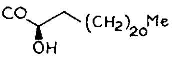
(a) $CO(CH_2)_{16}Me$

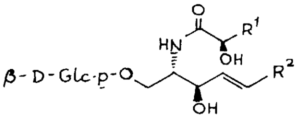
(b) $CO(CH_2)_{20}Me$

(c) $CO(CH_2)_{22}Me$

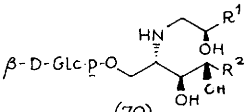
(d)

$COCH(OH)CH_2(CH_2)_{14}Me$

(e)

$COCH(OH)CH_2(CH_2)_{18}Me$

(f)

$COCH(OH)CH_2(CH_2)_{20}Me$



(69)

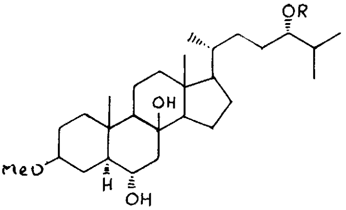


(70)

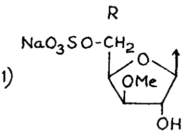
		R^1	R^2
(69)	(a)	$(CH_2)_{12}Me$	$(CH_2)_7CH=CH(CH_2)_7Me$
	(b)	$(CH_2)_{13}Me$	$(CH_2)_7CH=CH(CH_2)_7Me$
	(c)	$(CH_2)_{13}Me$	$(CH_2)_3CH=CH(CH_2)_{11}Me$
(70)	(a)	$(CH_2)_{12}Me$	$(CH_2)_8CH=CH(CH_2)_7Me$
	(b)	$(CH_2)_{13}Me$	$(CH_2)_{11}CHMe(CH_2)_2Me$
	(c)	$(CH_2)_{12}CH=CH(CH_2)_7Me$	$(CH_2)_{12}Me$

Starfish have also provided the steroidal pentoside sulfates (**71-74**).[103] 6-Deoxy-2-*O*-(6-deoxy-β-*D*-glucopyranosyl)-β-*D*-glucopyranose has been found as a glycoside in a starfish,[103A] and 2,6-dideoxy-4-*O*-(6-deoxy-3-*O*-methyl-β-*D*-glucopyranosyl)-3-*O*-methyl-*D*-*ribo*-hexose and related tri- and tetra-saccharides have been isolated from the roots of *Dregea sinensis*.[103B]

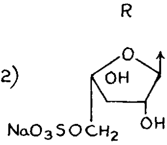
1.4 Synthesis of Disaccharides and their Derivatives.-Remarkably little appears to have been published in 1991 on the chemistry of non-reducing disaccharides. However, the transformation of [1-^{13}C]-*D*-glucose to [1,1-$^{13}C_2$]-*D*-trehalose *in vivo* within the cockroach *Gryllodes sigillatus* has been monitored by ^{13}C-n.m.r. methods.[104]



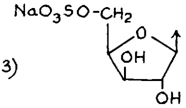
(71)



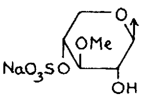
(72)



(73)



(74)

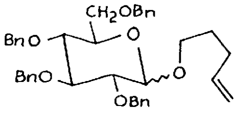


As usual, reducing disaccharide chemistry is treated according to the nature of the non-reducing moieties, but initially some references to matters of general significance are reported. A review entitled "Disaccharides" covered analytical, chromatographic, biochemical and historical aspects of the subject.[105] A further review dealt with the advantages and limitations of solid-phase methods in di- and oligo-saccharide synthesis.[106]

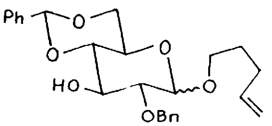
Polymers made of styrene units each having an amide-linked disaccharide (lactose, melibiose, cellobiose, maltose) have been made and used for studying the receptors for these oligosaccharides on hepatocyte cellular membranes.[107]

1,2-*trans*-Glycosyl thiocyanates with non-participating groups at *O*-2, on reaction with sugar trityl ethers in the presence of trityl perchlorate, gave 1,2-*cis*-related disaccharides specifically in what promises to be a very useful development.[108] A reaction to be compared with this for the synthesis of 1,2-*cis*-related compounds involves the use of perbenzylated 2-pyridyl-1-thiohexoside donors and sugar alcohol acceptors with methyl iodide as activator (Vol. 23, p. 25, ref. 78): yields were in the range 56-87%.[109] The same authors have also studied the rates of hydrolysis of and rates of glycosylation by 2-pyridyl 1-thioglucopyranosides bearing differing groups at O-2. Rates of both processes reduced in the order of the groups at O-2: OBu>NHAc>OBz>OAc which bear out Fraser-Reid's "armed"/"disarmed" insight and led to rational synthesis of glucotriose and tetraose compounds (see later).[110]

Fraser-Reid's group have now also reported theoretical studies as well as experimental observations on the reactivities of acetalated and nonacetalated pyranosyl glycosyl donors. The acetals rigidify the rings making acetalated pentenyl glycosides more stable to hydrolysis and less reactive as glycosyl donors on activation. These observations were then used to advantage in disaccharide synthesis. Thus, the unacetalated (**74a**) glycosylated the free hydroxyl gorup of the acetalated analogue (**74b**) without the latter undergoing self-condensation. Similar results were obtained when the corresponding benzylated galactoside and -mannoside were caused to react with corresponding 3,4- and 2,3-acetalated compounds, respectively.[111]

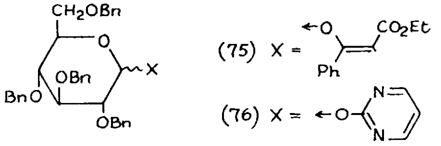


(74a)



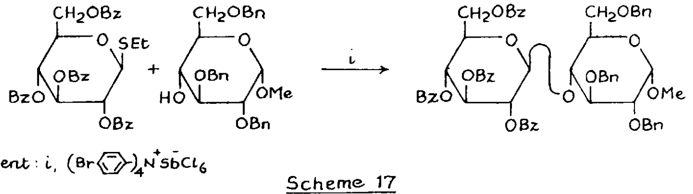
(74b)

In imaginative new work Schmidt's group have examined the glycosyl donors (**75**) and (**76**) and their *galacto*-analgoues with TMS triflate activation in acetonitrile or propionitrile as solvent in couplings with 4- and 6-unprotected hexose derivatives. Good β-selectivity was observed with (**76**) which can be used at -80° thereby permitting the formation of solvent-containing nitrilium intermediates which react to give the β-products.[112]



Tetra-*O*-benzyl-β-*D*-glucopyranosyl fluoride coupled with various monosaccharide secondary alcohols gave 50-80% yields of disaccharidses with good to excellent α-selectivity and appears to represent a useful procedure.[112a]

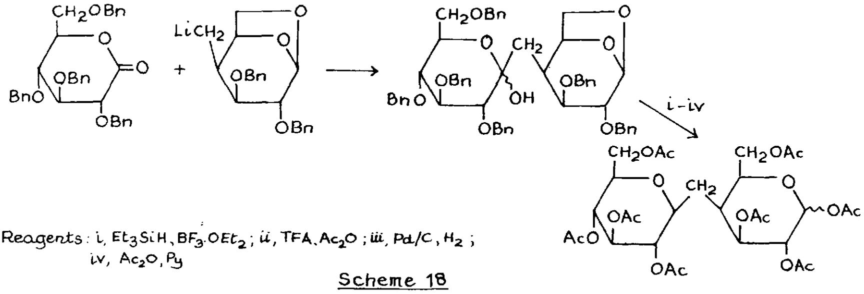
A further report of note relates to the reaction of ethylthio glycosides with "one electron transfer reagents" eg. tetrakis(*p*-bromophenyl)ammonium hexachloroantimonate as activators. Several examples were given (see Scheme 17 for a representative case); yields were >80% and anomeric ratios of products favoured β-linked disaccharides very significantly.[113]



Scheme 17

C-Linked disaccharides continue to be of considerable current interest. A *D*-glucosyl-

D-galactose analogue has been produced. (See Scheme 18 for outline).[114] Further related work is referred to under *C*-glycosides.

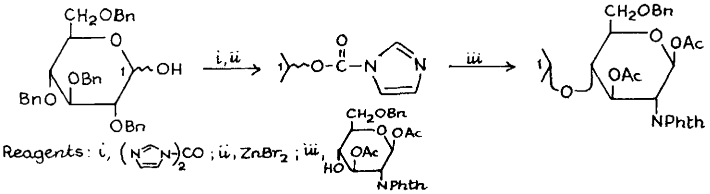


Reagents: i, Et_3SiH, $BF_3.OEt_2$; ii, TFA, Ac_2O; iii, Pd/C, H_2; iv, Ac_2O, Py

Scheme 18

2,3,4,6-Tetra-*O*-benzyl-*D*-glucose 1-*O*-α- or β-trichloroacetimidate with alcohols in nitrile solvents with TMS triflate as catalyst react at -40° to give 70-90% yields of disaccharides (from primary or secondary alchols) with β:α ratios of 8-24:1 by way, it is proposed, of intermediate ions which involve strong association with the solvent. With mannose disaccharides α:β ratios are about 1:1.[115]

In interesting contrast to the above, 2,3,4,6-tetra-*O*-benzyl-*D*-glucose, converted to a (1-imidazolylcarbonyl derivative, gave modest yields of mainly α-linked disaccharides when treated with one molar equivalent of alcohol and zinc bromide (Scheme 19).[116]

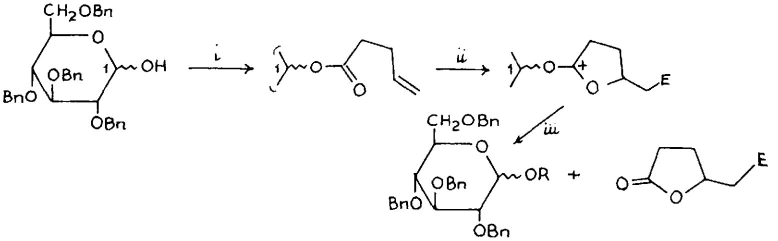


Reagents: i, $(N\diagup N)_2CO$; ii, $ZnBr_2$; iii, [CH$_2$OBn, OAc, OAc, HO, NPhth]

Scheme 19

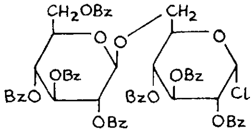
Glucosyl disaccharides of mixed anomeric configurations were made by exploiting the instability of pentenoyl groups to soft electrophiles (Scheme 20).[117]

Amygdalin has served as the source of the gentiobiose acceptors and donors (**77-81**) suitable for incorporation into higher saccharides, the transformations being carried out with standard reagents.[118] Curdlan (a microbial polysaccharide), on the other hand, was the source of laminaribiose α- and β-penta-acetate which were made by enzymic hydrolysis followed by appropriate acetylations.[119]



Reagents: i, $CH_2{=}CH(CH_2)_2CO_2H$, $\rangle\!-N{=}C{=}N\!-\!\langle$; ii, di-sym-collidine, iodonium perchlorate, or NIS, MsOH, or $\langle{}^{S}_{S}\rangle^{+}\,BF_4^-$; iii, ROH

Scheme 20



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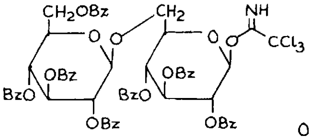

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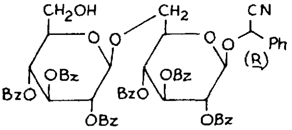

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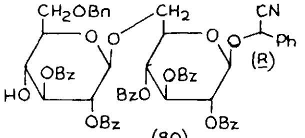

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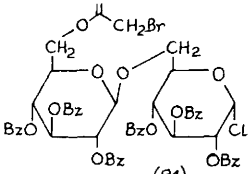
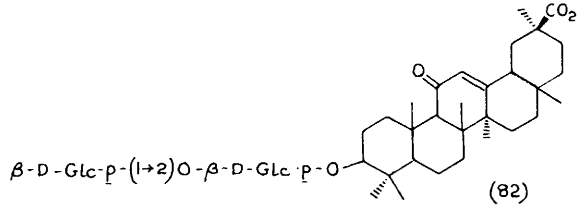


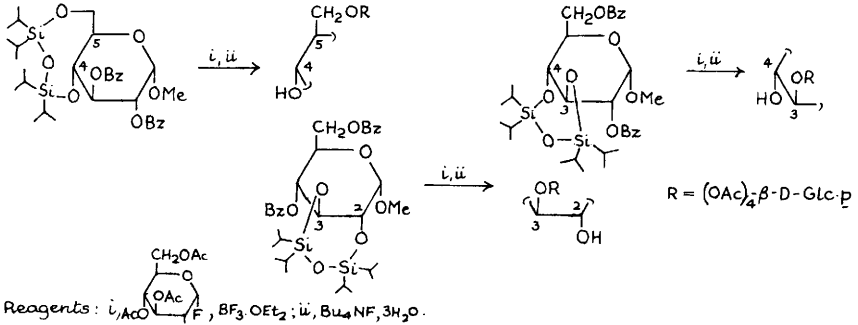
(81)

Also in the field of glucosyl disaccharides the 1,2-linked derivative (**82**) of glycyrrhizin was synthesized together with seven analogues comprising different disaccharides, and their cytoprotective effects on CCl_4-induced hepatic injury indicated that a terminal *D*-glucuronosyl unit is an important feature for positive activity.[120]



(82)

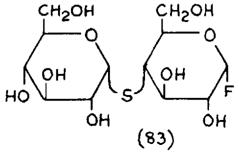
Different 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPS) derivatives of methyl α-*D*-glucopyranoside have been used to give access to 1,6- and 1,3-β-linked glucobioses (Scheme 21); in the last case substitution would have been favoured at O-2 in the absence of the cyclic protecting group.[121]



Scheme 21

2-Acrylamidoethyl 3-*O*-(α-*D*-glucopyranosyl and 2-*O*-acetyl-α-*D*-glucopyranosyl)-α-*D*-mannopyranoside have been made for conversion into artificial antigens,[112] and biological interests were also behind an investigation into the hydrolysis of sixteen (mainly deoxy and deoxyhalo) cellobiose derivatives by β-glucosidase of *Aspergillus niger.* The OH group at C-2′,3′,4′ were vital for activity.[123]

Reactions carried out on disaccharide derivatives included the conversion of peracetates to 1-phenylthio-β-derivatives by use of phase-transfer methods[124] and the epimerization at C-2 by calcium^{2+}-amine systems ($CaCl_2.2H_2O$, Et_3N, for example). By this means maltose, lactose, isomaltose and melibiose were converted into the corresponding glucosyl-*D*-mannoses.[125] An extensive range of variously substituted maltosyl fluorides have been made from maltose derivatives as substrates for cyclodextrin transferase. Only the 6′-methyl ether and 6′-acetate were transformed into cyclic products. In the course of the work the thio-derivatives (**83**) and (**84**) were made.[126]



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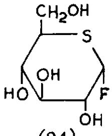
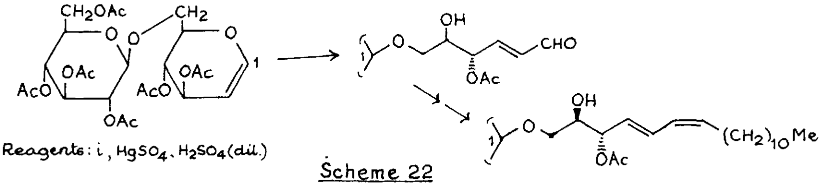


(84)

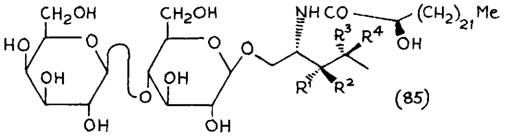
A convenient approach to the synthesis of sphingoglycolipids by acid-catalysed decylization of hexa-*O*-acetyl-*D*-gentiobal is illustrated in Scheme 22.[127] A report of the synthesis of several *carbo*-glucose-based disaccharides is referred to in Chapter 18.



Scheme 22

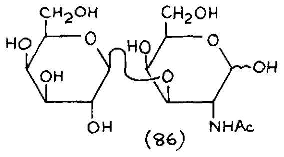
In the area of *D*-galactosyl disaccharides, transferase enzymes have been studied by several groups. The acceptor specificity of the bovine milk enzyme has been subjected to a detailed study using 35 examples.[128] The same group have reported separately on the 4-*O*-β-*D*-galactopyranosylation of *D*-glucal, 1-deoxynojirimycin and 5-thioglucose,[129] and several other acceptors and have described the resulting modified disaccharides.[130] The *E. coli* enzyme has been immobilized on cellulose beads. The product of linking via azo bonds showed the highest activity and thermal stability, and was used for the synthesis of disaccharide methyl glycosides.[131]

Acetobromolactose has been used to make 2-*O*-β-lactosyl glycerol, 1,2-di-*O*-β-lactosyl-(R,S)-glycerol and the trisubstituted glycerol.[132] Lactose has also been used to make the ceramide derivatives (**85, a-d**), the first being spectroscopically almost identical to natural acanthalactoside A.[133] Several sulfates of lactose are referred to in Chapter 7.

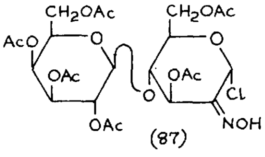


(85)

	R^1	R^2	R^3	R^4
a	OH	H	H	H
b	H	OH	H	H
c	H	H	OH	H
d	H	H	H	OH



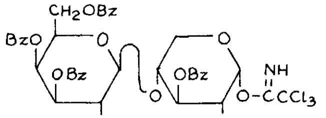
(86)



(87)

The amino-disaccharide (**86**) was made by a displacement of a triflyloxy group from a derivative of the corresponding galactosyl glucosamine,[134] and the lactose based 2-oximino-glycosyl chloride (**87**) has been used as the starting material to produce *O*-linked serine glycosides with the *α-gluco-* and *β-manno-* configurations and the 2-acetamido-2-deoxy analogues. Allylic displacements applied to the oximino-glycosides permitted introduction of azido-groups at C-3.[135]

S-Ethyl tetra-*O*-benzyl-1-thio-β-*D*-galactoside, an "armed" glycosylating agent, was condensed with *S*-ethyl 2,4-di-*O*-benzoyl-α-*L*-rhamnoside, a "disarmed" acceptor, using iodonium dicollidine perchlorate as activator, in a synthesis of the phosphate α-*D*-Glc*p*-(1→3)-α-*L*-Rha*p*-1-$PO_4^{=}$.[136] In like fashion, *S*-methyl 3,4-*O*-isopropylidene-2,6-*O*-bis(*p*-methyloxybenzyl)-β-*D*-galactoside, activated by copper(II) bromide and tetrabutylammonium bromide, was used to give an α-1,6-linked galactobiose exclusively.[137] Coupling of the galactosylxylose derivative (**88**) with a differentially substituted serine-glycine dipeptide gave a product which was used to make the hexamer region (**89**) of certain proteoglycans.[138]



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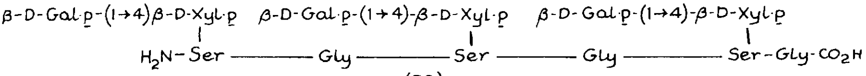
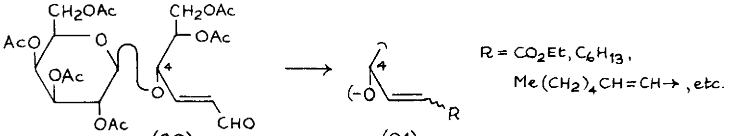


$$\begin{array}{ccccccccc} \beta\text{-D-Gal}p\text{-}(1\to4)\beta\text{-D-Xyl}p & & & & \beta\text{-D-Gal}p\text{-}(1\to4)\text{-}\beta\text{-D-Xyl}p & & & & \beta\text{-D-Gal}p\text{-}(1\to4)\text{-}\beta\text{-D-Xyl}p \\ | & & & & | & & & & | \\ H_2N\text{-Ser} & \text{———} & \text{Gly} & \text{———} & \text{Ser} & \text{———} & \text{Gly} & \text{———} & \text{Ser-Gly-}CO_2H \end{array}$$

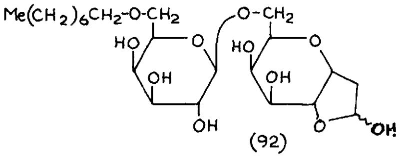
(89)

Acid-catalysed cleavage of hexa-*O*-acetyl-*D*-lactal followed by acetoysis gave the aldehyde (**90**) from which several alkenes (**91**) were derived.[139]

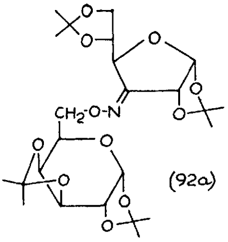


(90) (91)

Compound (**92**) was made by a glycosylation involving a 6-*O*-octylglycosyl bromide and a *C*-allyl galactoside derivative, followed by reductive ozonolysis of the allyl group. Its use was as an amphiphilic liposaccharide reagent.[140] Further work (cf. *Carbohydr. Res.*, 1990, *204*, 145) has appeared on the synthesis of several substituted disaccharide analogues (eg **92a**) linked by oximino interglycosidic bonding.

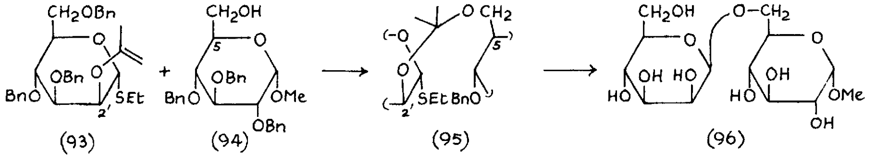


(92)



(92a)

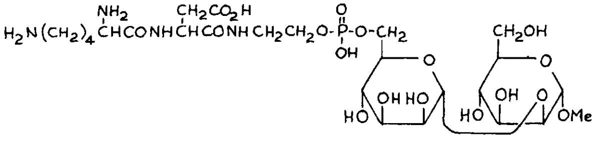
A noteworthy synthesis of β-*D*-mannopyranosides uses the novel but timely intramolecular approach. The 2-*O*-propenyl thioglycoside (**93**) was condensed with the 6-hydroxy acceptor (**94**) to give the bridged disaccharide (**95**) which, on activation of the glycosylating unit followed by quenching with water, gave the benzylated methyl 6-*O*-β-*D*-mannopyranosyl-α-*D*-glucopyranoside (**96**, Scheme 23). We venture to identify this paper as a landmark in glycoside and disaccharide synthesis. Methyl 4-*O*-β-*D*-mannopyranosyl-α-*D*-glucopyranoside was made in like manner.[141]



Reagents: i, TsOH, −40°; ii, NIS; iii, H_2O; iv, H_2, Pd/C

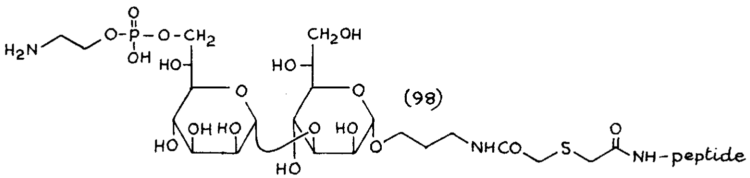
Scheme 23

5-*O*-α-*D*-Mannopyranosyl-KDO was made by conventional methods and conformational analysis of the calcium salt was carried out.[141a]

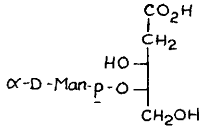


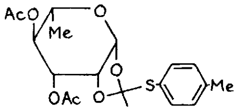
(97)

Methyl 2-*O*-α-*D*-mannopyranosyl-α-*D*-mannopyranoside was made by more conventional methods involving an ethylthio glycosylating agent, and detailed conformational analyses were carried out to assess the flexibility of the compound about the glycosidic bond.[142] The peptidyl phosphate (**97**) of the same disaccharide glycoside has been made,[143] and then the related heptobiose-based potential vaccine against *Neirseria meningitides* (**98**).[144]


(98)

In the area of 1,4-linked mannosyl disaccharides α-***D***-Man*p*-(1→4)-*O*-α-***D***-GlcNH$_2$-(1→6)-1D-*myo*-inositol[145] and 2-deoxy-4-*O*-α- and β-***D***-mannopyranosyl-***L***-*erythro*-pentonic acid (**98a**)[146] have been prepared, the latter by oxidation of the corresponding disaccharide. It was required to assist in the structural determination of the endotoxin of *Bordetella pertussis*.


(98a)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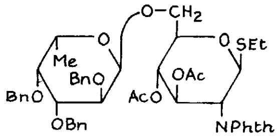
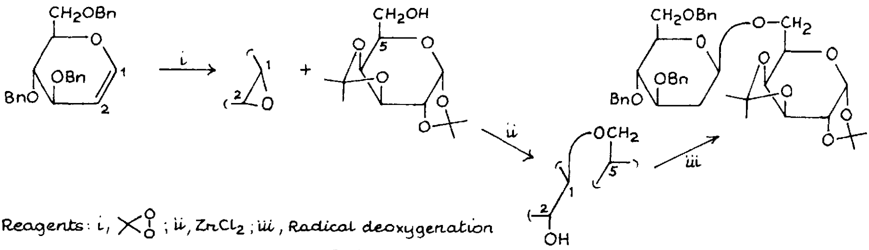

(100)

In the area of deoxy-sugar disaccharides ***L***-rhamnose compounds have been given considerable attention, 2-*O*-α-***L***-rhamnosyl-***L***-rhamnose,[147] 2-*O*-methyl-3-*O*-(α-***L***-rhamnosyl)-***L***-rhamnose,[148] and 3-*O*-α-***L***-rhamnosyl-***D***-glucuronic acid[149] having been prepared. The 1,2-thio-orthoester (**99**) has been used to give rhamnosylated 1,6-linked disaccharides either directly or via exchanged orthoesters which underwent rearrangement. Activation of (**99**) with iodonium dicollidene perchlorate gave the exchanged orthoesters whereas NIS led to the disaccharides.[150] Allyl 2-*O*-methyl-4-*O*-(4-*O*-methyl-α-***L***-rhamnosyl α-***L***-fucoside and similar disaccharides having 1,3-linkages have been made and then ozonized and coupled to bovine serum albumin to give epitopes of mycobacterial glycolipid antigens.[151]

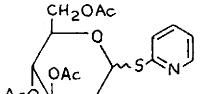
This last paper also described allyl 3-*O*-(2,3-di-*O*-methyl-α-***L***-fucopyranosyl)-α-***D***-rhamnopyranoside, and fucosylated disaccharides with fucose linked to ***D***-glucose (O-2, O-3, O-6), ***D***-galactose (O-6), and ***L***-fucose (O-2) were made and their ^{1}H and ^{13}C-n.mr. spectra were measured and correlated with conformations determined by HSEA methods.[152] *S*-Ethyl 2-*O*-methyl-β-***L***-fucoside derivatives, activated with iodonium dicollidene perchlorate, were used to give α-linked disaccharides. In this paper the arming, disarming effects of various substituents were assessed.[153] The disaccharide building block (**100**) was itself made using an *S*-ethyl thioglycosylating agent.[154]



Reagents: i, $\times\!\!\langle^{O}_{O}$; ii, $ZnCl_2$; iii, Radical deoxygenation

Scheme 24

2-Deoxy-β-*D*-*arabino*-hexopyranosides have been made by the elegant deoxygenation route illustrated in Scheme 24. Aryl compounds as well as the dissaccharide shown were described.[155] Tri-*O*-acetyl-*D*-glucal, treated with 2-mercaptopyridine and an acidic catalyst, gave the glycosylating agent (**101**) which, with 3,4-di-*O*-benzoyl-*D*-glucal, afforded the α-linked (**102**) which, by similar methods, also leads to α-linked trimers. Similar results were achieved in the *D*-galactal series.[156]



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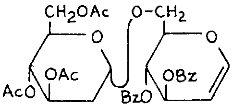

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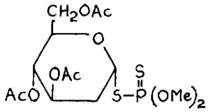

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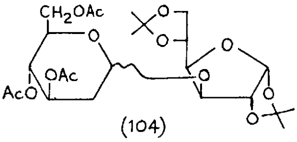
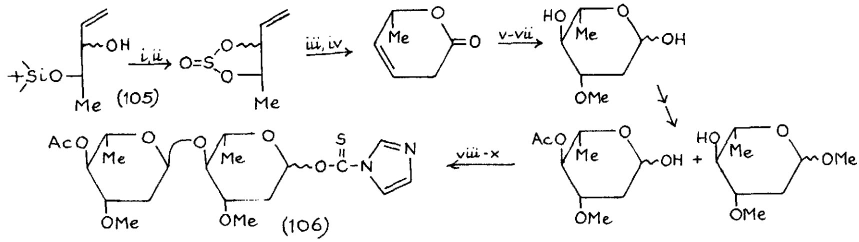


(104)

3,4,6-Tri-*O*-acetyl-2-deoxy-α- and β-*D*-*arabino*-hexopyranosyl fluoride (and corresponding 2-bromo compounds) were assessed as glycosyl donors in disaccharide syntheses, and solvent was found to have a large effect on the stereochemistry of the products. In hexane products of inversion dominated; in ether double inversion dominated, the solvent initiating reaction.[157] The 2-deoxyglycosyl phosphodithioates, e.g. (**103**), made by addition of dithiodialkyl phosphates to tri-*O*-acetyl-*D*-glucal, on activation with silver fluoride, gave the disaccharides, e.g. (**104**), the α,β-ratio being 2.5:1 and the yield 90%.[158] 2′-Deoxy-*N*-acetyllactosamine was made using UDP-2-deoxygalactose and galactosyl transferase, the substrate being derived form UDP-2-deoxyglucose by UDP galactose 4-epimerase. This is the first case of enzymic synthesis of a 2′-deoxydisaccharide and also of the use of a modified donor.[159]

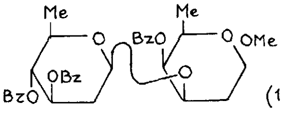
In the field of dideoxyhexose disaccharides compound (**106**) was made from the lactaldehyde-based (**105**) (Scheme 25) and coupled with the avermectin B1a aglycone to complete the synthesis of the natural product.[160]



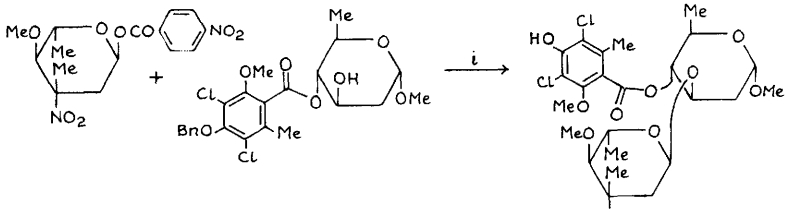
Reagents: i, MeOH, H^+; ii, $SOCl_2$; iii, $Fe_2(CO)_9$, ultrasound; iv, CO (230 atmos); v,  ; vi, Bu^i_2AlH; vii, MeOH, Et_3N; viii, Im_2CO, $AgClO_4$; ix, $LiEt_3BH$; x, Im_2CS

Scheme 25

A series of avermectin analogues have been prepared with spacer arms between the disaccharide and the aglycone. Some of the products showed considerable bioactivity.[161] This disaccharide (**107**) and epimers at C-4 and C-3′ were made for use in the synthesis of mithramycin and related antitumour agents,[162] and the AB disaccharide of olivomycin A, 2,6-dideoxy-3-*O*-(2,6-dideoxy-α-*D*-*lyxo*-hexosyl)-*D*-*lyxo*-hexose was produced using the highly selective synthesis of 2-deoxyhexoses from 4-deoxy-2,3-*O*-isopropylidene-*D*-threose (Chapter 12).[163]



(107)



Reagent: i, TMS·OTf

Scheme 26

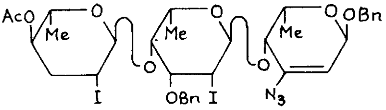
The terminal AB unit of the everninomicins was made as indicated in Scheme 26.[164]

Approaches to the C-B-A unit of dihydroaclacinomycin have involved compound (**108**) which was made by NIS-coupling.[165]

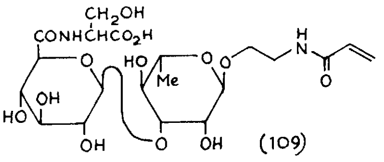
Other data on di- and tri-deoxy compounds are contained in Chapter 12.

As is to be expected, activity in the field of acidic derivatives has remained high. Synthesis has been reported of benzyl 3-*O*-β-*D*-glucuronosyl-β-*D*-galactopyanoside and its 4-, 6-sulfates and 4,6-disulfate,[166] and the *L*-serine-linked amide derivative (**109**) has also been described.[149] The corresponding heptulose derivative was condensed with various alcohols using pyridinium tosylate as catalyst to give disaccharides, and the liberated C-1 primary alcohol groups were oxidized to afford α-KDO compounds such as (**110**).[167]

Sialyl transferases have been used to give the β-*p*-nitrophenyl glycosides of α-Neu5Ac-(2→3)-β-*D*-Gal and α-Neu5Ac-(2→6)-β-*D*-Gal with CMP-Neu5Nc as transferring agent,[168] and the methyl analogue of the latter disaccharide was also made using an immobilized enzyme. Other neuraminic acid compounds were made, yields being in the region of 25%.[169] The xanthate (**111**), activated by TMS triflate, gave satisfactory α-linkage to the free 6-position of otherwise substituted galactopyanosyl compounds,[170] and also gave 40% 1,3-α-linked product when used with benzyl 6-*O*-benzyl-β-*D*-galactopyranoside.[171] The acetylated *S*-methyl glycosidic analogue of (**111**), activated with NIS, triflic acid in acetonitrile gave good α-selectivity in condensations with various partly substituted galactopyranosides.[172] Products of condensation of neuraminic acid to the primary position of *D*-glucose and -galactose having deuterium diastereospecifically substituted at C-6 have been conformationally examined by ^{1}H n.m.r. spectroscopy in order to determine the preferred rotamer states about C-5-C-6.[173]



(108)



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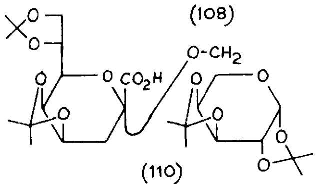

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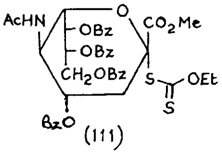
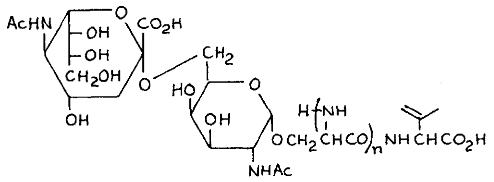


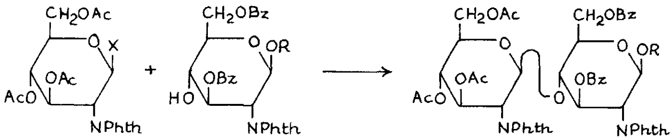
(111)

Di- and tri-meric sialosyl Tn epitopes (partial structures of glycophorin A) (**112**) have been made by appropriate use of substituted 2-azido-2-deoxygalactosyl fluoride and 2-thiophenylsialyl bromide as appropriate[174]



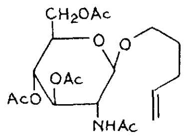
(112) n = 2, 3

Glycosylations with 2-aminohexosyl reagents continue their prominence. A very useful systematic study of the glycosylating agents **(113, a-f)**, when condensed with benzyl or allyl 3,6-di-*O*-benzoyl-2-deoxy-2-(-*N*-phthalloylamino)-β-*D*-glucopyranoside, is summarized in Scheme 27.[175]



X	$O\text{-}\overset{NH}{\overset{\|}{C}}\text{-}CCl_3$	Br	Cl	F	SEt	OAc
(113)	a	b	c	d	e	f
Activator	$BF_3.OEt_2$	AgOTf		TMSOTf	DMTST	TMSOTf.
Yield (%)	69	60	62	44	57	18

Scheme 27



(114)

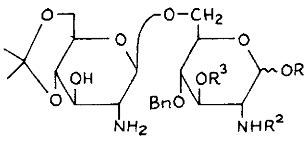
The phenylselenyl analogue of **(113e)**, activated with silver triflate, gave 84% yield of the disaccharide when coupled with *S*-ethyl-2,3,4-tri-*O*-benzyl-1-thio-β-*D*-glucopyranoside.[176] Related glycosylations with 1,3,4,6-tetra-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy-β-*D*-glucopyranose of variously substituted 1,6-anhydro-β-*D*-mamnopyranose have been reported.[177] The pent-4-enyl glycoside **(114)**, activated by epoxidation followed by trimethylsilyltriflate treatment, also gave β-products. The disaccharide involving methyl

2,3,4-tri-*O*-benzyl-α-*D*-glucopyranoside was made in this way.[178]

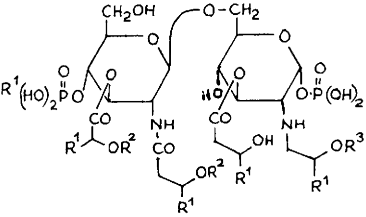
A modification of syntheses of this type involved attachment of the acceptors to polymers and glycosylations with the bromide **(113b)** in the presence of silver salts. Methyl 3-*O*-benzoyl-α-*D*-galactopyranoside, attached through O-2, gave the 6- and the 4,6-substituted products. In the alternative way a polymer-supported glucosamine derivative was galactosylated at O-4.[179]

N-Acetylglucosamine β-(1→3) linked to galactose and N-acetylgalactosamine α-(1→3) linked to the same sugar have been by made use of glycosidases from the mollusc *Chamelea gallina*. The same source provided an enzyme for the efficient synthesis of methyl 6-*O*-α-*L*-fucopyanosyl-β-*D*-galactopyranoside.[180]

Three members of the set of glucosamine disaccharides **(115)** were made for use in the total synthesis of lipid A of *Proteus mirabilis* **(116)**. The compound **(115**, R^1=α-allyl, R^2=$Cl_3CCH_2CO_2$, R^3=$Cl_3C(Me)_2CO_2$) was most efficiently for the synthesis.[181]



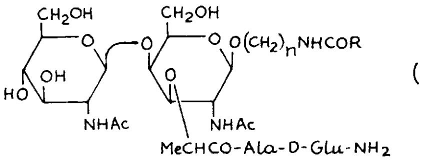
(115)



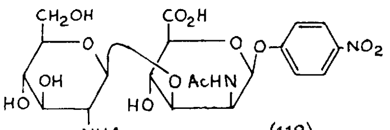
R^1 $(CH_2)_{14}Me$
R^2 $(CH_2)_{12}Me$
R^3 $(CH_2)_{16}Me$

(116)

The glucosaminylmuramic acid lipopeptide **(117)** was made by the oxazoline approach.[182]



(117) $n = 2, 6$; $R = C_{15}H_{31}$
$n = 2$; $R = CH(C_{12}H_{25})_2$



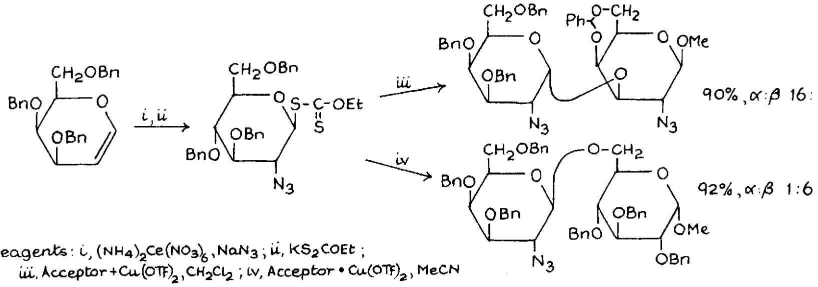
(118)

N-Acetylglucosamine was β-(1→3) linked to *p*-nitrophenyl-β-*D*-*N*-

acetylaminomannuronic acid, the product (**118**) corresponding to the repeating unit of the capsular polysaccharide of *Haemophilus influenzae* type d.[183]

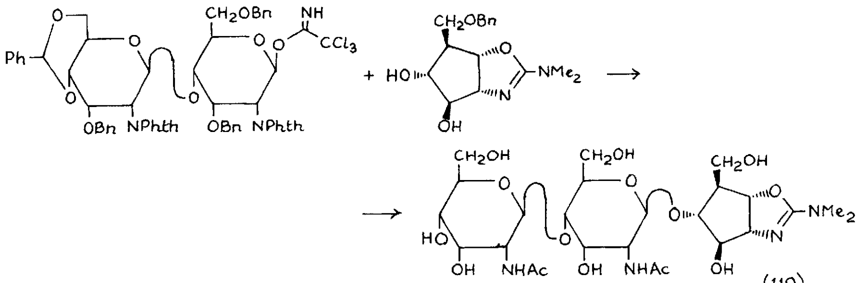
A glucosaminyl inositol compound, prepared as a potential insulin mimetic, is referred to in Chapter 18.

Sinai and coworkers have reported a very interesting new approach to the synthesis of galactosaminyl oligosaccharides involving the use of glycosylxanthates.[184,185] Very significantly, β-linked disaccharides are produced in acetonitrile following initial displacements by the solvent, whereas in dichloromethane, α-products are obtained. Attention is drawn to the impressive yields and anomeric selectivities noted in Scheme 28. *p*-Nitrophenyl 2-acetamido-2-deoxy-β-*D*-galactopyranoside served as glycosyl donor in an enzyme-catalysed transfer to excess of methyl β-*D*-glucopyranoside (*N*-acetylhexosaminidase from *Aspergillus oryzae*). A 49% yield of disaccharides having (1→3) and (1→4) linkages (ratio 4:1) was obtained; with methyl α-*D*-glucopyranoside as acceptor, however, a 36% yield of the (1→4) and (1→6)-linked products was obtained (in the ratio 5:1).[186]



Reagents: i, $(NH_4)_2Ce(NO_3)_6$, NaN_3; ii, KS_2COEt; iii, Acceptor + $Cu(OTf)_2$, CH_2Cl_2; iv, Acceptor • $Cu(OTf)_2$, MeCN

Scheme 28

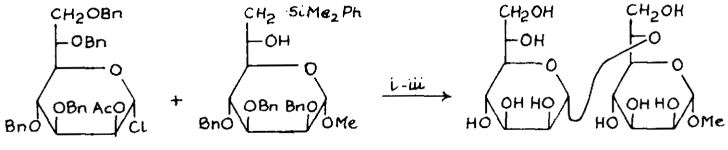


(119)

Scheme 29

A complete synthesis of the chitinase inhibitor allosamidin (**119**) has been published by a combined team led by Trost (*cf. J. Am. Chem. Soc, 1990* **112**, *1261*) and Vasella (Scheme 29).[187]

The synthesis of the C-Si bonded heptose derivative **(121)** is described in Chapter 2 and also its use as a heptose glycosyl acceptor and its conversion to the glycosyl donor **(120)**. 7-*O*-β-D-(*N*-Acetylglucosaminyl)-*L*-heptose was prepared as well as the 1,6-linked heptobiose **(122)** (Scheme 30).[188]

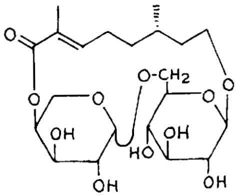


(120) (121) (122)

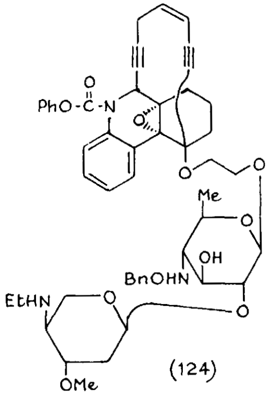
Reagents: i, AgOTf ; ii, $MeCO_3H$; iii, Deprotection

Scheme 30

Pentosyl disaccharides continue to be of interest - largely because of their occurrence in natural products. The cyclic 6-*O*-β-*D*-arabinopyranosyl-β-*D*-glucopyanose compound **(123)** has been isolated from *Lonicera nitida*,[189] and 6-*O*-β-*D*-xylopyranosyl-β-*D*-glucose has been obtained as the hexa-*O*-acetyl benzyl glycoside from the acetylated aqueous extracts of green fruit of *Prunus laurocerasus*.[190]



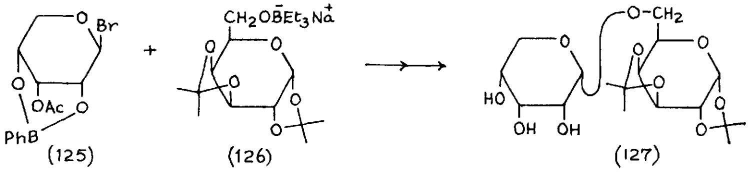
(123)



(124)

The protected disaccharide component of the calicheamicin **(124)** was coupled with the aglycone using trichloroacetimidate methodology notwithstanding the high sensitivity of the enediyne functionality.[191]

Coupling of the phenylboronate-protected ribosyl bromide **(125)** with sodium organotriethylborates eg **(126)** gave an α-linked product **(127)** (Scheme 31) with ≥95% stereoselectivity. The 3-*O*-α-*D*-ribopyranosyl-*D*-glucose and the non-reducing α-*D*-ribopyranosyl α-ribopyranoside were made similarly.[192]



Scheme 31

1.5 Hydrolysis and Other Features:—Fraser-Reid and colleagues have reported on an *ab initio* study of the transition states involved in the hydrolysis of glycosides using axial and equatorial 2-methoxytetrahydropyrans as model compounds.[193] A related study of the kinetics of hydrolysis of 2-substitutued-phenoxy-6-carboxytetrahydropyrans and 2-alkoxy-6-carboxytetrahydropyrans was undertaken to assist in the understanding of the mechanism of enzyme hydrolysis of hexuronosidic bonds.[194]

An efficient method for cleaving allyl glycosides with azido-groups at C-2 is reported in Chapter 10.

The permeability of human erythrocyte membranes to a variety of glycosides (arbutin, salicin, glycyrritin and the *p*-nitrophenyl glycosides of β-*D*-glucose, β-*D*-galactose, β-*D*-lactose and β-*D*-maltose) was examined and showed that the lower permeability of especially the disaccharide glycosides relative to those of the aglycones suggests that drugs converted to disaccharide glycosides would remain entrapped in membranes until released by erythocyte degradation. A new drug delivery system is therefore suggested.[195]

Microcalorimetry and HPLC were used to study the thermodynamics of hydrolysis of a range of disaccharides with enzymes. Data obtained indicated that additivity can be applied to the prediction of the thermodynamics of the processes.[196,197]

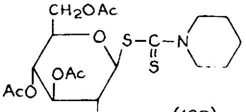
Spectrophotometric studies have been carried out on the kinetics and mechanism of the oxidation of lactose and maltose by bis(bipyridyl)copper(II) in alkaline media, the results suggesting that the oxidation rates correspond to the rates of ring opening.[198]

Synthesis and ^{13}C n.m.r. studies of disaccharides related to glucoxylans and xyloglucans have been carried out: β-*D*-glucose 1,2-,1,3-,1,4-linked to *D*-xylose and β-*D*-xylose 1,4-linked to glucose were made as well as acetylated anbd benzylated derivatives.[199]

Radicals induced by γ-irradiation at various temperatures of solid sucrose and aqueous solutions of the sugar have been studied by spin trapping (Chapter 22).

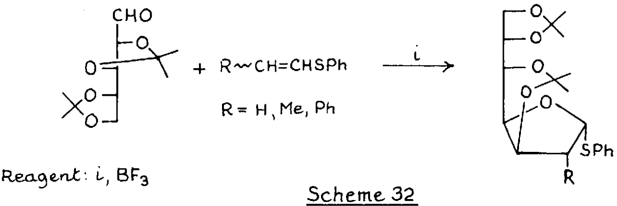
2 S-Glycosides

The important role now played by thioglycosides as glycosyl donors is well established in Section 1 by the large number of disaccharides, in particular, whose syntheses have been effected by their use. Variations such as *S*-pyridyl compounds and glycosyl xanthates were referred to and a further involves the use of acetylated glycosyl 1-piperidinecarbodithioates, eg **(128)**, which have been assessed as suitable as glycosyl donors for the production of 1,2-*trans*-related glycosides.[200]



(128)

A review covering structure and function and emphasizing biological aspects of the glucosinolates has been produced.[201] An ingenious synthesis of *S*-phenyl 3-azido and 3-fluoro-2,3-dideoxy-1-thio-α-*D*-*erythro*-pentofuranosides (cf. *Tetrahedron Lett.*, 1990, *31,* 5909) depends on highly efficient nucleophilic alkene addition to a free sugar with acetal migration (Scheme 32).[202]

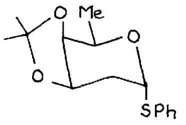


Scheme 32

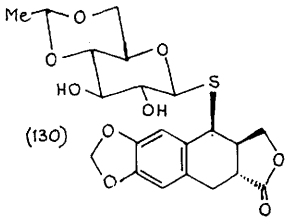
The rigid glycosyl donor **(129)**, used with NBS activation in dichloromethane, gave very high α, β-ratios for the glycosidic products (>8:1), whereas the corresponding 3,4-diacetate gave much poorer ratios which were, however, still > 1. The authors presume there is greater steric impedance to β-attack at C-1 in the former case. Perhaps, however, the greater inflexibility of the oxocarbonium ion derived from **(129)** (see Fraser-Reid, previous

Section) imposes greater stereoelectronic control which leads to greater axial selectivity.[203]

Two reports have appeared on the preparation of etoposide **(130)** which is a clinical anticancer substance. Both use 1-thio-*D*-glucose compounds, but the first employs a bromine atom and the second a coordinated hydroxy group for leaving purposes. A 45% yield is claimed in the latter; in the former report sulfoxide and sulfone analogues were described.

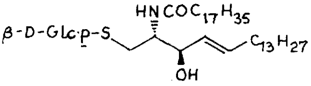


(129)



(130)

Other specific thioglycosides to have been made are the cerebroside **(131)** and analogues having galactose, lactose and α-NeuNAc-(2→3)-β-*D*-Gal*p*-(1→4)-β-*D*-Glc as the carbohydrate residues,[206] the related dithio-compound **(132)** and its C-4 (*D-galacto*-epimer),[207] and the β-*D*-galactosyl and 4-*O*-α-*D*-galactosyl-β-*D*-galactosyl derivatives of 3-mercaptopropanoic acid which were condensed with amino-acids by solid phase methods to give neo-glycopeptides.[72]



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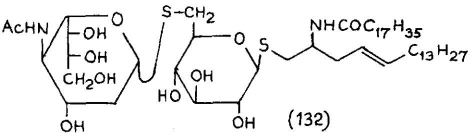


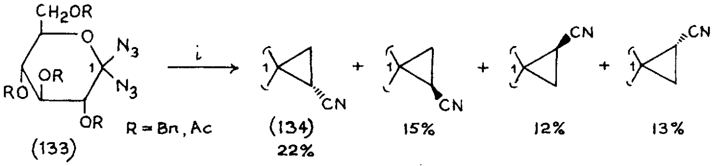
(132)

3 C-Glycosides

3.1 Pyranoid Compounds.—An extensive range of methods available for the synthesis of compounds of this type have been illustrated.

The use of cyanodiethylaluminium with glycosyl fluorides as a means of making glycosyl cyanides gave not just mixtures of anomers but mixed cyanides and glycosyl isocyanides. With 2,3:4,6-di-*O*-isopropylidine-*D*-glucosyl fluoride the corresponding α- and β-cyanides and α- and β-isocyanides were obtained in 3, 12, 4 and 25% yield, respectively. With 2,3:5,6-di-*O*-isopropylidine-*D*-mannofuranosyl fluoride the β-isocyanide was obtained in

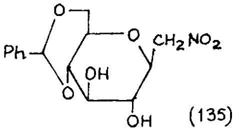
76% yield making this reaction appear to be more useful for synthetic purposes.[208] Photolysis of the diazide **(133)** (*Tetrahedron Lett.*, 1990, *31*, 4441) in benzene containing acrylonitrile likewise gave mixed products (Scheme 33), compound **(134)** being structurally characterized by X-ray crystallographic methods.[209]



Reagents: i, $CH_2{=}CHCN$, benzene, hν

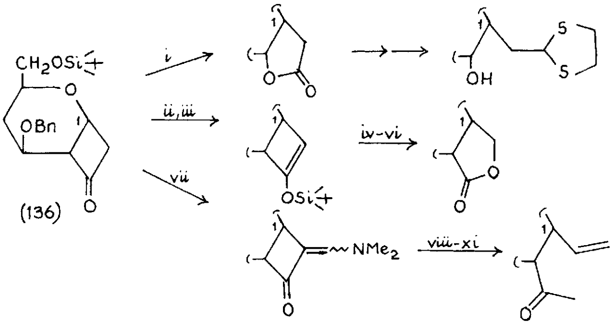
Scheme 33

Careful use of weakly basic conditions has allowed the synthesis of 4,6-*O*-acetalated-*D*-hexopyranosyl nitromethanes in good yield for the first time. In this way, 4,6-*O*-benzylidene-*D*-glucose, treated with nitromethane together with DBU, 2-hydroxypyridine and molecular sieves, gave the β-compound **(135)** in 69% yield. From it the amine and a triazine were produced.[210]



(135)

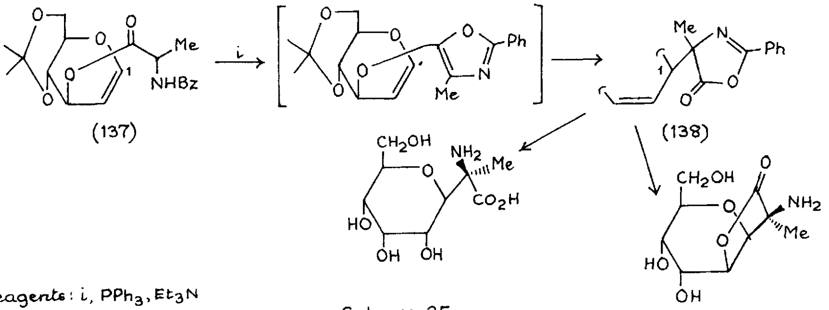
Unsaturated compounds continue to be a source of *C*-glycosides. Functionalization of the glycol-derived cyclobutanone **(136)** is illustrated in Scheme 34.[211]



Reagents: i, MCPBA; ii, $LiNPr^i_2$; iii, Bu^tMe_2SiCl; iv, O_3, MeOH; v, $NaBH_4$; vi, NH_4Cl, py, TsCl; vii, $Bu^tOCH(NMe_2)_2$; viii, Bu^i_2AlH; ix, MeMgBr; x, MeI; xi, DBU

Scheme 34

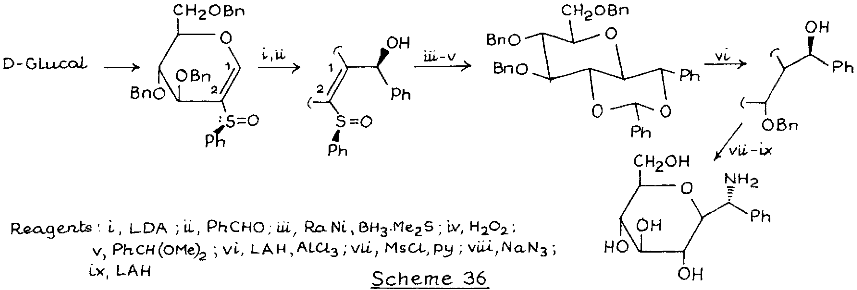
The glycal ester **(137)** was converted into **(138)** (Scheme 35) and hence into the illustrated *C*-glycosyl amino-acid derivatives.[212]



Reagents: i, PPh_3, Et_3N

Scheme 35

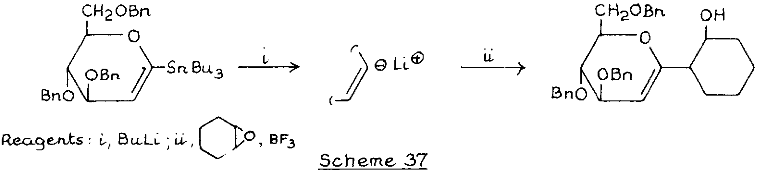
Scheme 36 indicates how a related amino-compound, which is a good *β*-glycosidase inhibitor, can be made from *D*-glucal.



Reagents: i, LDA; ii, PhCHO; iii, Ra Ni, $BH_3.Me_2S$; iv, H_2O_2; v, $PhCH(OMe)_2$; vi, LAH, $AlCl_3$; vii, MsCl, py; viii, NaN_3; ix, LAH

Scheme 36

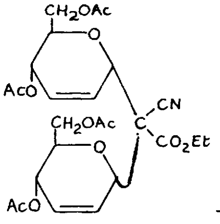
The alternative *S*-sulphoxide led to the epimeric amine.[213] An improved method for opening epoxides with glycal carbanions to give *C*-glycosides has been reported (cf. Vol. 23, p. 267) (Scheme 37)[214].

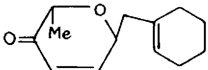


Reagents: i, BuLi; ii, , BF_3

Scheme 37

2,3-Unsaturated glycosyl carbonates, used with palladium catalysts, give good yields of corresponding *C*-glycosides with, for example, diethyl malonate. With corresponding cyanoacetates, novel examples of products of diglycosylation, e.g. (**139**), were reported.[215] Related 4-ketones (**140**)[216] and isomeric 2-ketones (**141**)[217] were tested for cytotoxicity, some being found to be active. From tri-*O*-acetyl-*D*-glucal a set of alkenes, e.g. (**142, 143**), which are related to the macrocyclic diester part of the trichothecene satratoxin, were prepared and also tested for cytotoxicity. All had activity against dividing cells, but compound (**143**) was most active against normal cells.[218]


(139)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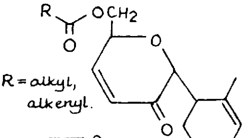

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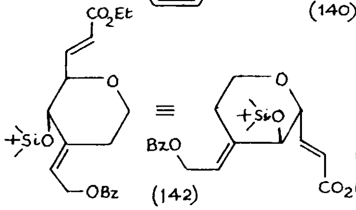
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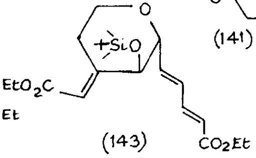
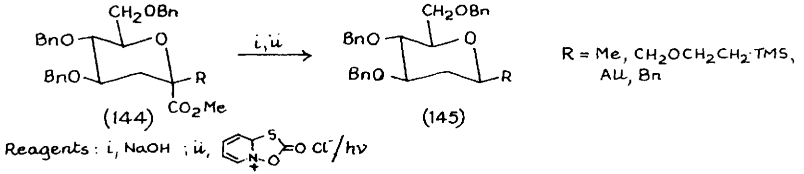

(143)

The esters (**144**), prepared using C-1 carbanionic species, were hydrolysed and decarboxylated by radical procedures to give the β-linked *C*-glycosides (**145**) (Scheme 38) in work that extends developments of equatorially linked *O*-glycoside syntheses.[219] Iron and manganese carbonyl complexes can be used to give glycosyl radicals from acetobromohexoses. Trapping with acrylonitrile gave the same adducts as were obtained using the more conventional tributyltin hyride.[220]

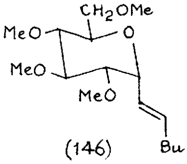


Scheme 38

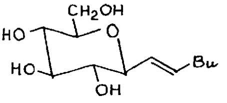
The acetylated glycosyl chloride of neuraminic acid ethyl ester, with allyltributyltin, gave α- and β-*C*-allyl derivatives which were epoxidized.[221, 222] *C*-Hydroxymethylation at C-2 of a related neuraminic acid derivative by carbanionic methods gave the α- and β-products in 3:1 ratio. Aminomethyl analogues were also made, but none of these products led to good inhibitors of sialidase.[223]

A useful method for equilibrating allyl α- and β-*C*-glucopyranosides involves treatment with triflic acid, and with this reagent the α-compound **(146)** comprised 10% of the mixture with the β-anomer at equilibrium. This provides suitable access to e.g. compound **(147)**. Benzyl ethers did not survive the procedure; pivaloyl esters did.[224]

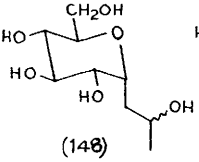
Conformations of the four isomers **(148)**, **(149)**, as determined by n.m.r., indicated that they were the same as those of the parent glycosides. Detailed analysis suggested that the preferences shown result from minimization of *gauche* interactions around the glycosidic bonds.[225]



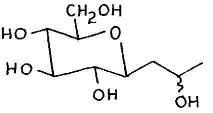
(146)



(147)

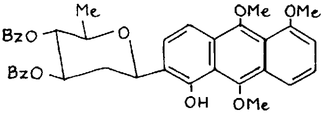


(148)

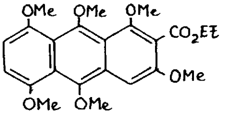


(149)

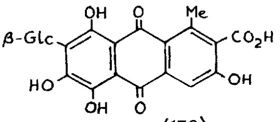
Considerable work has been done on *C*-aryl compounds. Reports of the use of acetobromoglucose together with oxygenated aryl Grignard reagents[226] and of 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranosyl fluoride with an oxygenated anthracene derivative[227] have been reported. In the latter case, the product **(150)** was used in the preparation of vincomycinone B_2 methyl ester and was produced by O→C glycosidic rearrangement promoted by $HfCp_2Cl_2/AgClO_4$.[227] In related work, *C*-glycosylation, using tetra-*O*-benzyl-1-*O*-trifluoroacetyl-β-*D*-glucose and BF_3 as catalyst, of **(151)** led to the synthesis of carminic acid **(152)**, the colorant principle of cochineal.[228]



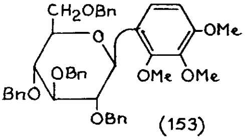
(150)



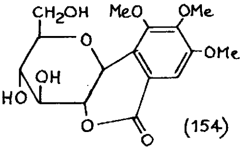
(151)



(152)

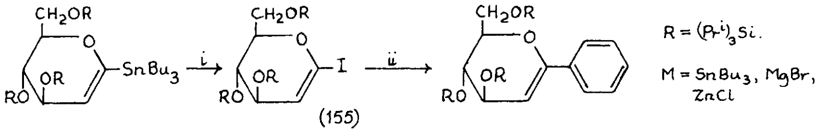


(153)



(154)

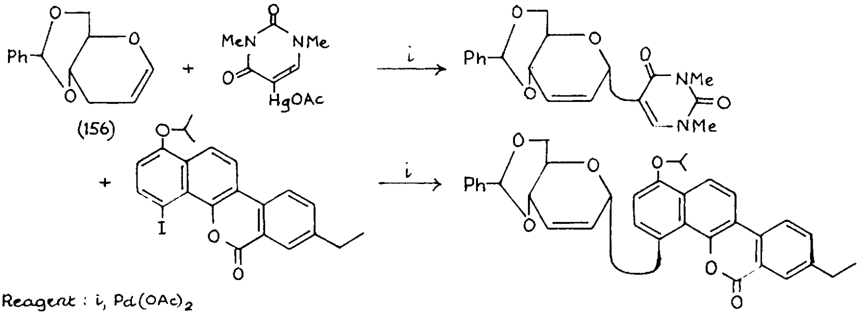
The same glycosylating agent with 1,2,3-trimethoxybenzene gave **(153)** which was converted to 8,10-di-*O*-methylbergenin **(154)**,[229] and the corresponding 1-*O*-α-trimethylsilyl reagent with Lewis acids gave β-linked *C*-glycosides in about 60% yields with several methoxylated benzenes.[230]



Reagents: i, I_2, CH_2Cl_2; ii, PhM, $Pd(PPh_3)_2Cl$

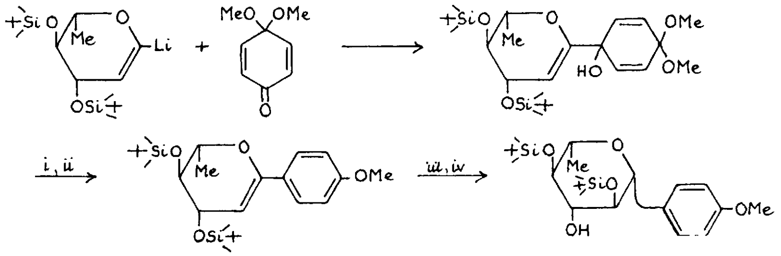
Scheme 39

A good method for making 1-*C*-arylated glycals involves the use of the iodo-compound **(155)** (Scheme 39),[231] and the 3-deoxyglycal **(156)**, together with palladium acetate, can be used to make 2,3-unsaturated *C*-glycosides (Scheme 40).[232]



Reagent: i, $Pd(OAc)_2$

Scheme 40

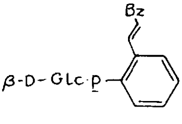


Reagents: i, DIBAL; ii, $POCl_3$, py; iii, BH_3.THF; iv, H_2O_2

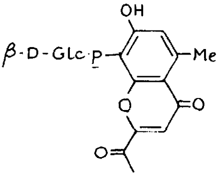
Scheme 41

A new approach to *C*-aryl compounds, involving a reductive aromatization of a quinol ketal as the key step, as illustrated in Scheme 41. A silyl migration is to be noted.[233]

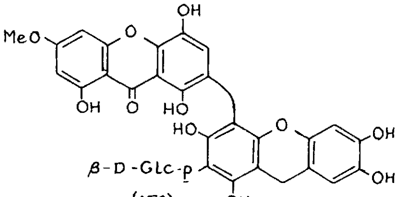
Compound **(157)** and other chalcone mono- and di-glycosides were prepared in the course of studies of their colour stabilization properties;[234] the *C*-glycosidic bond of the chromone aloesin **(158)** was cleaved by human intestinal bacteria;[235] the first bioxanthone *C*-glycoside **(159)** has been isolated from the whole plant of *Swertia punicea*.[236]



(157)

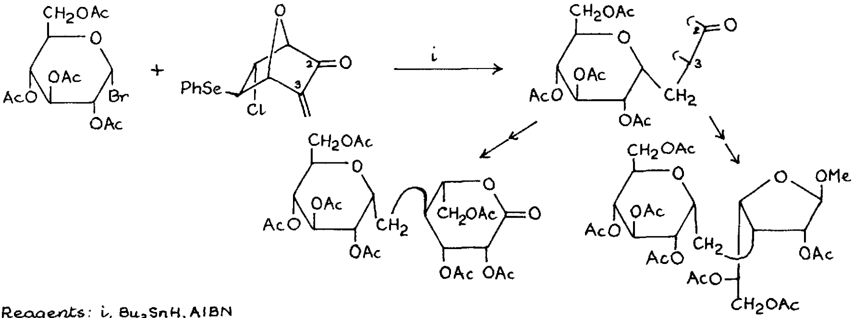


(158)



(159)

Several interesting developments have been reported on the topic of *C*-linked disaccharides, a particular one, which involves a radical addition followed by removal of a bridging silicon-containing group, is noted in Chapter 19. A second free radical addition approach is outlined in Scheme 42.[237]

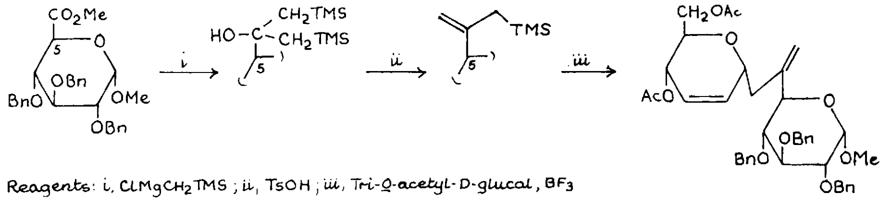


Reagents: i, Bu_3SnH, AIBN

Scheme 42

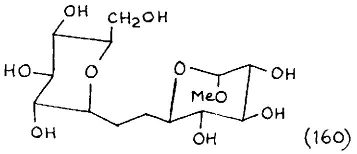
A very elegant alternative procedure involves the use of tri-*O*-acetylglucal and a sugar *C*-nucleophile (Scheme 43). A similar product was made involving a *D*-glucofuranose moiety.[238]

N.m.r. analyses showed that the methyl α-*D*-isomaltoside **(160)** and methly α-D-gentiobioside **(161)** analogues in aqueous solution adopt the conformations shown.[239] See Scheme 18 for a further example.

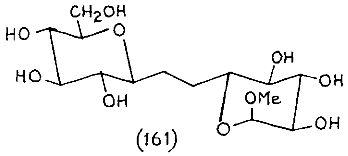


Reagents: i, $ClMgCH_2TMS$; ii, TsOH; iii, Tri-*O*-acetyl-D-glucal, BF_3

Scheme 43

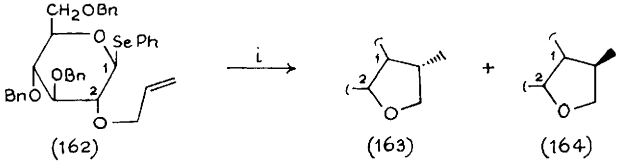


(160)



(161)

Several fused-ring *C*-glycosides have resulted from intramolecular radical cyclizations. Compound **(162)** gave **(163)** and **(164)** without selectivity at ambient temperature, but at -78° the ratio of products was 1.2:1 (Scheme 44). At the lower temperature the 4,6-*O*-benzylidene analogue of **(162)** gave products in the ratio 3.8:1 while the *D-galacto-* and *D-manno-*epimers of **(162)** gave notably different ratios of 99:1 and 32:1, respectively. These results were nicely correlated with the conformations previously found to be adopted by the radical intermediates (*J Chem. Soc., Perkin Trans.* 2, 1986, 1453). Thus, glucopyranosyl radicals adopt boat conformations and show low selectivity; galactosyl and mannosyl species adopt half-chairs and chairs.[240]

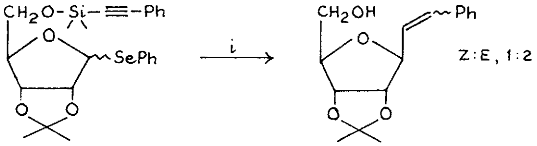


Reagent: i, Bu_3SnH

Scheme 44

Several papers referring to glycosyl *spiro*-ketals, which are anhydro derivatives of extended chain ketoses, are referred to in Chapter 2.

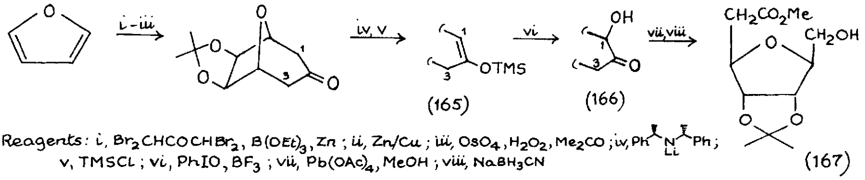
3.2 Furanoid Compounds.—An ingenious intramolecular route to styryl β-D-ribofuranose is shown in Scheme 45. Other examples of the use of the silyl bridge were given.[241]



Reagent : i, Bu_3SnH

Scheme 45

A homochiral lithium amide was used to introduce chirality in the synthesis of compound **(165)** from which *C*-nucleosides can be made (Scheme 46). Recrystallization of **(166)** permitted **(167)** to be obtained with >98% e.e.[242]



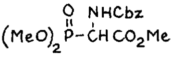
Reagents: i, $Br_2CHCOCHBr_2$, $B(OEt)_3$, Zn ; ii, Zn/Cu ; iii, OsO_4, H_2O_2, Me_2CO ; iv, PhCH(Me)N(Li)CH(Me)Ph ; v, TMSCl ; vi, PhIO, BF_3 ; vii, $Pb(OAc)_4$, MeOH ; viii, $NaBH_3CN$

Scheme 46

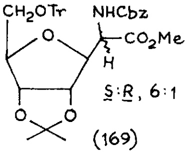
2,3-*O*-Isopropylidene-6-*O*-trityl-*D*-ribose treated with phosphonate **(168)** gave the *C*-ribofuranosylglycines **(169)** in high yield in a one-pot procedure. The (S)-isomer was characterized by X-ray cystallographic methods.[243]

A further one-pot synthesis gives tri-*O*-benzoyl-β-*D*-ribofuranosyl cyanide in 86% yield,[244]and a 2-deoxy analogue was made using cyanodiethylaluminium.[245]

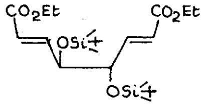
The diene **(170)** has been used to produce racemic compounds of the *C*-glycofuranosyl type (e.g. **171**)[246]and a new synthesis of muscarine (a further *C*-glycofuranoside) from *L*-rhamnose is referred to in Chapter 24.


$(MeO)_2P(O)-CH(NHCbz)CO_2Me$

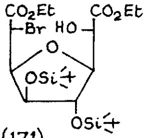
(168)



(169)

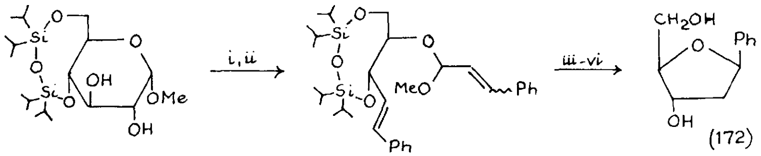


(170)



(171)

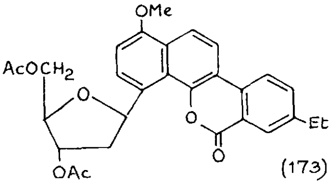
Aromatic members to have been prepared are β-ribofuranosides and 2-deoxy analogues of resorcinol[247] and 4-methylnaphthalene (glycosylation at C-1),[248]and 3-*C*-α-*D*-arabinofuranosylindole.[249] Methyl α-*D*-glucopyranoside was used as shown in Scheme 47 to produce the phenyl 2-deoxy compound **(172)**,[250] and the related **(173)** was made by palladium - catalysed coupling of an iodoaglycone to a glycal derivative.[251]



(172)

Reagents: i, $NaIO_4$; ii, $PhCH=PPh_3$; iii, H_3O^+; iv, $Hg(OAc)_2$, MeOH; v, $NaBH_4$; vi, $F^{\ominus}$

Scheme 47



(173)

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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 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 dealt with in their respective sections. Frequently, specific derivatives of the named compounds are involved, and this fact is often not recorded in the formulae used.

A review with 46 references has appeared on recent progress in oligosaccharide synthesis,[1] and others on the synthesis of glycosphingolipids and also the oligosaccharide of the antibiotic calicheamicin,[2] and on the current state of knowledge on the synthesis and conformational analysis of xylose-containing chains from *N*-glycoproteins.[3]

A general molecular modelling methodology suitable for studies of unbranched complex carbohydrates has been described which employs molecular dynamics and energy minimization procedures using NOESY-derived constraints. It was demonstrated using a fragment from the carbohydrate-protein linkage region of connective tissue proteoglycans.[4] A molecular model of the complex of antithrombin III and a heparin analogue has been considered.[5]

N.m.r. spectra of partially deacetylated chitotrisaccharides[6] and of branched oligosaccharides having the same monosaccharide substituents at 0-2 and 0-3 of α-*L*-rhamnose residues have been reported.[7]

A new method for sequencing linear oligosaccharides involves treating them with 7-amino-1,3-naphthalenedisulphonate (fluorescent and negatively charged) and reducing the glycosylamines formed with sodium cyanoborohydride. The resulting 1-aminoalditol derivatives were separated by preparative gel electrophoresis, transferred to charged nylon membranes and examined by f.a.b. - m. s. and 2D n.m.r. They were then partially cleaved enzymically and the fluroescent products were re-examined.[8] Glycosylamines were also involved in a new, reversible derivatization procedure for reducing oligosaccharides. The glycosylamines, prepared by use of aqueous ammonium bicarbonate, were treated with FmocCl to give the *N*-substituted glycosylamines. Excellent h.p.l.c. separations of milk oligosaccharides were obtained by this procedure[9]

Very considerable interest has been taken in the use of enzymes in the preparation of oligo- and poly-saccharides. Reviews have appeared on the following topics: the preparation of fructo-oligosaccharides,[10] of complex oligosaccharides and their glycosides (glycoprotein - related compounds particularly),[11] unnatural oligosaccharides[12] and malto-oligosaccharides.[13] A paper on the synthesis of cellulose by transglycosylation from a cellobiosyl fluoride,[14] and one on the synthesis of steviol glycosides aimed at producing sweeteners[15] have been published.

Symposia reports have been released on the preparation of hetero-oligosaccharides using glycosidases[16] and on the solid-phase preparation of glycopeptides on resins with allyl anchoring groups.[17]

High mannose-containing oligosaccharides have been isolated from yeast and mammalian glycoproteins,[18] and 2-amino-2-deoxy-*D*-glucose oligosaccharides (DP5-9) derived from crab chitosan have been separated and isolated crystalline as their hydrochlorides.[19]

Lactosamine oligomers (**1**, n 1-5) were produced by oligomerisation of the corresponding β-S-Et glycoside.[20]

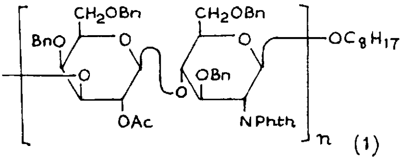
The cryoprotective effects of glucose, mannitol, glucitol, dextran and malto-oligosaccharides on the denaturation of catalase on freeze-drying has been found to be due to binding of a monomolecular layer of saccharide replacing water of hydration.[21]

2 Trisaccharides

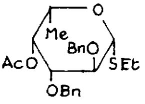
2.1 Linear Homotrisaccharides.—Pyrolysis of sucrose at 100°C in the presence of citric acid caused the formation of the fructofuranosyl cation and thence the six non-reducing trisaccharides comprising sucrose with fructofuranose α- and β- bonded to C-6, C-1′ and C-6′.[22] 4-*O*-α-*D*-Glucopyranosyl-α,α-trehalose was made by use of perbenzylated glucosyl fluoride.[22A]

The following linear glucotrioses have been prepared: *O*-α-*D*-Glc*p*-(1→6)-*O*-β-*D*-Glc*p*-(1→6)-*O*-α-*D*-Glc*p*1-*N*-asparagine,[23] (α,α-, β,α- and β,β-linked isomers of *O*-*D*-Glc*p*-(1→2)-*O*-*D*-Glc*p*-(1→3)-α-*D*-Glc*p*-OMe (^{1}H and ^{13}C n.m.r. spectra examined)[24] and *O*-α-*D*-Glc*p*-(1→4)-*O*-β-*D*-Glc*p*-(1→2)-β-*D*-Glc*p* bonded to a derivative of the diterpene stevioside. α-Glucosylation was by enzymic transfer; higher oligomers of this sweet glycoside were formed concurrently.[25]

O-α-*L*-Fuc*p*-(1→4)-*O*-α-*L*-Fuc*p*-(1→4)-α-*L*-Fuc*p*1-*O*Me was synthesized by use of compound (**2**) as the key glycosylating donor. Following condensation, deacetylation was effected and the process was repeated. The tetramer was made by a further repeat of the process.[26]

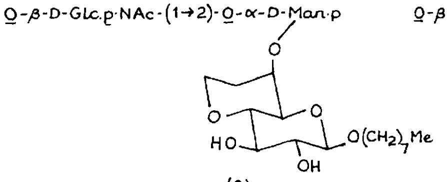


(1)

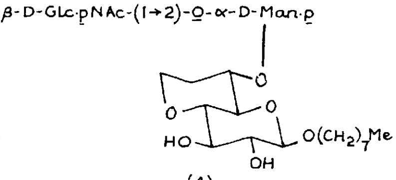


(2)

2.2 Linear Heterotrisaccharides.—The conformationally restricted trisaccharide derivatives (**3**) and (**4**) were made and listed as substrates for *N*-acetylglucosaminyl transferase,[27] and the following were made as analogues of glucoamylase and soyabean β-amylase substrates: *O*-α-*D*-Glc*p*-(1→4)-*O*-α-*D*-Glc*p*-(1→4)-*D*-Xyl, *O*-α-*D*-Glc*p*-(1→4)-*O*-α-*D*-Xyl*p*-(1→4)-*D*-Glc and *O*-α-*D*-Xyl*p*-(1→4)-*O*-α-*D*-Glc*p*-(1→4)-*D*-Glc.[28] Other compounds with *D*-glucose at the reducing end to have been synthesized are: *O*-α-*L*-Fuc*p*-(1→2)-*O*-β-*D*-Gal*p*-(1→4)-*D*-Glc,[29] the α-1,6-linked *D*-glucose trimer having deoxy groups at C-2 in the non-reducing and central moieties,[30] and *O*-α-*D*-Neu*p*5AC-(2→6)-*O*-β-*D*-Gal*p*-(1→4)-β-*D*-Glc*p*OMe.[30A]



(3)



(4)

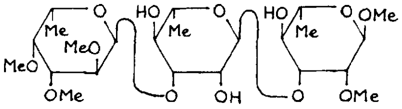
Compounds terminating in other hexoses to have been produced are: *O*-β-*D*-Glc*p*NAc-(1→2)-*O*-α-*D*-Man*p*-(1→3)-β-*D*-Man*p*-*O*-$(CH_2)_8CO_2Me$,[31] *O*-β-*D*-Gal*p*-(1→4)-*O*-β-*D*-Glc*p*-(1→6)-*D*-Man,[32] *O*-α-*D*-Glc*p*-(1→6)-*O*-α-*D*-Glc*p*-(1→6)-*D*-Gal[33] and *O*-α-*D*-Neu*p*-5Ac-(2→8)-*O*-α-*D*-Neu*p*-5Ac-(2→3)-β-*D*-Gal*p*-*O*-All.[34]

Considerable attention has been paid to the preparation of trimers ending with 2-amino-2-deoxy-sugars. These papers have reported the enzymic preparation of *O*-α-*D*-Neu*p*-5Ac-

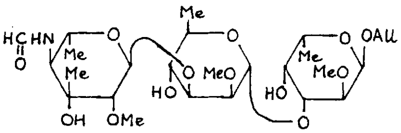
(2→6)-*O*-β-*D*-Gal*p*-(1→4)-*D*-GlcNAc,[35-37] and one of the analogues with a 3-deoxy group in the reducing moiety.[30A] The *D*-Gal, *D*-Gal, *D*-GlcNAc-linked trimers with the α-(1→3), β-(1→4),[38] α-(1→3), α-(1→3)[39] and α-(1→3), β-(1→3)[39] linkages have been reported as has *O*-α-Hep*p*-(1→5)-*O*-α-KDO-(2→6)-GlcNAc.[40]

The 6-deoxyhexose-based trisaccharides (**5**) and (**6**) were made, the former being a glycolipid fragment,[41] and the latter the outer portion of the hapten of serovar 14. Following ozonolysis it was coupled to bovine serum albumin for immunological work.[42] Related disaccharides were also reported.

The dideoxyhexose-based trisaccharides (**7**)-(**9**) are, unusually, linked by vinyl ether glycosidic bonds. The first came from *Tylophora sylvatica*[43] and (**8**) and (**9**) are pregnane derivatives from the roots of *D. lanceolota.*[44]



(5)



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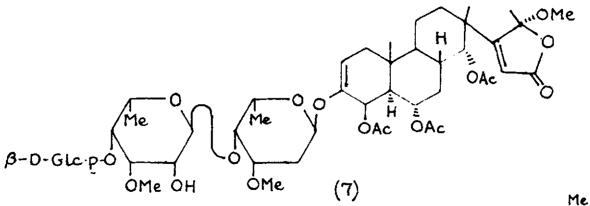
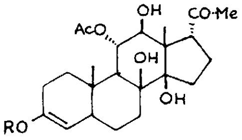
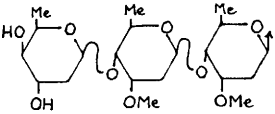


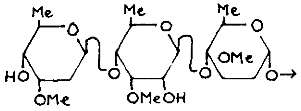
(7)

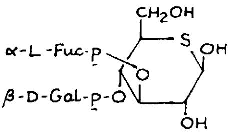


(8) R =



(9) R=





(10)

The *L-glycero-D-manno*-heptose-containing trisaccharide of the inner core region of lipopolysaccharide *O*-α-*L*-Hep*p*-(1→3)-*O*-α-*L*-Hep*p*-(1→5)-α-KDO-*O*-All has been synthesized.[45]

2.3 Branched Homotrisaccharides.—*O*-β-*D*-Glc*p*-(1→2)-*O*-[β-*D*-Glc*p*-(1→3)]-*D*-Glc is a component of a second sweet steviol (diterpene) glycoside. It was fructosylated enzymically at a single glucose unit also in the compound and the product had enhanced sweetness characteristics.[46] α-*D*-Man*p*-(1→3)-*O*-[α-*D*-Man*p*(1→6)]-β-*D*-Man*p*O$(CH_2)_8CO_2Me$ was synthesized and then enzymically 2-acetamido-2-deoxy-β-*D*-glucosylated at the *O*-2 positions of the terminal groups.[47]

2.4 Branched Heterotrisaccharides.—A novel oligosaccharide synthesis method involves supporting a monosaccharide acceptor on poly(ethylene glycol) monomethyl ether and carrying out glycosylation in solution. In this way methyl 3-*O*-benzoyl-β-D-galactopyranoside was bonded by way of *O*-2 and 2-amino-2-deoxy-β-*D*-glucopyranosyl units were introduced at *O*-4 and *O*-6 by use of the *N*-phthalloyl acetylated glycosyl bromide.[48]

The 3-*O*-fucosyl-5-thiolactose (**10**) was prepared using a 1,3/1,4 fucosyltransferase and the substrate-specificity of the enzyme was studied.[49] Other branched trisaccharides to have been synthesized in derivatized form are: *O*-β-*D*-Gal*p*-(1→3)-[*O*-α-*L*-Fuc*p*-(1→4)]-*D*-Glc*p*NH_2,[50] *O*-α-*L*-Rha*p*-(1→2)-[*O*-β-*D*-Glc*p*NAc(1→3)]-α-*L*-Rha*p*-*O*$(CH_2)_8CO_2Me$,[51] *O*-*L*-α-*D*-Hep*p*-(1→5)-[*O*-α-KDO-(2→4)]-α-KDO*p*-OAll and related compounds.[52]

3 Tetrasaccharides

As with the trisaccharides, the tetrasaccharides are classified according to whether they have linear or branched structures, and then by the nature of the sugar at the reducing termini.

The A, B and H (type 3) human blood group determinant tetrasaccharides have been prepared and converted into polyacrylamide conjugates.[53]

3.1 Linear Homotetrasaccharides.—An α-(1→3) linked *L*-rhamnose tetramer and several of its esters (notably acetates) have been isolated from the bark of *Mezzettia leptopoda*.[54]

3.2 Linear Heterotetrasaccharides.—*O*-α-*D*-Gal*p*-(1→4)-*O*-α-Neu*p*5Ac-(2→3)-*O*-β-*D*-Gal*p*-(1→4)-*O*-β-*D*-Glc*p*-Cer has been isolated from *Asteroidea* species together with analogues having α-*L*-Ara*f* attached,[55] and 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-*L*-Tal*p*-OMe from a *Mycobacterium*.[56]

The following compounds of this category have been synthesized: *O*-α-*D*-Neu*p*5Ac-(2→8)-*O*-α-*D*-Neu*p*-5Ac-(2→3)-*O*-β-*D*-Gal*p*-(1→4)-*O*-β-*D*-Glc*p*-Cer,[34] *O*-α-*L*-Fuc*p*-(1→3)-*O*-β-*D*-Glc*p*NAc-(1→3)-*O*-β-*D*-Gal*p*-(1→4)-β-*D*-Glc (and two closely related isomers required for the synthesis of *L*-fucosyl transferase).[57] *O*-β-*D*-Xyl*p*-(1→6)-*O*-β-*D*-Glc*p*-(1→4)-*O*-α-*D*-Xyl*p*-(1→6)-Glc,[58] *O*-α-*D*-Glc*p*-(1→4)-*O*-α-*D*-Glc*p*-(1→6)-*O*-α-*D*-Glc*p*-(1→6)-*D*-Gal,[33] *O*-α-*D*-Gal*p*-(1→3)-*O*-α-*D*-Gal*p*N$_3$-(1→3)-*O*-β-*D*-Gal*p*N$_3$-(1→6)-α-*D*-Gal-OMe,[59] *O*-*L*-α-*D*-Hep*p*-(1→5)-*O*-α-KDO*p*-(2→6)-*O*-β-*D*-Glc*p*NH$_2$-(1→6)-*D*-GlcNH$_2$[60] and α-KDO*p*-(2→4)-*O*-KDO*p*-(2→6)-*O*-β-*D*-Glc*p*NH$_2$-(1→6)-*D*-GlcNH$_2$. The last compound was prepared with complex substituents on N-2 and O-3 of the glucosamine units as an *E. coli* lipopolysaccharide component.[61]

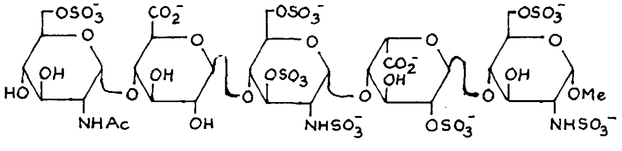
3.3 Branched Homotetrasaccharides.—The following have been synthesized, the first having the glucosamine attached by an enzymic procedure: *O*-β-*D*-Glc*p*NAc-(1→2)-*O*-α-*D*-Man*p*-(1→3)-[*O*-α-*D*-Man*p*-(1→6)]-β-*D*-Man*p*O-(CH$_2$)$_8$CO$_2$Me,[47] *O*-β-*D*-Glc*p*NAc-(1→2)-[*O*-β-*D*-Glc*p*NAc-(1→6)]-*O*-α-*D*-Man*p*-(1→6)-β-*D*-Man*p*-O(CH$_2$)$_8$CO$_2$Me,[31] *O*-β-*D*-Glc*p*-(1→4)-[*O*-α-*L*-Rha*p*-(1→2)]-*O*-β-*D*-Glc*p*-(1→4)-α-*L*-Rha*p*-O(CH$_2$)$_3$NH$_2$[62] and *O*-α-Neu*p*-Ac-(2→3)-*O*-β-*D*-Gal*p*-(1→4)-[*O*-α-*L*-Fuc*p*-(1→3)]-*D*-Glc*p*NAc.[63]

4 Pentasaccharides

Increasing interest in the synthesis of oligosaccharides is particularly apparent in the area of pentasaccharides.

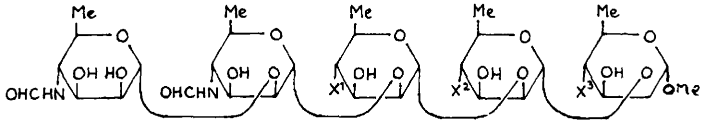
4.1 Linear Pentasaccharides.—Enzymic methods have been used to prepare *p*-nitrophenyl α- and β-maltopentaoside.[64] Hasegawa's group has reported the chemical synthesis of ganglioside GMIb, i.e. *O*-α-Neu*p*NAc-(2→3)-*O*-β-*D*-Gal*p*-(1→3)-*O*-β-*D*-Gal*p*NAc-(1→4)-*O*-β-*D*-Gal*p*-(1→4)-β-*D*-Glc*p*-O-Cer[65, 66] and several analogues linked in the following manner: α-(2→6)-β-(1→3)-β-(1→4)-β-(1→4),[65, 66] α-(2→3)-β-(1→6)-β-(1→4)-β-(1→4),[65] α-(2→6)-β-(1→6)-β-(1→4)-β-(1→4).[65] They also prepared closely related α-(2→6)-β-(1→X)-β-(1→3)-β-(1→4) linked compounds with Glc*p*NAc in place of the central Gal*p*NAc[67] and then closely related branched compound (see below).

Several syntheses have been reported of heparin fragments and related compounds—notably the first total synthesis of the *N*-acetylglucosamine-containing pentasaccharide (**11**) to the major natural sequence in heparin for binding antithrombin III.[68] An analogue in which sulfated glucose replaced glucosamine at the reducing end,[69] and one with a phosphate at C-6 of the non-reducing terminol unit,[70] were also prepared. The latter was devoid of binding activity. Some analogues containing ring opened components are noted in the last section of this Chapter.



(11)

The pentasaccharide analogues (**12**) - (**14**) of the Brucella A antigen have been prepared as their methyl glycosides.[71] Further analogues with a hydroxyl group instead of the formylamino group in the penultimate unit were also reported.[72]



(12) X^1 = NHCHO, X^2 = X^3 = OH (13) X^1 = X^3 = NHCHO, X^2 = OH (14) X^1 = OH, X^2 = X^3 = NHCHO

4.2 Branched Pentasaccharides.—The synthesis of the following have been reported: *O*-β-*D*-Glc*p*NAc-(1→2)-*O*-α-*D*-Man*p*-(1→3)-[*O*-β-*D*-Xyl*p*-(1→2)]*O*-β-*D*-Man*p*-(1→4)-*D*-Glc,[73]*O*-β-*D*-Gal*p*-(1→4)-*O*-β-*D*-Glc*p*-(1→6)-[*O*-β-*D*-Gal*p*-(1→4)-*O*-β-*D*-Glc*p*-(1→2)]-*D*--Man,[32] and *O*-β-*D*-Glc*p*NAc-(1→2)-*O*-α-*D*-Man*p*-(1→6)-[*O*-β-*D*-Glc*p*NAc-(1→2)-*O*-α-*D*-Man*p*-(1→3)]-*O*-β-*D*-Man*p*-O(CH$_2$)$_8$CO$_2$Me.[47]

5 Hexasaccharides

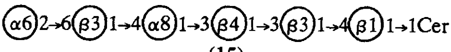
Because of their increasing complexity, specific oligosaccharide structures will henceforth be reprepresented diagramatically by a further abbreviated method. Sugars will be numbered as follows, and linkages will be indicated in the usual way:

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**

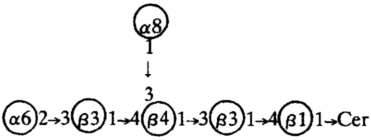
5.1 Linear Hexasaccharides.— *p*-Nitrophenyl α-maltohexaoside was made by enzymic transglycosylation (probably of enzyme bound maltopentaose) between maltohexaose and *p*-nitrophenyl α-*D*-glucopyranoside in water containing DMSO (40%) or butan-1-ol or propan-2-ol (20%).[74] A methyl glycoside of the hexaose based on 4-deoxy-4-formylmethyl-α-*D*-rhamnopyranose has been made by the thioglycoside procedure.[72]

Compound (**15**), an isomer of sialyl Lewis X antigen varying in the position of substitution of the sialic acid, has been synthesized.[75]



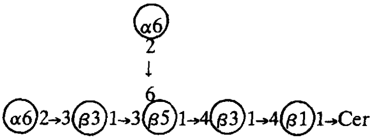
(**15**)

5.2 Branched Hexasaccharides.—Hasegawa's group have synthesized the tumour-associated ganglioside sialyl Lewis X (**16**) [cf. **15**],[76, 77]



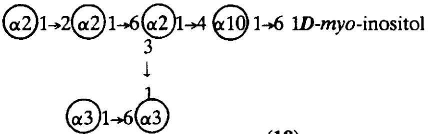
(**16**)

and also the related disialoganglioside GD1α (**17**).[78]



(**17**)

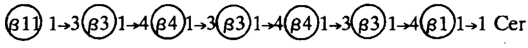
The mannose-rich glycophosphatidylinositol anchor compound of *Trypanosoma brucei* (**18**) has been prepared bonded to appropriate phospholipids.[79]



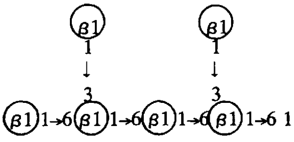
(18)

6 Heptasaccharides

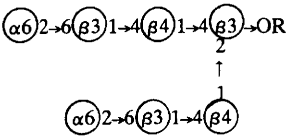
Syntheses of compounds (**19**),[80] (**20**),[81] (**21**),[82] (**22**),[82] have been reported.



(19)



(20)



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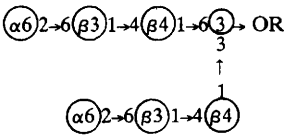
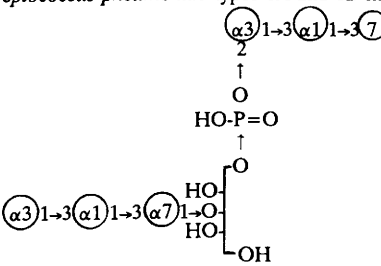


(22)

Likewise the phosphated fragments (**23**) and (**24**) of the capsular polysaccharide of *Streptococcus pneumoniae* types 6A and 6B have been made.[83]



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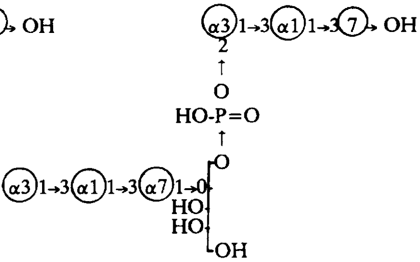
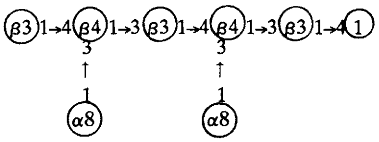


(24)

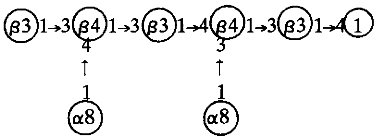
For the conversion of oligosaccharides containing branched chains with 6-8 mannose units terminating in *N*-acetylglucosamine it is reported that TMS bromide in the presence of boron trifluoride etherate and collidine provide means of obtaining the oxazoline from which bonding to spacer groups can be effected.[84]

7 Higher Saccharides

Octasaccharide (**25**)[85] and the closely related (**26**)[86] have been made.



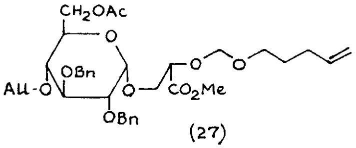
(**25**)



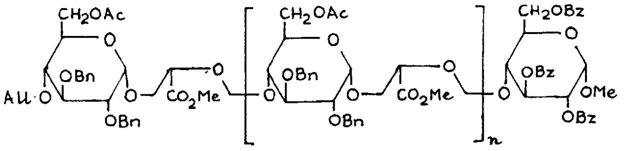
(**26**)

Likewise, the nonasaccharide, derived by fucosylation of (**26**) at 0-2 of the terminal galactose residue has been reported.[86]

The interesting oligomers (**28**) containing "open-chain" uronic acid analogues were prepared by use of the pentenyl disaccharide analogue (**27**). The pentamer was converted into the polysulfate which is related to the heparin repeating unit.[87]

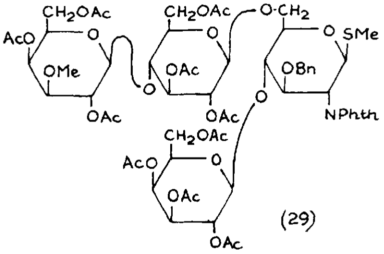


(27)

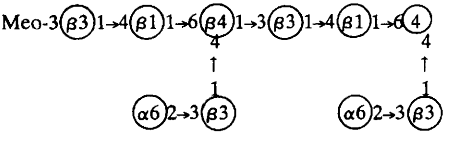


(28) n = 1,2,3

Compound (**29**) was coupled with a close analogue containing a methyl glycosidic link in place of the thiomethyl group and being devoid of the methyl ether group to give an octamer which was deprotected and enzymically sialated to give the decamer (**30**).[88]



(29)



(**30**)

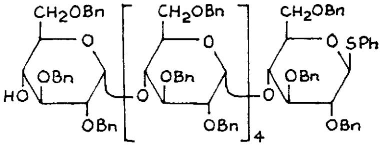
8 Cyclodextrins

Two reviews (in Japanese) have appeared on aspects of cyclodextin chemistry: a) on structure, physical properties, toxicity, metabolism, entrapping characteristics and uses in the pharmaceutical and food industries,[89] and on the construction of chemically modified cyclodextrins that recognize anions.[90]

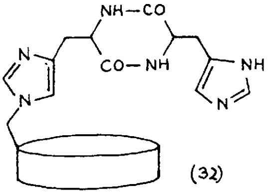
X-ray and neutron diffraction analyses of a partially deuterated β-cyclodextrin ethanol octahydrate have appeared[91] as well as force field calculations of the cyclodextrins. They are not rigid and the normal symmetrical structures that are drawn are time-averaged.[92]

Chromatographic separations of cyclodextrins and glucosylcyclodextrins and various other carbohydrates on Hypercarb, a graphitized carbon column, have been reported[93] and three positional isomers of dimaltosylcyclomaltoheptaose, prepared from maltose and β-cyclodextrin, were separated and structually characterized.[94] The same group has also reported on several diglucosyl β-cyclodextrins.[95]

In the area of synthesis of members of the series cyclo-*L*-rhamnohexaose has been made from an acyclic hexamer having an activatable methylthio group at the reducing terminus and a 4-OH at the other.[96] Along similar but extended lines, compound (**31**) was prepared follow acetolysis of β-cyclodextrin, and coupled with 6-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-*p*-methoxybenzyl-*D*-glucose trichloroacetimidate to give a heptaose which was cyclized to give access to a β-cyclodextin having a 2-amino-2-deoxy-*D*-glucose constituent.[97]



(31)

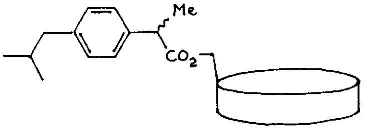


(32)

Significant interest has been taken in cyclodextrins having each ring inverted by conversion to a 3,6-anhydride. The pertosylates of α- and β- cyclodextrins with sodium hydroxide gave good yields,[98] otherwise the tosyl dibenzoate gave the 3,6-anhydro derivative with triethylamine in aqueous methanol.[99] The 6-bromo-6-deoxy derivatives of the α- and β-compounds gave further access (aqueous sodium hydroxide used).[100] Other workers have found that the hepta-*O*-tosyl-β-cyclodextrin bearing an additional single ester group at O-2 also gave the 3,6-anhydride in 92% yield. It seems probable that this process involved an intermediate 2,3-*D*-*manno*-epoxide which then opened by hydroxide attack at C-2.[101]

Considerable progress has been made with the study of substituted derivatives. The *L*-histidyl-*L*-histidyl derivative (**32**), which is a potential enzyme mimic with two recognition sites, has been made from a 6-deoxy-6-iodo-β-cyclodextrin.[102] A somewhat related pair of substances, 6-*N*-(*N'*-formyl-*D*- and *L*-phenylalanyl)-6-amino-6-deoxy-β-cyclodextrin, were made from the 6-amino compound and their inclusion behaviour was studied.[103] In similar work the 6-monoazide was partially methylated and reduced, and the amino product was coupled with both enantiomers of *N*-protected phenylalanine.[104] Other workers have reported the fully *O*-methylated 6-azido-6-deoxy β-compound.[105]

The mono-6-tosylated β-cyclodextrin gave mixed diastereoisomers (**33**) when treated with the cesium salt of the appropriate acid (Ibuprofen), and the isomer derived from the (R)-acid was 10 times more sensitive to hydrolysis at pH 11.5.[106] Tosylates have also given access to derivatives carrying one and two 7,8-dimethylalloxazine groups.[107]



(33)

Partial silylation of β-cyclodextrin with TBDMSCl in pyridine gave mixed diethers which were separated and characterized.[108] The heptakis ether, available in 73%, was selectively tosylated (*N*-tosylimidazole, NaOMe) to give 22% of the mono-2-ester which was converted into the mono-2,3-*D-manno*-anhydride in 87% yield. It is proposed that this compound will allow the attachment of catalytic groups in a specifically defined manner.[109]

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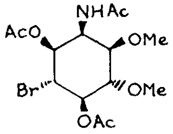
5

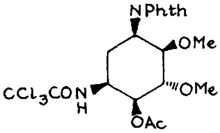
Ethers and Anhydro-sugars

1 Ethers

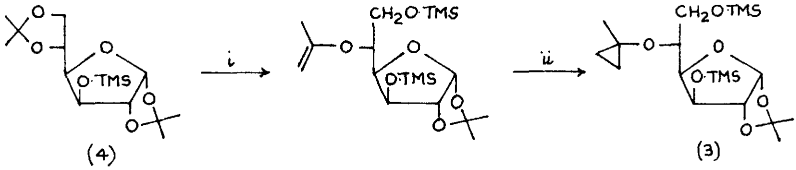
Methyl Ethers. - Some partially methylated glucose and glucoside derivatives have been prepared by the Haworth method and separated by reverse-phase HPLC,[1] while the tetra- and tri-*O*-methyl ethers of methyl α-D-mannopyranoside, and their respective acetates have been synthesized.[2] A study of the partial methylation of 1,6-anhydro-β-D-glucopyranose employing methyl iodide, dimethyl sulfate or diazomethane has found that the formation of intermediate complexes with transition metal ions dramatically changes the relative reactivity of the hydroxyl groups.[3] Improved preparations of 2,3,3′,4,4′-penta-*O*-methyl sucrose and 1 ,2,3,3′,4,4′-hexa-*O*-methyl sucrose have been described,[4] while, contrary to earlier claims,the 6-*O*-methylation of methyl 2,3,4-tri-*O*-acetyl-α,β-D-mannopyranoside (BF_3OEt_2, CH_2N_2) was accompanied by a small amount of acetyl migration.[5] Demethylation of methyl ethers has been achieved by initial oxidation to formate esters. For example, di-*O*-methyl ethers (**1**) and (**2**) were oxidized by chromium trioxide to the corresponding formate esters and subsequently hydrolysed to the respective diols.[6]



(1)



(2)



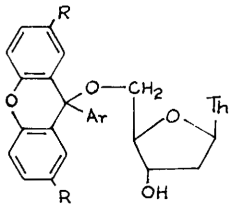
Reagents: i, TMSOTf, Pr^i_2NEt, CH_2Cl_2 ; ii, Et_2Zn, CH_2I_2

Scheme 1

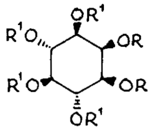
Other Alkyl and Aryl Ethers. - The preparation of selectively *O*-alkylated saccharides, including benzyl, allyl, triphenylmethyl, and arylalkyl ethers has been reviewed.[7] Analogues of lipids A and X incorporating 3-*O*-alkyl (rather than acyl) linkages have been described,[8,9] and some carbohydrate monoalcohol derivatives have been alkylated with haloacetic acid ester derivatives.[10] 3-*O*-Carboxymethyl D-glucose and D-fructose compounds have been coupled *via* the carboxylic acid group to L-lysine in a search for acrosin inhibitors.[11]

The 1-methylcyclopropyl (MCP) ether has been proposed as a protecting group for hydroxyl groups. Ether (3) was prepared in two steps from acetal (4) (Scheme 1). The MCP ether is stable to strong base, moderate acid, reduction and most organometallics. Deprotection is achieved by use of NBS, bromine or DDQ in wet organic solvents or by trifluoroacetic acid treatment.[12] The 9-phenylxanthene-9-yl protecting group has been used with success. These derivatives tend to be crystalline and have good UV chromophoric properties. Deprotection of derivative (5) was effected by 1 M trifluoroacetic acid.[13] Convenient syntheses of 2,3,5-tri-*O*-benzyl-L-arabinofuranose, 2,3,5-tri-*O*-benzyl-D-ribofuranose, and 2,3,4-tri-*O*-benzyl-L-arabinopyranose from the corresponding free sugars in overall yields of ≥ 70% have been reported.[14]

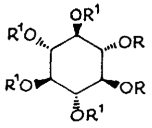
α-Cyclodextrin has been alkylated (NaOH, $CH_3(CH_2)_4Br$, DMSO) to give hexakis-(2,6-di-*O*-pentyl)-α-cyclodextrin which was further alkylated (NaH, $CH_3(CH_2)_4$ Br, THF) to give hexakis-(2,3,6-tri-*O*-pentyl)-α-cyclodextrin.[15]



(5) R = H or Br



(6) R = H, $R^1 = C_nH_{2n+1}$, n = 4-8
(7) R^1 = H, R = C_6H_{13}

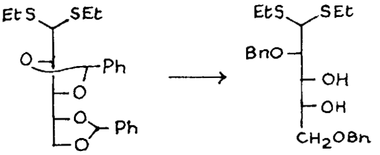


(8) R = H, $R^1 = C_nH_{2n+1}$, n=4-8
(9) R^1 = H, R = C_6H_{13}
(10) R = R^1 = C_6H_{13}

Some new inositol ethers (**6**) - (**10**) with liquid crystalline behaviour have been prepared from *myo*-inositol,[16] and a symposium has reported on the use of 4-nitrobenzyl and 4-pivaloylaminobenzyl groups for the protection of hydroxyl groups in the synthesis of complex carbohydrates.[17] A modified procedure whereby the 3-*O*-alkylation and 3-*O*-benzylation of methyl α-D-manno-, α-L-rhamno- and β-L-fuco-pyranoside can be effected directly in good yield *via* organotin derivatives has been described.[18]

Reduction of 2,3:4,5-di-*O*-benzylidene D-arabinose diethyldithioacetal (**11**) with $LiAlH_4/AlCl_3$ gave the single product (**12**), whereas the 2,4:3,5-substituted analogues of the

D-*lyxo*-and D-*xylo*- compounds gave the 4,5-and 2,3-dibenzyl ethers, respectively. Other related acetals gave mixed products.[19] Reduction of isopropylidene derivative (**13**) with $ClBH_2.SMe_2$ has afforded the isopropyl ether (**14**)[20] while fluorenylidene acetal (**15**) with $AlClH_2$ gave the 2-*O*-(axial) fluorenyl ether (**16**).[21]



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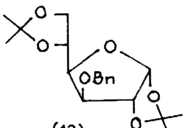

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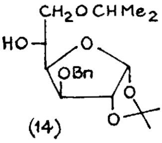

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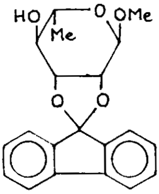

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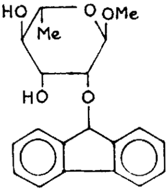

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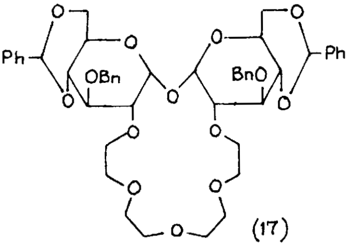


(17)

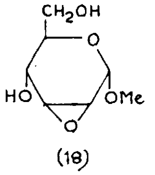
A number of trehalose-based crown ethers such as (**17**) have been prepared, and their conformations determined by NMR spectrometry.[22] The NMR study of several other glucose-derivative-containing crown ethers is discussed in Chapter 21. The intramolecular cyclization of some 4-*O*-oligoethylene glycol derivatives of 1,6-anhydro-β-D-glucopyranose to form crown ethers has been described.[23]

2 Intramolecular Ethers (Anhydro-sugars)

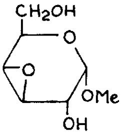
Oxirans. - Methyl α-D-glucopyranoside has been oxaphosphoranylated with diethoxytriphenylphosphorane and the product mixture was thermolysed to give epoxides (**18**) and (**19**). The thermolysis was accelerated by the presence of LiBr, and in this case only epoxide (**18**) was obtained.[24] An improved five-step synthesis of methyl 2,3-anhydro-α- and β-D-lyxofuranosides from D-xylose reports no need for intermediary purifications.[25]

Other Anhydrides. - The metabolism of 1,6-anhydro-β-D-glucopyranose by several microorganisms has been studied and it was concluded that the anhydro-sugar is converted directly into glucose-6-phosphate by a specific enzyme, levoglucosen kinase.[26] D-Galactose has been converted into the anhydro-nonenose (**20**) which was hydrolysed by a D-galactosidase in

D_2O specifically affording the deuterated derivative (**21**) which was converted into the 1,6-anhydrononose (**22**) and its C-4 epimer.[27] The structure-activity relationships of a series of carbohydrate derived herbicides incorporating 1,6-anhydro-4-*O*-benzyl-3-deoxy-2-*O*-methyl-β-D-*ribo*-hexopyranose as the core structure have been disclosed.[28]



(18)



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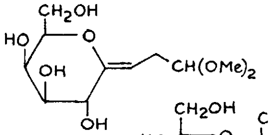

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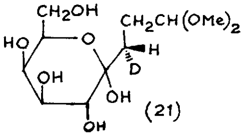

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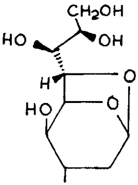
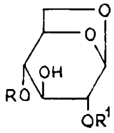


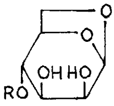
(22)

The glycosylation of some substituted 1,6-anhydro-β-D-mannopyranose derivatives is discussed in Chapter 3. Acetolysis of 1,6-anhydrosugars has been effected by reaction in Ac_2O catalysed by triethylsilyl triflate at 0°C - conditions under which a wide variety of protecting groups are unaffected.[29] Dialdehydes produced by periodate cleavage of anhydrosugars (**23**) and (**24**) undergo pinacol coupling in the presence of samarium diiodide affording *cis*-products (**25**) and (**26**) respectively.[30] Levoglucosenone has been converted into 1,6-anhydro-β-D-allopyranose by procedures involving selective reduction of the carbonyl group and *cis*-hydroxylation of the double bond,[31] whereas 6-hydroxy pyranose glycals in the presence of iodonium *sym* dicollidine perchlorate have afforded 1,6-anhydro-2-deoxy-2-iodo-β-D-hexopyranoses.[32]



(23) R = $SiPh_2Bu^t$, R^1 = H

(24) R = H, R^1 = $SiPh_2Bu^t$



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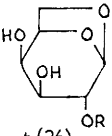
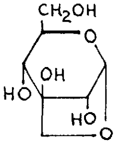


R = $SiPh_2Bu^t$ (26)



(27)

2,6-Anhydro-β-D-fructofuranose has been synthesized in 70% yield by heating sucrose at 170°C in dibenzyl ether.[33] 1,5-Anhydro-β-D-ribofuranose has been converted into its 2- and 3-deoxy derivatives in order to synthesize polydeoxyriboses by polymerization,[34] and the ring-opening polymerization of 1,4-anhydro-6-deoxy-β-L-talopyranose derivatives has led to 6-deoxy-(1→4)-α-L-talopyranan, the first synthetic deoxyhexopyranan with cellulose type structure.[35] The 3-*C*-hydroxymethyl derivatives of D-xylose, L-lyxose, D-ribose and D-glucose have each been shown to be in equilibrium with a new type of anhydrosugar-1,3′-anhydro-3-*C*-hydroxymethylaldoses, *e.g.* (**27**).[36]

When D- and L-sorbose were mixed with hydrogen fluoride in liquid sulfur dioxide α-D-sorbopyranose-α-L-sorbopyranose 1,2′:2,1′-dianhydride was formed preferentially, and similar treatment of D-sorbose and D-fructose afforded β-D-fructopyranose-α-D-sorbopyranose 1,2′:2,1′-dianhydride.[37] Some 1,3-anhydro-β-D-mannopyranose derivatives have been prepared by conventional means,[38] and the NMR spectra of some 1,3-anhydro-β-L-rhamnopyranose and -β-D-mannopyranose ethers are covered in Chapter 21.

A novel enzyme which releases 2,7-anhydro-α-*N*-acetylneuraminic acid from glycoproteins has been identified in the leech *Macrobdella decora*,[39] and the fungus *Peziza echinospora* has enzymic activity that degrades α-(1→4)-D-glucans (*e.g.* starch) to 1,5-anhydro-D-fructose and thence to the cyclopentane antibiotic echinosporin.[40] The synthesis of 3,6-anhydro-α and β-cyclodextrins is discussed in Chapter 4.

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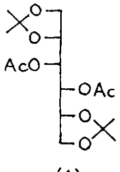
6

Acetals

Acetonation of D-mannitol with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in pyridine followed by *in situ* acetylation, then by isolation and deacetylation of the crystalline diacetate (**1**), has been recommended as a practicable procedure for the preparation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol.[1] Acrylates and methacrylates of xylitol diacetonides are referred to in Chapter 7.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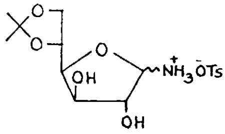
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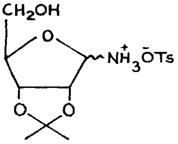
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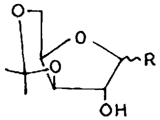
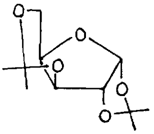

(4) R = $\overset{+}{N}H_3\overset{-}{O}Ts$

(5) R = OH

5,6-*O*-Isopropylidene-D-glucofuranose, 2,3-*O*-isopropylidene-D-ribofuranose, and 3,5-*O*-isopropylidene-D-xylofuranose are readily available by acetonation of the corresponding glycosylamines to give the known intermediates (**2**)-(**4**), respectively, and subsequent hydrolysis of the amino function at pH 5.[2] 2,3-*O*-Isopropylidene-D-lyxofuranose was obtained in 68% yield in the *p*-TsOH-catalysed, kinetic reaction of D-lyxose with 2 molar equivalents of 2-methoxypropene in DMF. Under identical conditions, D-xylose gave a mixture of the monoacetal (**5**) and the diacetals (**6**) and (**7**) (*ca.* 4:3:2).[3]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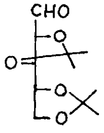
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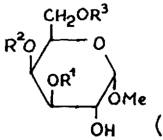
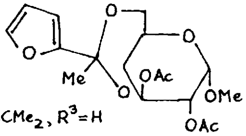
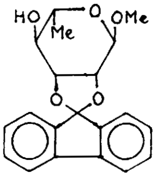

(8) R^1,R^2 = :CMe$_2$, R^3=H

(9) R^1=H, R^2,R^3= :CMe$_2$


(10)

2-Chloro-2-methoxypropane has been found to be an excellent reagent for the fast and clean isopropylidenation of methyl glycopyranosides. The 3,4-acetal (**8**), for example, was obtained in 74% yield from methyl α-D-galactopyranoside. However, when 4Å molecular sieves as acid scavengers were present, the kinetic 4,6-monoacetals, *e.g.* compound (**9**), were formed as the main products.[4]

4,6-*O*-Pyruvate acetals of methyl hexopyranosides have been prepared by oxidation of the corresponding furan-2-ylidene derivatives, *e.g.* compound (**10**), which in turn were obtained by facile acetal exchange between the sugar 4,6-diol and 2-acetylfuran dimethylacetal (see Vol.24, Chapter 6, Scheme 1).[5] Fluoren-9-ylidene acetals, such as the methyl L-rhamnoside derivative (**11**), have been synthesized by use of 9,9-dichlorofluorene in pyridine at 100°C. Their hydrogenolysis to fluorenyl ethers is covered in Chapter 5.[6]



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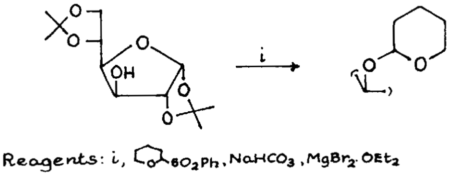

Scheme

A new method for the preparation of tetrahydropyranyl ethers under mild, basic conditions by treatment of sugar alcohols with tetrahydro-2-(phenylsulfonyl)-pyran under sonication in the presence of $MgBr_2.Et_2O$ is illustrated in the Scheme.[7]

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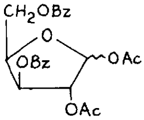
7

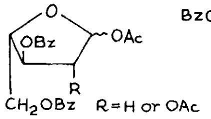
Esters

1 Carboxylic Esters

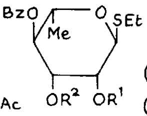
1.1 Synthesis and Reactions.- The new peracylated furanose derivatives (**1**) and (**2**), versatile intermediates in the synthesis of various β-D- and β-L-pentofuranosyl nucleosides, respectively, have been prepared by standard methods.[1,2] All possible monobenzoates and the 3,4-dibenzoate of methyl β-D-xylopyranoside, as well as the 2,4-dibenzoate of the α-anomer, have been obtained by tin-mediated regioselective acylation of suitable precursors.[3]



(1)

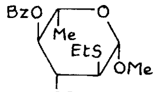


(2)



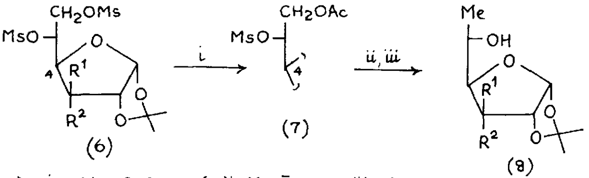
(3) $R^1,R^2 = CH\overset{Ph}{\underset{OMe}{}}$

(4) $R^1 = Bz, R^2 = H$



(5)

Treatment of ethyl 1-thio-α-L-rhamnopyranoside with trimethyl orthobenzoate and catalytic *p*-TsOH in DMF gave, after benzoylation, the orthoester (**3**) which was hydrolysed to the 2,4-dibenzoate (**4**). The same procedure, carried out in acetonitrile, furnished the rearranged product (**5**) instead.[4] The key-step in an improved, large scale synthesis of 6-deoxy-1,2-*O*-isopropylidene-β-L-talo - and -β-L-ido-furanoses (**8**) (Scheme 1) was the selective transformation of the dimesylates (**6**) to the 6-acetate-5-mesylates (**7**).[5]

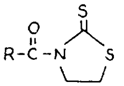


R1, R2 = H,OH

Reagents: i, KOAc, 18-Crown-6 ; ii, MeO⁻, MeOH ; iii, LAH

Scheme 1

The synthesis of 1-*O*-acyl-β-D-glucopyranose tetraacetates by reaction of acetobromoglucose with carboxylic acids (mainly substituted benzoic and cinnamic acids) under phase transfer conditions has been reported.[6,7] 1-*O*-Pivaloyl β-D-glucopyranuronic acid, a metabolite of various pivaloyloxy(alkyl)-containing prodrugs, was prepared by direct, stereo- and regio-selective acylation of D-glucose at the anomeric centre and subsequent oxidation of the primary hydroxyl group with molecular oxygen over platinum.[8]



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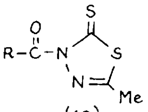

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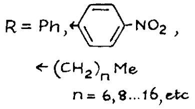
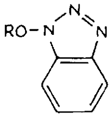
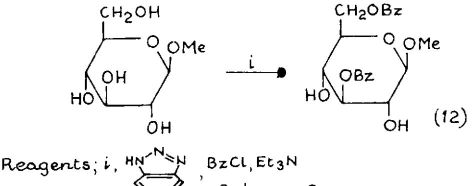




(11) R = Bz, Ts

Efficient, selective 6-*O*-acylation of unprotected free hexoses and hexopyranosides has been achieved with the 3-acylthiazolidine-2-thiones (**9**) or with the more reactive 3-acyl-5-methyl-1,3,4-thiadiazole-2(3*H*)thiones (**10**) in pyridine containing NaH or DMF containing DBU, respectively (see Vol.21, p.62, ref.13).[9] An application of reagents (**10**) is shown in Scheme 3 below. A simplified, one-pot procedure has been devised for the acylation of monosaccharide derivatives by use of 1-acyloxy-1*H*-benzotriazoles (**11**) (see Vol.24, Chapter 7, ref.25), with *in situ* generation of the reagents from 1-hydroxy-1*H*-benzotriazole and acid chlorides in the presence of triethylamine. Unusual regioselectivity was observed in some cases; an example is given in Scheme 2. [The dibenzoate (**12**), isolated in 50% yield, is a new compound.][10]



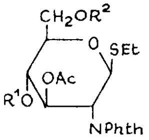
Scheme 2

Peracetylated D-glucal, D-galactal, and D-rhamnal were selectively deprotected at O-4 by treatment with hydrazine acetate in DMF (see Vol.20, Chapter 13, ref.3). The possibility of initial deacetylation at the primary position followed by 4→6 acetyl migration was excluded on the basis of experiments with deuteroacetylated starting compounds.[11] The 4→6 acetyl migration to give the 3,6-diacetate (**14**) from its 3,4-isomer (**13**) has been studied in some detail and optimized in order to prepare (1→4)- and (1→6)-linked disaccharides from a common carbohydrate aglycon (see Chapter 3).[12]

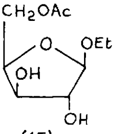
The selective acylation of some aryl *C*-gluco- and -galacto-pyranosides has been studied by use of ^{13}C-n.m.r. spectroscopy as the preferred method for product analysis.[13]

The application of lipases to the preparation of sugar esters has been reviewed,[14] and a short section with 18 refs. on the formation and hydrolysis of carbohydrate esters is included in a review on the use of esterolytic and lipolytic enzymes in organic synthesis.[15]

Several 6-*O*-acetyl derivatives, *e.g.*, compound (**15**), were obtained with excellent regioselectivity and in high yields by the pancreatin-mediated transesterification of ethyl hexopyranosides and -furanosides with vinyl acetate in THF/Et_3N,[16] and methyl α-D-glucopyranoside was protected at O-6 with a variety of acyl groups under lipase-catalysis with oxime esters as acyl transfer agents.[17] For the selective primary acylation of aminosugars, nucleosides, and related substrates mutants of subtilisin engineered for stability and high activity in DMF have been used.[18] The tripivaloate (**16**) and similar compounds were hydrolysed preferentially at O-6 on exposure to partially purified esterase from rabbit serum.[19]



(13) $R^1 = Ac, R^2 = H$
(14) $R^1 = H, R^2 = Ac$



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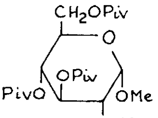
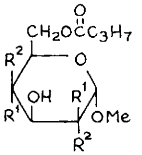
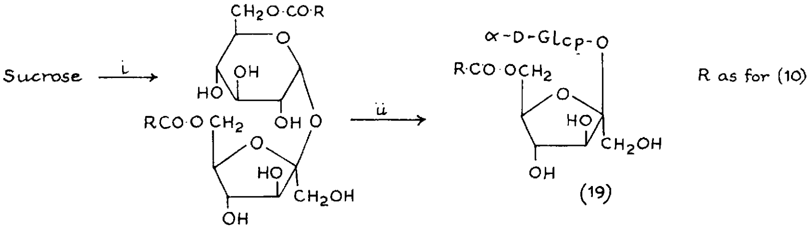


(16)



(17) $R^1 = H, R^2 = OH$
(18) $R^1 = OH, R^2 = H$

The secondary butanoylation of 6-*O*-butanoyl esters (**17**) and (**18**) and their enantiomers by a number of lipases in organic solvents has been investigated in some detail. Good yields of the 2,6- and 2,4-diester, respectively, were obtained from the D-galactoside and from the L-mannoside.[20]



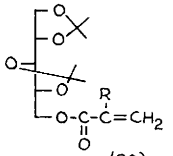
Reagents: i, (10), DMF; ii, Lipase from *Candida cylindracea*

Scheme 3

6′-*O*-Acylsucroses (**19**) have become available for the first time by the chemoenzymatic procedure shown in Scheme 3.[21] The 1′-butanoate and the 6,1′-dibutanoate of sucrose were prepared by enzyme-mediated ester transfer from 2,2,2-trifluoroethyl butanoate in anhydrous pyridine, but the analogous reaction with 2,2,2-trifluoroethyl adipate showed little regioselectivity.[22] Exposure of peracetylated sucrose to lipase OF, alcalase, *Candida* lipase, or chymotripsin caused preferential hydrolysis at O-6, O-1′, O-4′, and O-6′, respectively, giving the various heptaacetates as the main products,[23] whereas hydrolysis by a *Pseudomonas* lipase afforded a mixture containing the 2,3,4,6,1′,3′,6′-heptaacetate and the 2,3,4,6,3′,6′-hexaacetate in 20 and 41% yield, respectively.[24]

The resolution of racemic synthetic glycals by means of enantioselective lipase-mediated acetylation is referred to in Chapter 13.

In the course of a study on hydrogels containing xylitol moieties, the polymerizable esters **(20)** and **(21)** were prepared from the corresponding xylitol diacetonides by use of standard methods (acid anhydride/pyridine or acid chloride/NaH).[25]



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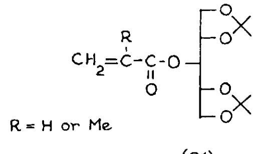

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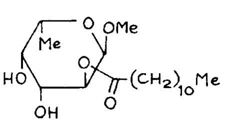
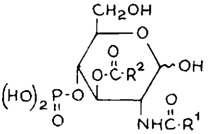


(22)

The sodium salts of phosphated caproyl and myristoyl acyl derivatives of mannitol have been synthesized and evaluated as surfactants.[26] Methyl 2-*O*-dodecanoyl-α-L-fucopyranoside **(22)**, obtained from the free sugar *via* methyl 3,4-*O*-isopropylidene-α-L-fucopyranoside, is a representative of a new type of liquid crystal (see also Chapter 12).[27] An improved procedure has been devised for the preparation of 6-mono- and 6,6′-di-*O*-corynomycoloyl-α,β-trehalose and related trehalose esters which involved coupling of the TBDMS-protected hydroxyacids to the partially trimethylsilylated sugars in the presence of DCC and DMAP,[28] and 6,6′-di-*O*-mycoloyl-α,β- and β,β-trehalose have been synthesized for use in biological activity tests, *via* benzyl-protected intermediates.[29] A series of 6-mono- and 6,6′-di-polyfluoroalkanoates of α,α-trehalose have been obtained by application of Mitsunobu methodology.[30] *C*-Glycosides of 2,3-dideoxy-2-enopyranos-4-uloses esterified at O-6 with long-chain fatty acids are covered in Chapter 3.

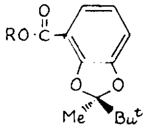


(23) $R^1 = CH_2CH(OH)(CH_2)_nMe$, n = 8,10,12

$R^2 = CH[(CH_2)_{13}Me]_2$

(24) $R^1 = CH[(CH_2)_{13}Me]_2$

$R^2 = CH_2CH(OH)(CH_2)_nMe$, n = 8,10,12

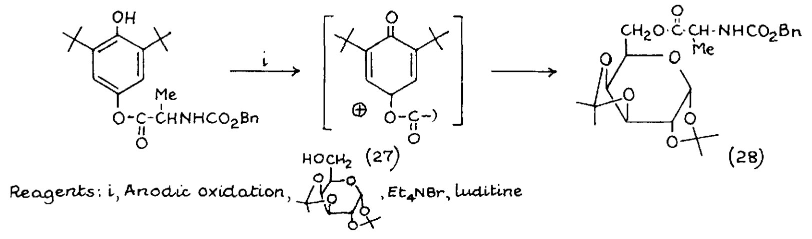


(25) $R = \beta$-D-Glc*p*$(OAc)_4$

(26) $R = \beta$-L-Glc*p*$(OAc)_4$

The synthesis of novel lipid A subunit analogues **(23)** and **(24)**, which carry an alkyl-branched instead of an ester-branched long-chain fatty acyl group at N or O-3, respectively, followed the general protocol established for this class of compounds.[31] Further Lipid A and Lipid X analogues are referred to in Chapters 5 and 8.

Diastereomeric 1-*O*-acyl-β-glycopyranosyl tetraacetates, such as compounds **(25)** and **(26)** [formed by reaction of (-)-2-*t*-butyl-2-methyl-1,3-benzodioxole-4-carboxylic acid with acetobromo-D- and -L-glucose, respectively], are readily distinguished by ^{1}H-n.m.r. spectroscopy due to the characteristically different chemical shifts of the respective *t*-butyl and methyl resonances. A method for determining the absolute configuration or enantiomeric purity of monosaccharides based on these findings is envisaged.[32]



Scheme 4

Electrochemically produced phenoxonium ions (**27**) reacted with sugar alcohols, *e.g.*, diacetonegalactose, to give glycosamino acid esters (**28**), as outlined in Scheme 4.[33] The preparation of the carbohydrate-enkephalin conjugates (**29**) by solution fragment coupling has been reported (see also Chapter 9).[34]

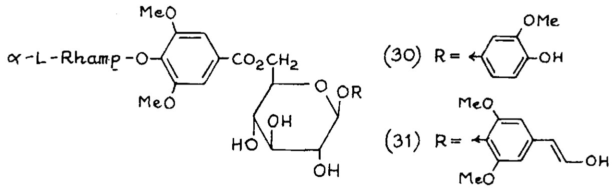
(**29**) 6-*O*-(H-Tyr-Gly-Gly-Phe-X)-Glc X = Leu or Met

A simple procedure for the resolution of 2,3-dideoxy-DL-2-enopyranos-4-uloses *via* their l-alanine esters is referred to in Chapter 13.

1.2 Isolation from Natural Sources.- The very bitter tasting constituents of certain stone-fruit have been shown to be 1,6,2′,6′-tetra- and 1,6,2′,4′,6′-penta-*O*-acetyl-3-*O*-coumaroyl-sucrose.[35] Six derivatives of octyl 4-*O*-acetyl-a-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-acetyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-hexanoyl-α-L-rhamnopyranoside, extracted from the bark of *Mezettia leptopoda*, have been characterized by n.m.r. and m.s. methods.[35a]

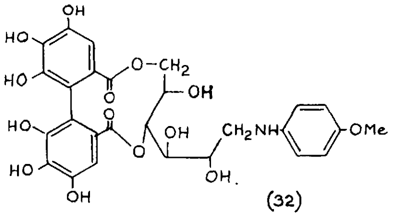
Sitosterol 3-*O*-(2′-*O*-acetyl-6′-*O*-stearoyl)-β-D-xylopyranoside and sitosterol 3-*O*-(2′-*O*-stearoyl)-β-D-xylopyranoside have been isolated from the aquatic plant *Pistia stratiotes*,[36] and the highly piscicidal factors of the flower *Edgeworthia chrysantha* have been identified as sitosterol 3-*O*-(6′-*O*-linoleoyl)- and 3-*O*-(6′-*O*-linolenoyl)-β-D-glucoside.[37]

The ether soluble resin glycosides from the roots of *Ipomoea operculata* were found to be linear tetrasaccharides containing decanoyl and/or dodecanoyl ester groups as well as a lactone macrocycle.[38] Kalopanaxin B (**30**) and C (**31**), two new phenolic glycosides from the bark of *Kalopanax pictus*, are remarkable in that they consist of two phenolic glycoside moieties joined by an ester linkage.[39] The major violet-blue anthocyanin pigment of *Pharbitis nil* flowers has been characterized as peonidin 3-[6″-(4-glucosyl-*trans*-caffeoyl)-sophoroside]-5-glucoside, a structure comprising a rather unusual, caffeoyl-bridged trisaccharide moiety.[40]

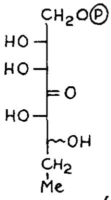


1,2,6-Tri-, 1,3,6-tri-, and 1,2,3,6-tetra-*O*-galloyl-β-D-allopyranoses have been extracted from the roots of *Euphorbia fischeriana*,[41] and five new elagitannins containing interlinking xylose or the unusual lyxose residues between polyphenolic units have been isolated from the heartwood of English oak.[42] An unusual tannin with a sugar acid core is referred to in Chapter 16.

Some naturally occurring hydrolysable tannins have been reductively aminated (*p*-anisaldehyde/$NaBH_3CN$) without concomitant hydrolysis of the ester linkages, thereby providing iminoalditol derivatives such as compound (**32**) which have relatively simple n.m.r. spectra, since they do not tautomerize.[43]



(32)

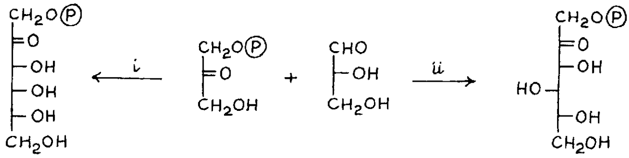


(33)

2 Phosphates and Related Esters

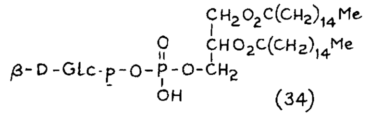
N.m.r. studies on glucose 1-phosphate and fructose 6-phosphate are referred to in Chapter 21. The synthesis of ketose 1-phosphates catalysed by aldoses from genetically engineered *E. coli* has been reported. As shown in Scheme 5, the new carbon-carbon bond was formed with high D-*erythro*- or L-*threo*-selectivity by use of L-fuculose 1-phosphate aldolase (FucA) and L-rhamnulose 1-phosphate aldolase (RhuA), respectively.[44] In a 3-hexulose phosphate synthase-mediated aldol reaction, D-ribulose 5-phosphate was condensed with a wide range of aldehydes. Use of propanol, for example, gave the two (5*S*)-configurated 7,8-dideoxy-4-octulose 1-phosphates (**33**) in 1:2.4 (6*S*)/(6*R*) ratio.[45]

α ,β-Mixtures of glycosyl dibenzyl phosphates have been obtained by treatment of protected 4-pentenyl glycosides with dibenzyl phosphate in the presence of NBS.[46] By use of the same phosphorylating agent protected 1,2-*trans*-glycosyl phosphates have been synthesized from perbenzoylated ethyl 1-thioglycosides under iodonium ion catalysis,[47] and from peracetylated glycosyl bromides under phase transfer conditions.[48] Exposure of perbenzylated or peracetylated β-L-fucopyranosyl trichloroacetimidates to dibenzyl phosphate in the presence of boron trifluoride etherate (thermodynamic conditions) or very pure dibenzyl phosphate (kinetic conditions) gave the protected α- or β-L-fucopyranosyl phosphates, respectively, in excellent yields and with high stereoselectivity.[49] The use of these phosphates in the preparation of GDP-fucose is covered in Chapter 20. The trichloroacetimidate approach has also been employed in the stereoselective synthesis of β-phosphatidylglucose (34).[50]



Reagents: i, L-Fuculose-1-phosphate aldolase; ii, L-Rhamnose 1-phosphate aldolase

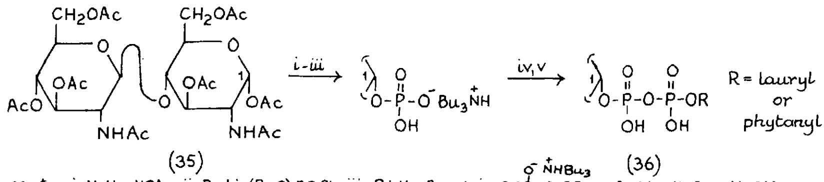
Scheme 5



β-D-Glc-p-O-P(O)(OH)-O-CH$_2$-CH(O$_2$C(CH$_2$)$_{14}$Me)-CH$_2$O$_2$C(CH$_2$)$_{14}$Me

(34)

The simple analogues (36) of the natural mannosyl transferase acceptor substrate (GlcNAc)$_2$-pyrophosphate-dolichyl have been synthesized from chitobiose octaacetate (35) as shown in Scheme 6.[51,52]

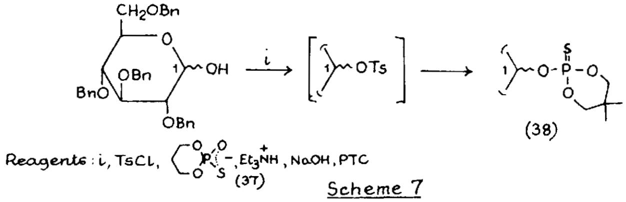


Reagents: i, N_2H_4, HOAc; ii, BuLi, $(BnO)_2POCl$; iii, Pd, H_2, Bu_3N; iv, $\mathrm{RO\underset{O}{\overset{O^-\,\overset{+}{N}HBu_3}{P}}-O-\underset{S}{P}Bu_2}$, AgOAc, H_2S; v, NaOMe

Scheme 6

A new, high-yielding preparation of *O*-glycosyl phosphorothioates, such as the glucose derivative (38), involved tosylation at O-1 of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and subsequent displacement of the tosyloxy group by the 5,5-dimethyl-2-hydroxy-2-thiono-1,3,2-dioxophosphorinane anion (37) in a one-pot procedure under phase transfer conditions, as exemplified in Scheme 7.[53] The application of glycosyl phosphorodithioates to the synthesis of

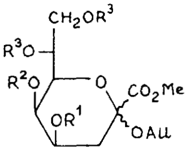
2′-deoxydisaccharides is referred to in Chapter 3, and ^{31}P-n.m.r. spectroscopic studies on a variety of glycosyl phosphite derivatives are covered in Chapter 21.



Reagents: i, TsCl, $\overset{+}{Et_3NH}$, NaOH, PTC (37)

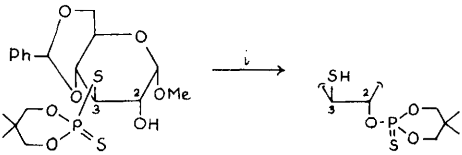
Scheme 7

The monophosphorylated allyl glycosides (**40**) and (**41**) of KDO were prepared by non-selective phosphorylation of compound (**39**) by use of the phosphoramidate method, chromatographic separation of the resulting 1:1 mixture and acetal hydrolysis.[54] Various Lipid A analogues (derivatives of 2-amino-4-phosphono-D-glucose) are referred to in Part 1.1 of this Chapter and in Chapters 5 and 8. The mechanism of the migration of thiophosphoryl groups from O to S in sugar β-hydroxyphosphorodithioates (an example is given in Scheme 8) has been investigated.[55]



(39) $R^1 = R^2 = H$, $R^3, R^3 = C(Me)_2$
(40) $R^1 = R^3 = H$, $R^2 = PO_3H_2$
(41) $R^1 = PO_3H_2$, $R^2 = R^3 = H$

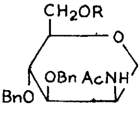
The aminosugar (**42**) (see Chapter 9 for its synthesis) was converted to its 6-phosphate (**43**) *via* 1*H*-tetrazole-mediated phosphitylation with bis(benzyloxy)-*N*,*N*-diisopropylaminophosphine,[56] and the D-fructofuranose 6-phosphate derivative (**45**) was obtained from the selectively protected precursor (**44**) (see Chapter 2 for its synthesis from sucrose) by exposure to 2-chloro-1,3,2-dioxaphosphorinane-2-oxide followed by debenzylation.[57]



Reagent: i, Py

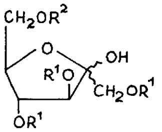
Scheme 8

The preparation of the peptidyl dimannosyl phosphate (**46**) by conventional methodology has been described (see Chapter 3 for the synthesis of the dimannosyl moiety).[58] The synthesis of ribonucleoside 5′-triphosphates is referred to in Chapter 20.



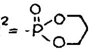
(42) R = H

(43) R = $-\overset{O}{\overset{\|}{P}}(OH)-O(CH_2)_{15}Me$

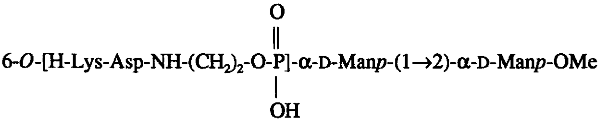


(44) R¹ = Bn, R² = H

(45) R¹ = H, R² =

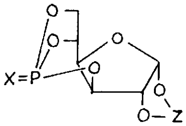


A series of glucose 6-phosphate analogues bearing at C-6 an acylester-, thioacylester-, phosphonate-, thiophosphate-, or thiophosphoramidate-group have been prepared as potential hexokinase inhibitors, starting from chlorophosphites or by Arbuzov-type reaction.[59] 6-Thioglucose 6-phosphate is also referred to in Chapter 11, and phosphorylated 6-aminosugars are covered in Chapter 9.

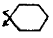


(46) $6\text{-}O\text{-}[\text{H-Lys-Asp-NH-}(CH_2)_2\text{-O-}\overset{O}{\overset{\|}{\underset{OH}{\underset{|}{P}}}}]\text{-}\alpha\text{-D-Man}p\text{-}(1\rightarrow2)\text{-}\alpha\text{-D-Man}p\text{-OMe}$

1,2-*O*-Alkylidene-α-D-glucofuranose 3,4,5-bicyclic phosphites (**47**) have been ozonized to the corresponding bicyclic phosphates (**48**). Hydrolysis of compound (**48**, Z = CMe_2), followed by esterification, furnished the monocyclic phosphate products (**49**).[60]

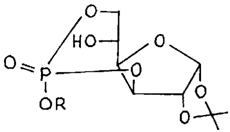


Z = >CMe₂, >CHCCl₃, or



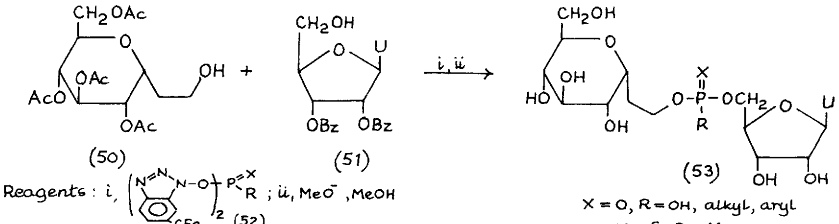
(47) X = :

(48) X = O



(49) R = H, Me, Et, or Bu

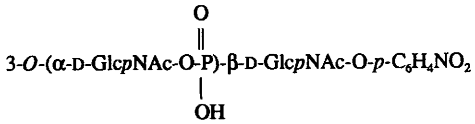
Analogues (**53**) of UDP glucose have been prepared by one-pot coupling of the peracetylated (2-hydroxyethyl) *C*-glycoside (**50**) and 2′,3′-di-*O*-benzoyl-uridine (**51**) with



Scheme 9

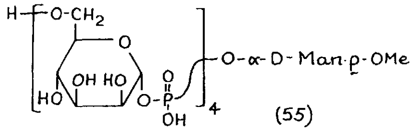
bifunctional phosphorylation-, phosphonylation-, and thiophosphonylation-reagents (**52**) as shown in Scheme 9.[61] The syntheses of sugar phosphate diesters of biological interest such as the (1→3)-linked 2-acetamido-2-deoxy-D-glucose derivative **(54)**[62] and the (1→6)-linked oligomer **(55)**[63] have been reported.

(54)

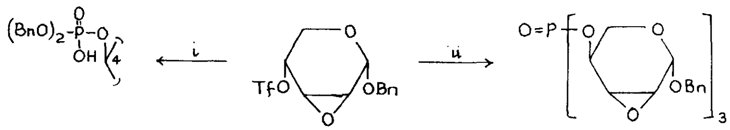


$$\text{3-}O\text{-}(\alpha\text{-D-Glc}p\text{NAc-O-}\overset{\overset{\displaystyle \text{O}}{\|}}{\underset{\underset{\displaystyle \text{OH}}{|}}{\text{P}}})\text{-}\beta\text{-D-Glc}p\text{NAc-O-}p\text{-}C_6H_4NO_2$$

An efficient new approach to novel mono- and tri-sugar phosphates makes use of triflate displacements with dibenzyl phosphate and tetrabutylammonium dihydrogenphosphate, respectively. Examples are given in Scheme 10.[64]



(55)



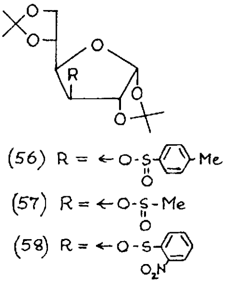
Reagents: i, $(BnO)_2P(O)OH$, collidine, THF ; ii, $Bu_4NH_2PO_4$, collidine, THF

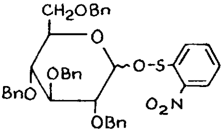
Scheme 10

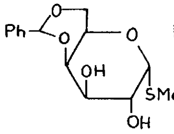
3 Sulfonates and Related Esters

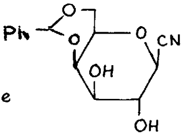
The allylsulfonyl group, introduced by reaction with allylsulfonyl chloride in the presence of a tertiary amine, has been shown to be a useful new hydroxyl protecting group. While stable towards deacetylation, desilylation, and acetal hydrolysis, it is selectively removed under mild conditions by palladium (0)-mediated allyl transfer to morpholine.[65]

The sulfinates **(56)** and **(57)** have been prepared in high yields by reaction of diacetoneglucose with tosyl- or mesyl-cyanide in the presence of DBU or DABCO,[66] and the diasteres (+)**(57)** and (-)**(57)** were obtained in *ca.* 90% d.e. by use of methanesulfinyl chloride in pyridine or ethyldiisopropylamine, respectively.[67] Their application to the synthesis of enantiomeric sulfoxides is referred to in Chapter 24. Carbohydrate sulfenates such as the glucofuranose derivative **(58)** and the glucopyranosyl derivative **(59)** were formed on treatment of the corresponding hydroxy compounds with 2-nitrobenzenesulfenyl chloride.[68]


(56) R =
(57) R =
(58) R =

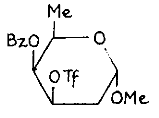

(59)

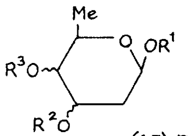

(60)

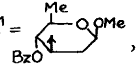

(61)

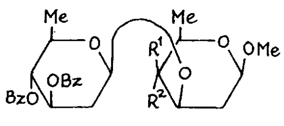
The monotosylation of methyl glycosides *via* dibutylstannylene complexes proceeded with interesting selectivity. The 3-O-tosylates of methyl α- and β-D-galactoside and of methyl α-D-mannoside, for example, were obtained regiospecifically in 62, 78, and 65% yield, respectively.[69] Good regioselectivity was achieved in the monotriflation of several carbohydrate diols and triols under conventional reaction conditions (1.1 molar equivalents of Tf_2O in pyridine). It was observed, in confirmation of previous findings, that hydroxyl groups flanked by a *cis*-vicinal heteroatom, *e.g.*, 2-OH of compound **(60)**, 3-OH of compound **(61)**, have enhanced reactivity.[70] The preparation of tosylated cyclodextrins is covered in Chapter 4.

The fragmentation of triflate **(62)** in aqueous pyridine (see Vol.24, Chapter 7, ref.91) has been investigated in more detail and the reaction path originally proposed has been firmly established.[71] The eight possible monobenzoylated methyl 2,6-dideoxy-β-D-hexopyranosides **(63)** have been interconverted *via* their triflates **(64)**, the triflyloxy group being displaced either intramolecularly by the neighbouring benzoyl group (see Vol.24, Chapter 7, ref.86) or intermolecularly with tetrabutylammonium nitrite. The inversion reactions were also applied to several disaccharides **(65)**, required in the synthesis of mithramycin and related antitumour agents.[72] In addition, the perbenzoylated disaccharides **(66)** were prepared by use of the 3-*O*-benzoyl-*arabino*- and -*lyxo*-isomers **(63)** as glycosyl acceptors.[73]

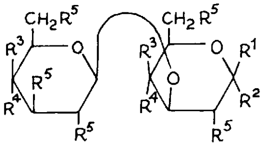

(62)


(63) $R^1 = Me, R^2, R^3 = H, Bz$
(64) $R^1 = Me, R^2, R^3 = Tf, Bz$
(65) $R^1 =$


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


(66) $R^1, R^2 = H, OBz$

Derivatives of the biologically important disaccharide sequence β-D-Gal*p*-(1→3)-D-Gal, *e.g.*, compounds **(69)** and **(70)**, were prepared from laminaribiose octaacetate **(67)** in seven steps *via* the ditriflate **(68)**.[74] An improved synthesis of 2,3-anydro-α- and -β-D-lyxofuranosides involving mesylated intermediates is covered in Chapter 5, and the ring contraction of certain glycopyranoside monotosylates on exposure to LAH in Chapters 12 and 14. Further displacement reactions of sugar sulfonates are found in Part 1 of this Chapter, and in Part 4 just below, and a sulfonate analogue of adenosine is referred to in Chapter 11.

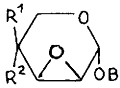


(67) $R^1 = H$, $R^2 = OAc$, $R^3 = H$, $R^4 = R^5 = OAc$
(68) $R^1 = OBn$, $R^2 = R^3 = H$, $R^4 = OTf$, $R^5 = OBn$
(69) $R^1 = OBn$, $R^2 = H$, $R^3 = OBz$, $R^4 = H$, $R^5 = OBn$
(70) $R^1 = OBn$, $R^2 = H$, $R^3 = SAc$, $R^4 = H$, $R^5 = OBn$

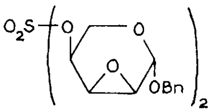
4 Other Esters

The product formed on reaction of triflate (**71**) with $Bu_4{}^+HSO_4{}^-$, reported to be the sulphate (**72**) (see Vol.24, Chapter 7, ref.99), has now been identified as the diglycos-4-yl-sulphate (**73**).[75]

The sulfation of methyl 4,6-*O*-benzylidene-α-D-idopyranoside with SO_3/Me_3N in DMF at -50°C has been examined in an attempt to understand the difference in the sulfation patterns of dermatan and modified heparin. No selectivity was detected.[76] The 4′-sulfate, 6′-sulfate, and 4′,6′-disulfate of β-D-Gal*p*-(1-4)-β-D-Glc*p*A-OBn, *i.e.*, the benzyl glycosides of the repeating units of chondroitin sulphates, have been synthesized by standard procedures in seven steps from lactose *via* the common intermediate (**74**)[77], and their isomers, the 4-sulfate, 6-sulfate, and 4,6-disulfate of β-D-Glc*p*A-(1→3)-β-D-Gal*p*-OBn, have been obtained from precursor (**75**), which was constructed from monosaccharide units.[78]



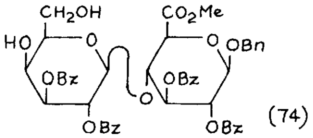
(71) $R^1 = H$, $R^2 = OTf$
(72) $R^1 = OSO_3H$, $R^2 = H$

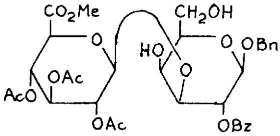


(73)

The characterization of synthetic methyl α-D-mannopyranoside sulfates by n.m.r. spectroscopy and by FAB m.s. is referred to in Chapters 21 and 22, respectively. New sulfated steroidal glycosides from a starfish are mentioned in Chapter 3.

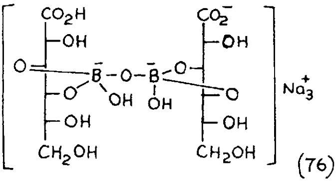
A convenient method for the removal of nitrate groups from the anomeric position, *e.g.*, those introduced by azidonitration of glycals, involving treatment with benzenethiol and ethyldiisopropylamine, has been developed.[79] A study on denitration with hydroxylamine in pyridine established that, whereas trinitrocellulose reacts at the 2-position with high selectivity, the denitration of monomeric model compounds (tetranitrates of methyl α- and β-D-glucopyranoside, methyl α-D-mannopyranoside, methyl β-D-galactoside) takes place preferentially at O-4, to a lesser extent at O-3, and hardly at all at O-2.[80]

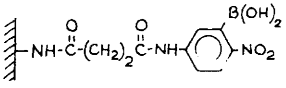

(74)


(75)

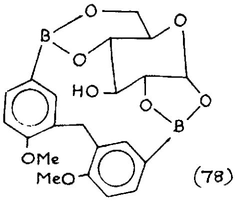
Boron-oxygen-boron bridged gluconatoborate (76) and related complexes of boron with gluconate ions have been prepared and characterized by a variety of analytical techniques.[81] The examination by ^{11}B- and ^{13}C-n.m.r. spectroscopy of borate esters derived from carbohydrate oximes in solution indicated the formation of relatively stable 6-membered borate ester rings between the oxime-OH and C-2-OH.[82]

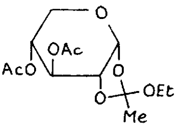
Analysis of pH depression data revealed that, contrary to previous assumptions, the complexation of phenylboronic acid with glucose and galactose to form a 1:2 polyol-phenylboronic acid complex involves positive cooperativity, *i.e.*, the formation of a 1:2 complex is assisted by formation of the 1:1 complex.[83] The complexation of *cis*-diols with various substituted phenylboronic acids was probed with methyl β-D-ribopyranoside. Based on the findings that an aromatic nitro group enhances binding at lower pH, a new boronate affinity column matrix (77) for the fast complexation-decomplexation of methyl β-D-ribofuranoside, sytidine and adenosine was constructed.[84] Highly cross-linked polymers for the racemic resolution of free sugars were prepared by copolymerization of β-D-fructopyranose 2,3:4,5-bis[(4-vinylphenyl)boronate] and the α-D-galactopyranose 1,2:3,4-isomer, respectively, with large amounts of cross-linking agents and subsequent hydrolytic removal of the sugar templates. The former polymer selectively absorbed-D-glucose and L-galactose from racemates, the latter had reverse selectivity.[85] 3- And 4-hexadecyloxyphenylboronic acids selectively extracted saccharides from solids and from neutral or alkaline aqueous solution into $CDCl_3$. The order of extractability was D-fructose > D-glucose > maltose > sucrose.[86]


(76)

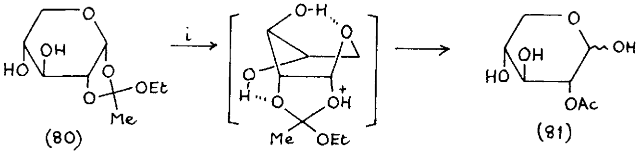

(77)

2,2′-Dimethoxydiphenylmethane 5,5′-diboronic acid became CD active after complexing with D- and L-glucose, with negative or positive Cotton effects, respectively, at 275 nm. Negative CD bands at 275 nm were also displayed on complexation with maltose, cellobiose, and lactose, while a variety of other sugars gave CD inactive complexes. Cyclic structures such as (78) involving two-site binding to the 1,2- and 4,6-diols are thought to be responsible for CD activity.[87]


(78)

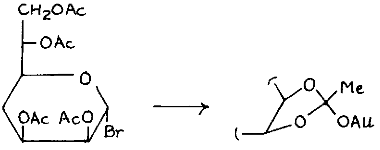

(79)

In a detailed study of the hydrolysis of α-D-gluco- and β-D-manno-pyranose 1,2-orthoesters, various intermediates such as hemiorthoesters, tricyclic 1,2,6-orthoesters, and acyloxonium ions have been detected.[88] Unusual regiochemistry was observed in the opening of α-D-xylopyranose 1,2-ethylorthoacetates. Whereas the protected derivative (**79**) gave the expected 2-hydroxy-1-acetate on exposure to aqueous acetic acid, the more basic O-2 being preferentially protonated, its unprotected analogue (**80**) was protonated at O-1, due to hydrogen bonding between 4-OH and O-2, to give the 2-ester (**81**), as shown in Scheme 11.[89] The orthoester (**83**), rather than the desired allyl α-glycoside, was formed exclusively on treatment of the glycosyl bromide (**82**) with allyl alcohol and silver triflate.[90]

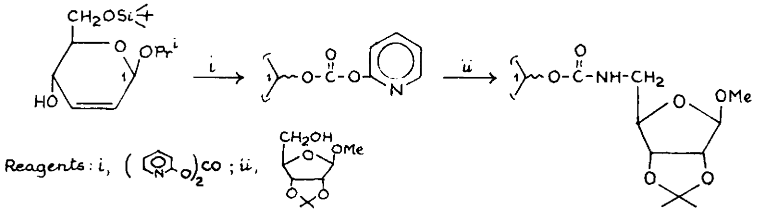


Reagents: i, HOAc, H_2O.

Scheme 11

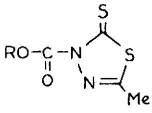

(82) (83)

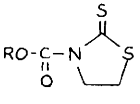
The preparation of mixed carbonates and their transformation to functionalized carbamates by use of di(2-pyridyl) carbonate has been reported. A carbohydrate example is given in Scheme 12.[91]



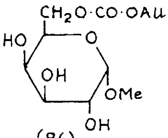
Scheme 12

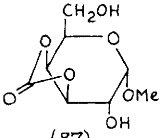
3-Alkoxycarbonyl-2-mercapto-5-methyl-1,3,4-thiadiazoles (**84**) and 3-alkoxycarbonylthiazolidine-2-thiones (**85**) have been evaluated as reagents for the selective derivatization of unprotected methyl glycosides. Depending on the reaction conditions, 6-carbonates or 1,2-*cis* cyclic carbonates, such as the methyl α-D-galactoside derivatives (**86**) and (**87**), respectively, were the main products.[92]


(84)


(85)

R = Bn, All, or Bu^t


(86)


(87)

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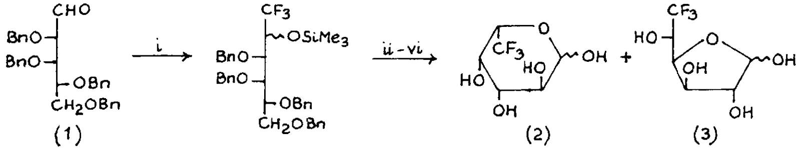
8

Halogeno-sugars

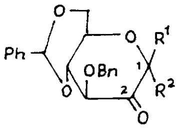
1 Fluoro-sugars

The chemistry of fluorinated carbohydrates has been reviewed[1] as has the application of aldolases to the synthesis of fluorosugars.[2] Nucleophilic trifluoromethylation of aldehyde (**1**) has allowed the synthesis of 6-deoxy-6,6,6-trifluoromethyl-L-fucose (**2**) and -D-altrose (**3**) from D-lyxose (Scheme 1),[3] and other 6-deoxy-6,6,6-trifluoromethyl - hexoses have been prepared by similar methodology.[4] Treatment of the β-glycoside 2-ulose (**4**) with DAST afforded the corresponding 2-deoxy-2,2-difluoride (**5**), whereas the α-glycoside (**6**) was unreactive under the same conditions. Under extended reaction times it gave the 1,2-difluoride (**7**)[5]. The reaction of methyl 2-*O*-benzyl-3,6-dideoxy-α-D-*ribo*- or -*arabino*- hexopyranosides with DAST gave the 4-deoxy-4-fluoro products exclusively with retention of configuration, whereas the products of inversion were the major products obtained by triflate displacements.[6] Syntheses of 4,6-dideoxy-4-fluoro-L-glucose[7] and 2,6-dideoxy-2-fluoro-L-glucose[8] from L-fucose and L-rhamnose respectively have been reported, and some 6-deoxy-6-fluoro-compounds related to lipid X have been described[9], as well as a number of 3′-deoxy-3′-fluoro-nucleosides.[10]



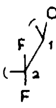
Reagents: i, CF_3SiMe_3, Bu_4NF ; ii, H_3O^+ ; iii, H_2, $Pd(OH)_2$; iv, Me_3SiCl, $(Me_3Si)_2NH$, Py ; v, CrO_3, Py ; vi, MeOH, H_2O

Scheme 1

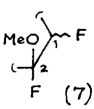


(4) $R^1 = OMe, R^2 = H$

(6) $R^1 = H, R^2 = OMe$



(5)



(7)

The formation of glycosyl fluorides by the action of DAST on reducing sugars is known to give variable yields depending on the solvent. A study has now shown that this can be due to the formation of 2,2-*O*-orthoacyl fluorides which hydrolyse back to the starting material on workup.[11] Glycosyl fluorides have been prepared from aryl 1-thioglycosides by use of 4-methyl(difluoroiodo)benzene[12], and treatment of some 1,2-*O*-isopropylidene derivatives with HF in acetic anhydride/nitromethane has afforded the corresponding acetylated glycosyl fluorides.[13,14] The preparation of some 2-deoxy- and 2,6-dideoxyglycosyl fluorides has been described using standard procedures[15], while 2-trifluoroacetamido-2-deoxy-β-D-galactopyranosyl fluoride has been reported as a new glycosylating agent in the synthesis of chromogenic and fluorogenic substrates of α- and β- *N*-acetylgalactosaminidases.[16] The reactions of several anionic nucleophiles with α-D-glucopyranosyl fluoride in aqueous solution has been shown to proceed *via* a concerted SN_2 mechanism[17], and the acid or base catalysis of the hydrolysis of this substrate has been discussed.[18] The use of 2-deoxyglycosyl fluorides in disaccharide synthesis is covered in Chapter 3, while the testing of some glycosyl fluorides as substrates for cyclodextrin glucosyl transferase is mentioned in Chapter 4.

2 Chloro-, Bromo-, and Iodo-sugars

Some 2-amino-2-deoxyglycoside derivatives have been transformed directly into glycosyl bromides ($Me_3SiBr/ZnBr_2$)[19], and treatment of some 1-imidazolylcarbonyl derivatives with acetyl chloride has afforded the corresponding glycosyl chlorides.[20] Attempted preparation of the 3,5-cyclic thiocarbonate from 1,2-*O*-isopropylidene-α-D-xylofuranose using thiophosgene gave instead 5-chloro-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose.[21] A number of *N*-acylated 2-amino-2-deoxy-hexoses have been selectively halogenated at *C*-6 using CCl_4 or CI_4 with Ph_3P in pyridine,[22] and 4-deoxy-4-iodo-L-glucose derivatives have been prepared from L-fucose.[7]

The preparation of glycopeptides by glycosylation of peptides with glycals using *N*-iodosuccinimide is covered in Chapter 3, and the preparation of chlorodeoxy-1,4:3,6-dianhydroalditols is mentioned in Chapter 18. The synthesis of 1-chloro-1-deoxy-ketoses by a 1 carbon homologation of lactone derivatives is outlined in Chapter 12.

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9

Amino-sugars

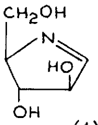
1 Natural Products

The triterpenoid oligoglycosides isolated from the Palauan marine sponge *Asteropus sarasinosum* all contained 2-amino-2-deoxy-D-gluco- and -galacto-pyranosyl residues.[1] Full details have been published on the isolation of the fungal metabolite nectrisine (**1**), its synthesis from D-glucose, and several of its reactions, *e.g.* catalytic reduction to 1,4-dideoxy-1,4-imino-D-arabinitol (*cf.* Vol.22, p.265).[2] Other nitrogen-containing sugar natural products are covered in Chapters 16 and 19, and in Section 4 of this chapter.

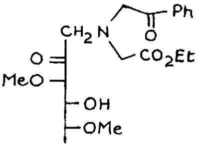
2 Synthesis

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

Reaction of 3,5,6-tri-*O*-methyl-D-glucose with *N*-phenacyl-glycine ethyl ester gave a glucofuranosylamine derivative that underwent Amadori rearrangement to the 1-amino-1-deoxy-D-fructose derivative (2) under acidic conditions.[3] The tryptophan-D-glucose Amadori rearrangement product has been synthesized, and the kinetics and mechanism of its thermal decomposition have been studied;[4] its tautomeric forms have been separated by reversed-phase h.p.l.c., the β-pyranose, α-furanose, β-furanose, α-pyranose and keto-forms being observed in the ratio 45:27:13:10:5.[5]

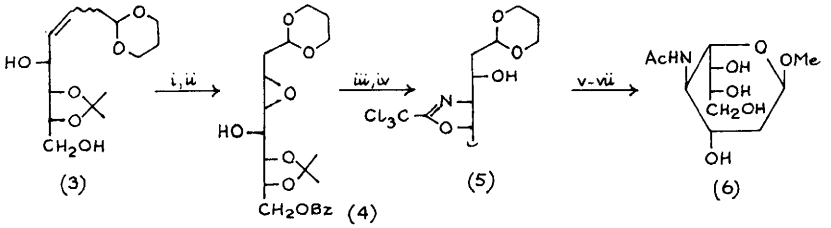


(1)



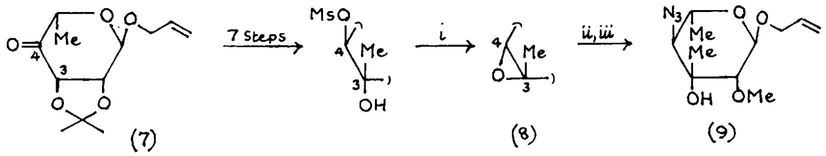
(2)

The 4-acetamido-2,4-dideoxy-octoside (**6**), a decarboxy-analogue of methyl neuraminate, has been synthesized from D-arabinose *via* the (mostly *cis*) Wittig chain-extension product (**3**) (Scheme 1), intramolecular opening of the epoxide (**4**) to form the oxazoline (**5**) being the key step.[6] The kansosamine precursor (**9**) has been obtained from L-rhamnose *via* the 4-uloside (**7**). Its 3-*C*-methyl branch was introduced *via* enolate alkylation, and its azido-group *via* nucleophilic opening of the epoxide (**8**) (Scheme 2). It was utilized in syntheses of di- and tri-saccharides with a terminal 4-*N*-formyl-α-L-kansosaminyl residue, in connection with the preparation of *Mycobacterium* haptens (see Chapter 4).[7] Further details on the preparation of *N*-(6-deoxy-D-glucos-6-yl)-amino acid derivatives (*cf.* Vol.24, p.108) have been published.[8]



Reagents: i, BzCN, Et_3N; ii, MCPBA; iii, Cl_3CCN, KH; iv, $BF_3\cdot OEt_2$; v, TsOH; vi, Bu_3SnH; vii, MeOH, HCl

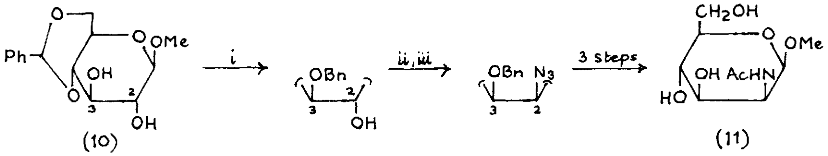
Scheme 1



Reagents: i, KOH, MeOH; ii, MeI, NaH; iii, NaN_3, Et_4NCl, DMF

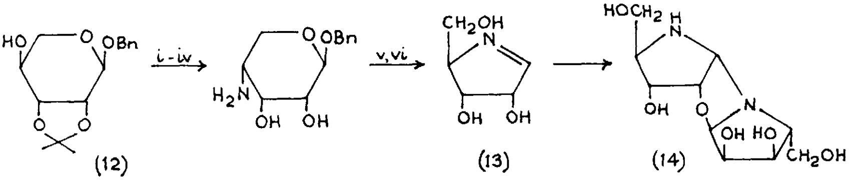
Scheme 2

Triflate displacement continues to be effective for introducing an amino-function. Reaction of 2,3:4,5-di-*O*-isopropylidene-1-*O*-triflyl-β-D-fructopyranose with the allyl esters of L-phenylalanine, L-tyrosine, and L-tryptophan provided the corresponding protected Amadori products (*i.e.*, 1-amino-1-deoxy-D-fructose derivatives).[9] A facile synthesis of methyl 2-acetamido-2-deoxy-β-D-mannopyranoside (**11**) involved selective 3-*O*-benzylation of the β-D-glucoside (**10**), and displacement of a 2-triflate with azide (Scheme 3). This chemistry was similarly used to obtain the *p*-nitrophenyl β-glycoside of β-GlcNAc*p*-(1→3)-ManNAcA*p*, the disaccharide repeating unit of the capsular polysaccharide of *Haemophilus influenzae* type d, suitable for the synthesis of an artificial antigen.[10] Methyl 3-amino-3-deoxy-α-D-allopyranoside was obtained from methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside in five steps involving azide displacement of a 3-triflyloxy-group. Alternatively a mixture of anomeric methyl 3-amino-3-deoxy-D-allo-pyranoside and -furanoside derivatives was obtained from 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl-α-D-glucofuranose *via* azide displacement (using tetramethylguanidinium azide) followed by methanolysis.[11] The potent α-glucosidase inhibitor (**13**), which is the C-2 epimer of nectrisine (see ref.1), was obtained from the L-lyxose derivative (**12**) (Scheme 4). Acidification of an alkaline solution of imine (**13**) led to the formation of its hydrate (4-amino-4-deoxy-D-ribose) and the dimer (**14**).[12] A seven step synthesis of the Lpersosamine derivative, methyl 4,6-dideoxy-4-trifluoroacetamido-α-L-mannopyranoside, from L-rhamnose has been described.[13]



Reagents: i, NaH, CuCl$_2$, BnBr, Bu$_4$NI ; ii, Tf$_2$O, py ; iii, NaN$_3$

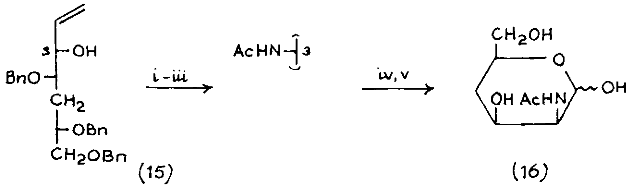
Scheme 3



Reagents: i, Tf$_2$O, py ; ii, Bu$_4$N.N$_3$; iii, HS$\diagdown\diagup\diagdown$SH, Et$_3$N, MeOH ; iv, HCl, H$_2$O ; v, 10 M HCl; vi, strong OH$^-$

Scheme 4

A rather long synthesis of 2-acetamido-2,4-dideoxy-D-mannose (**16**) from D-glucose involved Mitsunobu reaction of the allylic alcohol (**15**) for introduction of the amino-functionality (Scheme 5).[14] 1-Deoxy-analogues of 2-acetamido-2-deoxy-D-mannose are covered in Chapter 18.

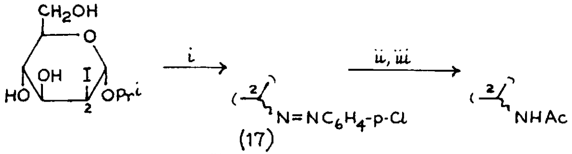


Reagents: i, DEAD, Ph$_3$P, phthalimide ; ii, N$_2$H$_4$; iii, Ac$_2$O, py, DMAP ; iv, Na, NH$_3$; v, O$_3$, then Me$_2$S

Scheme 5

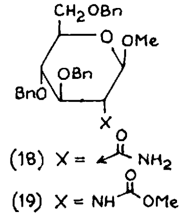
A new method for converting the products of iodoglycosylation of glycals into 2-amino-sugar glycosides involves coupling C-2 radicals with diazonium ions, and is exemplified in Scheme 6. With tributyltin hydride as radical reductant, the gluco-and manno-isomers of the 2-azo-derivative (17) were obtained along with the C-2 deoxy-product in 25, 12, and 30-50% yield, respectively. Better yields of these gluco- and manno-isomers of (17), 40 and 20% respectively, were attained using tributylstannyl(pyridine)cobaloxime as reductant.[15] *N*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-6-yl)amino acid methyl esters were conveniently prepared by *N*-alkylation of amino acid esters with the corresponding 6-deoxy-6-iodo-galactose derivative in dimethylformamide in the presence of triethylamine.[16] 1′-Deoxy-1′-

guanidino- and 1′-deoxy-1′-hydrazino-sucrose were obtained from 1′-chloro-1′-deoxysucrose heptaacetate, and converted into pyrimidine and pyrazole derivatives, respectively, by condensation with β-dicarbonyl compounds.[17] 6,6′-Diamino-6,6′-dideoxy-hexa-*O*-methyl-sucrose was prepared from a sucrose pentamethyl ether derivative which had HO-1′,-6 and -6′ unprotected by sequential selective dichlorination (Ph_3P, CCl_4), 1′-*O*-methylation, azide displacement and reduction.[18] Syntheses of aminocyclodextrins and aminoaldonolactones are covered in Chapters 4 and 16, respectively.

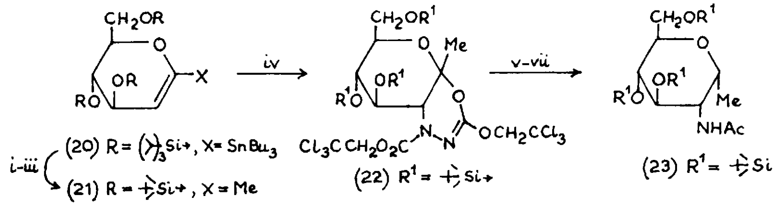


Reagents: i, Bu_3SnH, $Cl{-}C_6H_4{-}N_2^+BF_4^-$; ii, H_2, Pd/C; iii, Ac_2O, py

Scheme 6

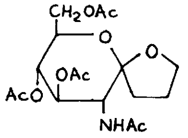


N-Acetylhyalobiuronic acid [β-D-Glc*Ap*-(1→3)-D-GlcNAc] was synthesized from β-laminaribiose octaacetate (see Chapter 3), the amino-group being introduced by azidonitration of a glycal intermediate.[19] Hofmann rearrangement of 2-*C*-carbamoyl-2-deoxy-glycosides, obtained on cycloaddition of trichloroacetyl isocyanate to glycals followed by methanolysis (Vol.22, p.151-2), yielded 2-amino-2-deoxy-glycoside derivatives, as for example in the conversion of (**18**) to (**19**) (using Br_2-NaOMe-MeOH).[20] The *C*-methyl 2-amino-2-deoxy-glucoside (**23**) was obtained from the C-1 stannylated glucal (**20**) *via* its *C*-1-methylated analogue (**21**), and its cycloadduct (**22**) (Scheme 7). The 2-amino-2-deoxy-*C*-glucoside spiroketal (**24**) was obtained in a similar way *via* the *C*-1-(3-acetoxypropyl)-analogue of (**21**).[21]



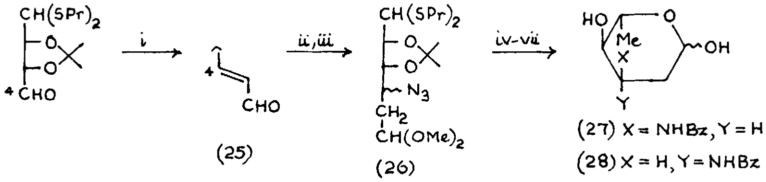
Reagents: i, BuLi, then MeI, CuBr·Me_2S; ii, Bu_4NF; iii, $^tBuMe_2SiCl$; iv, $Cl_3CCH_2O_2CN{=}NCO_2CH_2CCl_3$; v, $NaBH_3CN$; vi, Zn, HOAc; vii, Ac_2O, py.

Scheme 7



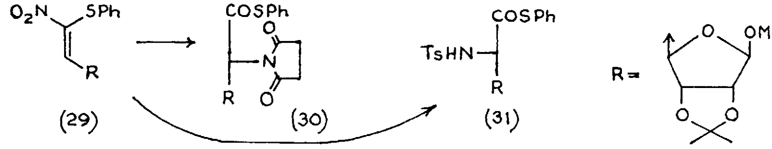
(24)

Addition of hydrazoic acid to the D-ribose derived enal (**25**) led to a mixture of epimeric azides (**26**) which were separately converted into *N*-benzoyl-L-ristosamine (**27**) and *N*-benzoyl-L-acosamine (**28**) (Scheme 8).[22] 2,3-Dideoxy-3-amino-nucleosides synthesized from a sugar enal derivative, are covered in Chapter 20. The 5-amino-5-deoxy-L-taluronic acid derivative (**30**) was obtained by addition of succinimide anion to the nitro-olefin (**29**) followed by ozonolysis, whereas the D-allo-derivative (**31**) was obtained when the nucleophile was a sulphonamide anion (Scheme 9).[23]



Reagents: i, $Ph_3P=CHCHO$; ii, NaN_3, HOAc; iii, $(MeO)_2CMe_2$, H^+, MeOH; iv, LAH; v, BzCl, py; vi, Raney Ni; vii, AcOH, H_2O

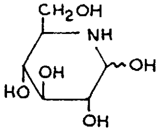
Scheme 8



Scheme 9

Amino-groups have been introduced by formation and reduction of oxime derivatives. 3-Amino-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose was synthesized in five steps from the oxime derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose, involving reduction (LAH) and periodate cleavage reactions.[24] Nojirimycin (**32**) was obtained in high yield by borane reduction of the *O*-methyloxine derivative (**33**) followed by deisopropylidenation and rearrangement (with SO_2-H_2O).[25] Improved syntheses of the 3-amino-2,3-dideoxy-D-*erythro*-pentofuranosides (**34**) from D-xylose utilized methodology reported earlier (Vol.20, p.110) but employing 5-*O*-protection with a pivalate rather than a benzoate group.[26] A 3-amino-3-deoxy-D-allopyranose derivative has been prepared in a multistep synthesis from D-glucose.[27]

A new approach to 3-amino-3-deoxy-sugars involves the modification of branched-chain sugars such as (**35**), obtained by condensation of acyclic dialdehyde precursors with



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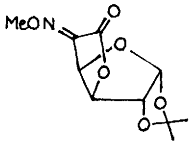

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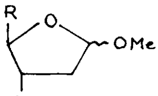
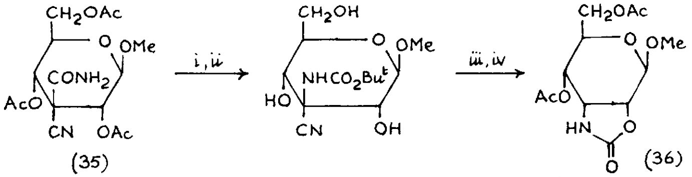


(34) R = CH_2OH, CH_2OBz, CH_2OPiv, CO_2H, CO_2Me

2-cyanoacetamide (Vol.24, p.168, ref.28), by sequential Hofmann rearrangement[28] and reductive decyanation[29] reactions, as shown in Scheme 10 for the synthesis of the 3-amino-3-deoxy-β-D-alloside (**36**).



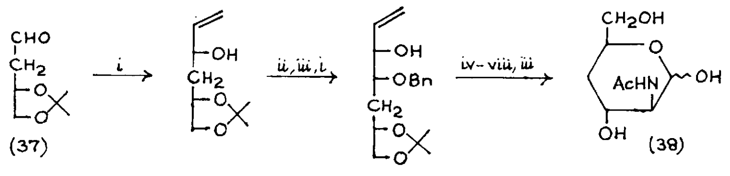
Reagents: i, $Pb(OAc)_4$, Bu^tOH, DMF ; ii, NaOMe, MeOH ; iii, $NaBH_4$, Pr^iOH ; iv, Ac_2O, Py

Scheme 10

A number of synthesis of amino-sugars from chiral non-carbohydrate starting materials have been reported. A reaction sequence used previously to synthesize 2-amino-2-deoxy-D-ribose from 2,3-*O*-isopropylidene-D-glyceraldehyde (Vol.16, p.92-3) has been improved to achieve better stereoselectivity in the initial aldol condensation used to extend the chain by two carbon atoms.[30] The synthesis of a 6,6,6-trifluoro-L-daunosamine derivative from 2,3-*O*-cyclohexylidene-D-glyceraldehyde is covered in Chapter 8, and of 2,5-dideoxy-2,5-imino-pentonic acids from tartaric acid in Chapter 16.

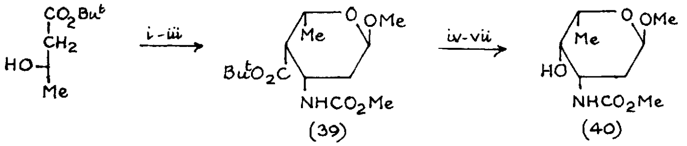
All four diastereomeric 2-acetamido-2,4-dideoxy-D-hexopyranoses have been synthesized from the (*S*)-malic acid derived four-carbon aldehyde (**37**) (Scheme 11) as potential inhibitors of *N*-acetylneuraminic acid synthase. The intermediates involved in the synthesis of the D-*arabino*-isomer (**38**) are shown in Scheme 11. The two vinyl Grignard addition reactions provided separable equimolar mixtures of C-3 epimers; the analogous reactions applied to these yielded the three other isomeric amino-sugars.[31] *N*-Acyl-derivative (**40**) of L-daunosamine has been synthesized from the *C*-4-carboxy-branched intermediate (**39**), obtained by a stereoselective enolate-imine condensation (Scheme 12). The *C*-4-epimeric L-acosamine derivative was obtained by a similar sequence when compound (**39**) was first epimerized at C-4 (LiOH-H_2O-MeOH).[32]

A variety of approaches have been used to convert amino acids into amino-sugars by chain extension. Casiraghi and co-workers have synthesized the 6-amino-6-deoxy-α-D-*glycero*-D-*talo*-heptopyranuronic acid derivative (**43**) from the D-serinal derivative (**41**) in 9 steps, 20% overall



Reagents: i, $CH_2{=}CH$MgCl ; ii, NaH, BnCl ; iii, O_3, then Me_2S ; iv, DEAD, Ph_3P, phthalimide ; v, N_2H_4 ; vi, Ac_2O, Py ; vii, Na, NH_3 (l) ; viii, H^+

Scheme 11

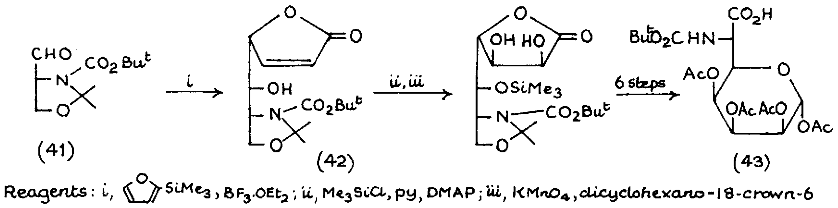


Reagents: i, LDA, LiCl, then N CO$_2$Me SPh; ii, HCl; iii, AgNO$_3$, Ag$_2$O, MeOH; iv, HCl, MeOH; v, MCPBA, DCC; vi, CCl$_4$, 60°; vii, NaOH, MeOH

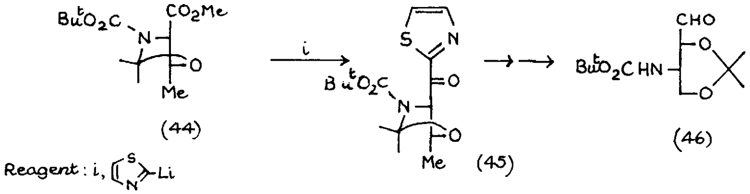
Scheme 12

yield, using highly stereoselective butenolide chain extension and *cis*-hydroxylation reactions (Scheme 13). Epimerization of the D-*arabino*-intermediate (**42**) at C-4 (Et_3N-DMAP) provided the D-*ribo*-analogue from which the C-4 epimer of (**43**) was obtained. The enantiomers of these compounds were produced in the same way from an L-serinal derivative.[33,34] Dondoni and co-workers have utilized thiazole intermediates as masked aldehydes in their chain extension methodology. The L-threonine derivative (**44**) was converted into either the 3-amino-3,5-dideoxy-D-*xylo*-pentose derivative (**46**) or its D-*lyxo*-isomer depending upon the strategy employed to reduce the C-2 ketone functionality generated in (**45**) (Scheme 14).[35] (-)-Galactostatin (**49**), the unnatural enantiomer, was synthesized from the L-serine derivative (**47**) *via* a series of thiazole intermediates in 21% overall yield (Scheme 15). The *cis*-hydroxylation (step viii) gave a separable 3:1 mixture of the *anti*-(**48**) and *syn*-addition products.[36] Golebiowski, Jurczak and co-workers have employed either high pressure or Lewis acid catalysed Diels-Alder reactions to chain extend aldehydes derived from amino acids. When applied to the D-*allo*-threoninal derivative (**51**) these methods yielded the potential lincosamine precursors (**50**), as a 2:1 mixture with its C-5 epimer,[37] and (**52**), as a mixture of C-4 epimers, one of which was converted to the lincosamine diastereomer (**53**) (Scheme 16).[38] This methodology was similarly applied to D-threoninal[37,38] and D-alaninal derivatives.[39] A variety of 4-amino-2,3,4,6-tetradeoxy-4-*C*-methyl-L-hexose derivatives, *i.e.* (**54**) - (**56**), have been synthesized from the L-threonine derived unsaturated acid (**57**), the C-3 heteroatom being introduced by Michael-like addition.[40] 4-Amino-4-deoxy-2,3-*O*-isopropylidene-L-ribono-1,4-lactam featured as an intermediate in the synthesis of a gastroprotective *Bacillus* metabolite from (*R*)-glutamic acid.[41]

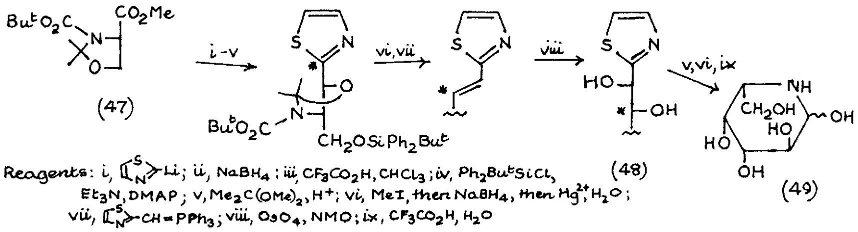
Vogel has applied his 'naked sugar' chemistry to the synthesis of 5-*C*-methyl-*talo*-nojirimycin (**60**), and its 6-deoxy-analogue, from the bicyclic lactone (**58**) derived from a chiral 7-oxanorbornane (Scheme 17). The amino-group was introduced by Curtius rearrangement of the acyl azide (**59**).[42,43]



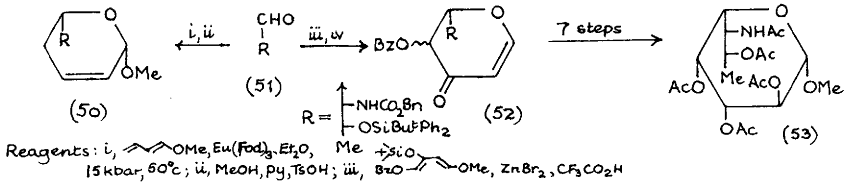
Scheme 13



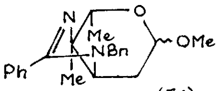
Scheme 14



Scheme 15



Scheme 16



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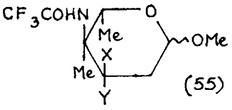
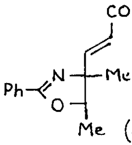


(55) X = SH, OH, or NHCOCF$_3$; Y = H

(56) X = H, Y = NHCOCF$_3$



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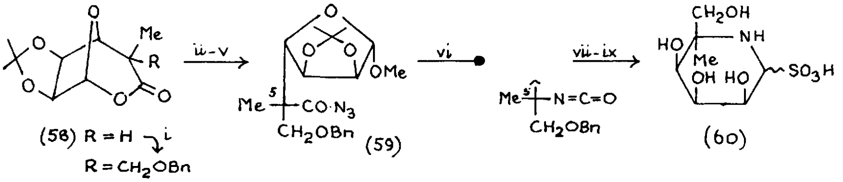
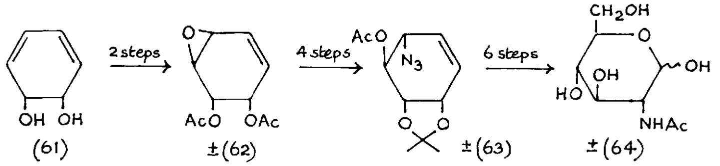


Reagents: i, $(Me_3Si)_2NLi$, $BnOCH_2Br$; ii, K_2CO_3, MeOH; iii, $HC(OMe)_3$, H^+; iv, KOH; v, $ClCO_2Et$, Et_3N, then NaN_3; vi, Δ, C_6H_6; vii, BnOH; viii, H_2, Pd/C; ix, SO_2, H_2O

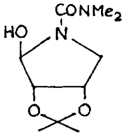
Scheme 17

5-Acetamido-5-deoxy-L-*xylo*-hexulose and 7-amino-5,7-dideoxy-L-*xylo*-heptulose were obtained by using fructose 1,6-diphosphate aldolase to couple dihydroxyacetone phosphate with *N*-acetyl-D-serinal (from 2-acetamido-2-deoxy-D-glucose, Vol. 24, p.315) and racemic 4-azido-3-hydroxy-butanal (from but-3-enal diethyl acetal), and phosphatase to deprotect the product.[44]

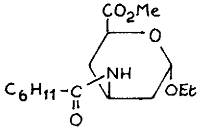
Several syntheses of racemic amino-sugars have been reported. 2-Acetamido-2-deoxy-DL-glucose (**64**) was synthesized in 12 steps from the benzene microbial oxidation product (**61**), the amino group being introduced by opening of epoxide (**62**) with hydrazoic acid, and ozonolysis being used to cleave the double bond in the cyclohexene derivative (**63**) (Scheme 18).[45] The 4-amino-3-deoxy-DL-erythrose derivative (**65**) was elaborated from the hetero-Diels-Alder adduct of 1-(*tert*-butyldimethylsilyloxy)-buta-1,3-diene with a nitroso-reagent (Me_2NCONO).[46] The 3-amino-2,3,4-trideoxy-DL-hexuronoside (**66**) was elaborated from the hetero-Diels-Alder adduct of ethyl vinyl ether and methyl 4-benzamido-but-3-en-2-onoate,[47] and the racemic 4-deoxydaunosamine and acosamine derivatives, (**67**) and (**68**), respectively, were similarly elaborated from the adduct of methyl vinyl ether and 3-phenylthio-4-phthalimido-but-3-en-2-one.[48]



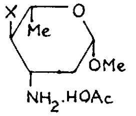
Scheme 18



±(65)



±(66)



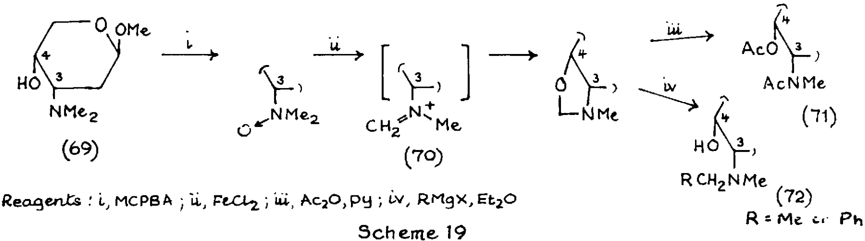
± (67) X = H

± (68) X = OH

3 Reactions

The browning reactions of amino-sugars in a variety of sterile buffers at 25-37°C have been studied. It was shown that 2,5-bis(tetrahydroxybutyl)pyrazine was formed by autocondensation of 2-amino-2-deoxy-D-glucose. Other evidence implicated metal-mediated free radical reactions in the formation of products absorbing in the 325-360 nm range. Prolonged incubation gave some high molecular weight compounds.[49] Other work on this reaction is covered in Chapter 10, section 6.

N-Demethyl-(**71**) and *N*-allyl-(**72**) analogues of L-rhodosamine (**69**) were obtained by way of the presumed imminium ion (**70**) (Scheme 19).[50]

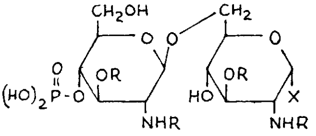


Reagents : i, MCPBA ; ii, $FeCl_2$; iii, Ac_2O, Py ; iv, RMgX, Et_2O

Scheme 19

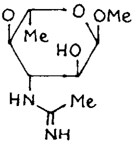
An efficient synthesis of 2-[^{11}CO]acetamido-2-deoxy-D-glucose has been reported. It utilized $^{11}CO_2$, took 60 min, and provided a 50% radiochemical yield of product of greater than 98% purity.[51] Multistep syntheses of four derivatives of 2-amino-2-deoxy-D-glucose have been reported (in Chinese).[27]

A variety of Lipid A analogues have been synthesized in multistep sequences from amino-sugar precursors. Certain disaccharide analogues such as (**73**) have been shown to have low toxicity and yet retain antitumor activity, the first successful separation of these activities in Lipid A analogues. Evidently 1,3-dicarboxyisopropyl or phosphonoxyethyl groups can substitute for the α-glycoside phosphate group, and *N*-(dodecanoyl)glycyl moieties for the 3-hydroxytetradecanoyl groups, in the natural product.[52,53] A total synthesis of the *Proteus mirabilis* Lipid A [(**73**) with X=OP(O)$(OH)_2$ and R=various complex lipids], and improved preparations of three partially protected 1,6-linked glucosamine disaccharides suitable for the construction of other Lipid A's, have been detailed.[54] Analogues bearing *N*-glycoloylneuraminyl and 3-deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid (KDN) residues glycosidically attached at O-6 of a 2-amino-2-deoxy-D-glucose 4-phosphate residue possessed mitogenic activity and weak antitumor activities.[55] The synthesis of a trisaccharide analogue of Lipid A is covered in Chapter 4. A fluorine-containing analogue of GLA60, an esterified 2-amino-2-deoxy-D-glucose 4-phosphate derivative with an *N*-(2,2-difluoro-3-hydroxytetradecanoyl) group, has also been prepared.[56]



(73) X = $OCH(CH_2CO_2H)_2$ or $OCH_2CH_2OP(O)(OH)_2$

R = tetradecanoyl, (R)-3-hydroxytetradecanoyl, or N-(dodecanoyl)glycyl



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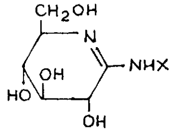


(75) X = NH_2 or OH

Syntheses of *N*-acetylmuramoyl-L-alanyl-D-isoglutamylglycine and its hexadecyl β-glycoside, and isotopomers containing [1-^{14}C]glycine have been reported (in Russian).[57] Carbohydrate-enkephalin conjugates have been prepared by solution fragment coupling. These products have a pentapeptide residue *N*-acylated onto 2-amino-2-deoxy-D-glucose, 6-amino-6-deoxy-D-glucose, or β-D-glucopyranosylamine, or *O*-acylated onto D-glucose at position -6 or -1-β.[58,59]

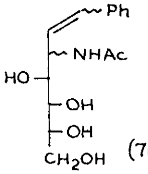
In a novel approach to enzyme stabilization, chymotrypsin, trypsin and subtilisin have been separately coupled by reductive amination ($NaBH_3CN$) to polymers prepared from *N*-methacrylamido-sugar monomers, themselves synthesized from 2-,3- or especially 6-aminodeoxy-D-glucose. About 3 lysines residues per enzyme molecule are conjugated, and the conjugates are more stable than the native enzymes.[60]

Hexokinase catalysed syntheses of 6-amino-6-deoxy-D-glucose and -D-gluconate 6-phosphates, 6-amino-6-deoxy-D-fructose 6-phosphate and 1,6-bisphosphate, and 5-amino-5-deoxy-D-ribulose 5-phosphate have been reported. From a study of the properties and reactivity in enzymic reactions of these compounds, it was concluded that they were excellent isosteric analogues of the normal metabolic intermediates except for reactions catalysed by kinases.[61] A preparative enzymic synthesis of uridine 5′-diphospho-2-acetamido-2-deoxy-D-glucose used chemically synthesized 2-acetamido-2-deoxy-D-glucose 1-phosphate and uridine triphosphate as reactants, and a calf liver enzyme extract containing uridine-5′-phospho-*N*-acetylglucosamine pyrophosphorylase.[62]

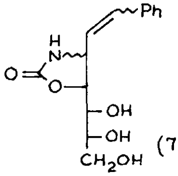
4-*O*-*p*-Nitrobenzoyl-*N*-trifluoroacetyl-L-daunosaminyl bromide has been prepared from commercially available methyl L-daunosamine hydrochloride, and coupled to 4-demethoxy-daunomycinone.[63]

The 3-acetamidino-3,6-dideoxy-L-glucoside **(74)** was synthesized from the corresponding 3-nitro-sugar (i, NH_2NH_2-Raney Ni; ii, MeC(=NH)OEt.HCl).[64] Azido-sugar and -nucleoside derivatives have been converted into the corresponding amino-sugars by radical reduction (Bu_3SnH - AIBN).[65] A new protecting group for amines, the 2,2,2-trifluoro-1,1-diphenylethanesulphenyl group [$CF_3C(Ph)_2S$-], is covered in Chapter 18.

Ganem and Papandreou have synthesized the two transition state mimics **(75)** from a thiolactam precursor (see Vol.24, p.120), and shown them to be potent, broad spectrum glycosidase inhibitors.[66] Wittig reaction of either 2-acetamido-2-deoxy-D-glucose or -D-mannose gave the same mixture of isomeric alkenes (76; *gluco*:*manno*, 1:2) indicating that epimerization occurs prior to olefination. Derivatives of L- and D-homophenylalanine were obtained by separate reduction of these alkenes followed by oxidative cleavage of their polyhydroxyalkyl chains. 2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannitol, an intermediate in a recent sialic acid synthesis (*cf.* Csuk *et al.*, Vol. 22, p.163), was available from the *manno*-isomer of (**76**) through an ozonolytic cleavage of the double bond. Wittig reaction of 2-*tert*-butyloxycarbonylamino-2-deoxy-D-glucose could be induced to yield the isomeric cyclic carbamates (77), from which chiral 3-amino-1,2-diol building blocks could be prepared.[67] Schiff bases have been prepared by condenstation of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose with various aldehydes (*e.g.*, 2-HOC_6H_4CHO) and characterized.[68]



(76)

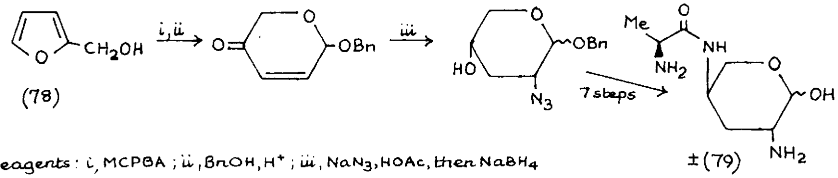


(77)

Branched-chain analogues of neuraminic acid are covered in Chapter 14, 2-alkylamino-2-deoxy-D-gluconic acids in Chapter 16, and syntheses of kifunensine, 8-*epi*-kifunensine, and some cytotoxic copper(II) complexes with amino-sugars in Chapter 19.

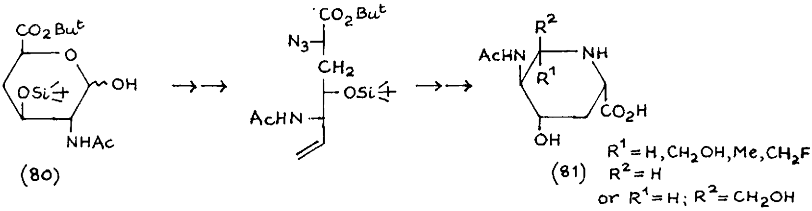
4 Diamino-sugars

A novel 4-*N*-aroylated 4-amino-2,3,4,6-tetradeoxy-3-dimethylamino-β-*lyxo*-hexopyranoside unit of unknown absolute stereochemistry has been identified as a constituent residue of a new macrolide antibiotic.[69] Syntheses of neamine derivatives *N*-acylated with amino acid residues are covered in Chapter 18. Racemic 3-deoxy-prumicin (**79**), which is still active as an antibiotic, was synthesized from furfuryl alcohol (**78**) (Scheme 20), the 4-amino-group being introduced by sulphonate displacement with azide ion.[70] A variety of six and seven carbon analogues (**81**) of 6-acetamido-2,6-dideoxyneuraminic acid have been synthesized from 2-amino-2-deoxy-D-glucose *via* the 4-deoxy-hexuronic acid derivative (**80**) (Scheme 21). It was evident from their weak sialidase inhibitory properties that the intact carbon chain is required for good binding.[71]



Reagents: i, MCPBA; ii, BnOH, H^+; iii, NaN_3, HOAc, then $NaBH_4$

Scheme 20



$R^1 = H, CH_2OH, Me, CH_2F$; $R^2 = H$
or $R^1 = H$; $R^2 = CH_2OH$

Scheme 21

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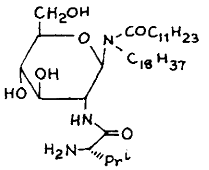
10

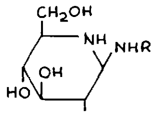
Miscellaneous Nitrogen Derivatives

1 Glycosylamines

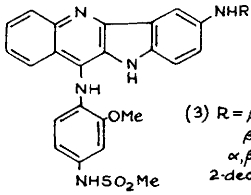
The work of Bayer researchers on the synthesis, structure and immunomodulatory activity of a range of glycosylamides with two long chain lipid moieties, i.e. *N*-(fatty acyl)-*N*-(fatty alkyl)-β-D-glycopyranosylamines, has been reviewed. Unlike natural glycolipids that are generally immunosuppressive, many of these synthetic glycolipid analogues enhance the specific immune response (adjuvant effect). The 2-amino-2-deoxy-D-glucosylamine derivative (**1**), in particular, showed marked immunostimulation and was selected for detailed biological evaluation.[1]



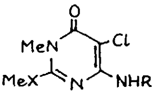
(1)



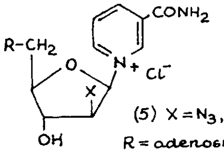
(2) R = H or Bn



(3) R = β-D-Glc-p,
β-D-Gal-p,
α,β-L-Ara-p, or
2-deoxy-α,β-D-Rib-f

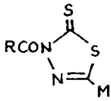


(4) R = β-D-Glc-p,
or β-D-Xyl-p
X = O or S

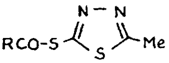


(5) X = N₃, NH₂, F
R = adenosine diphosphate

(6) X = H, NH₂, OH, NHAc, N₃, F
R = OH



(7) R = Me(CH₂)ₙ-, n = 6-16;
pO₂N·C₆H₄-, or BnO-



(8)

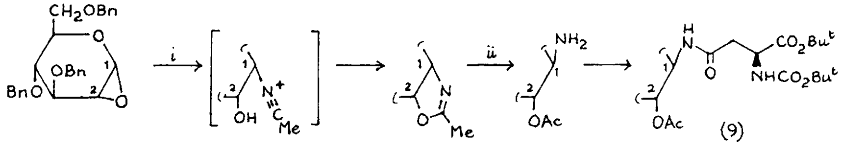
2,3,4,6-Tetra-O-methyl, -ethyl, -isobutyl, or -benzyl-β-D-glucopyranosylamines have been synthesized from the corresonding pyranoses (i, MsCl-Et_3N; ii, NH_3 at -30°C) and utilized as chiral auxiliaries in the construction of amino acids.[2] Such applications of glycosylamines as chiral auxiliaries are now covered in Chapter 24. Ganem and co-workers have synthesized the 1-β-amino-1-deoxynojirimycins (**2**) by reaction of nojirimycin bisulphite adduct with ammonia or benzylamine in methanol, and shown them to be β-glucosidase inhibitors.[3] The isolation, chemistry and synthesis of the 5-amino-5-deoxy-D-mannosylamine derivative kifunensine and its 8-epimer (with the D-*gluco*-configuration) are covered in Chapter 19.

The *N*-β-D-glucopyranoside of 5-aminosalicylic acid has been synthesized by direct coupling of the amine with glucose,[4] and was detected in considerable amounts when plasma containing 5-aminosalicylic acid was stored at -20°C, indicating that it might be an artifact of storage rather than a genuine metabolite as previously considered.[5] Three *N*-glucuronides of lamotrigine and one of its metabolites have been detected by h.p.l.c.-thermospray m.s.[6] Reaction of 3,5,6-tri-*O*-methyl-D-glucose with *N*-phenacyl-glycine ethyl ester gave an *N*-glycoside that underwent Amadori rearrangement under acid conditions.[7]

Other conventional glycosylamine syntheses were of the 1-β-D-ribo-furanosyl and -pyranosyl derivatives of 6-nitroindole,[8] nitrofurantoin *N*-β-glucopyranoside tetra-*O*-acetate using phase transfer catalysis conditions,[9] the 7-(*N*-glycosylamino)indolo[3,2-*b*]quinolines (**3**) using the acetohalosugars and pyridine with the 7-β-D-galactosylamino derivative proving to be much more active against P388 leukaemia than the 7-unsubstituted heterocycle,[10] seven 5-chloro-4-glycopyranosylamino-6-oxopyrimidine derivatives, *e.g.* (**4**),[11] and some *N*-β-D-glucopyranosyl-2-aryl-4(3*H*)-quinazolinones and their thione derivatives, as well as the corresponding *O*- and *S*-glucosides, using acetohaloglucose-KOH.[12]

The NAD$^+$ -analogues (**5**) have been synthesized from the corresponding 2-azido- or 2-fluoro-glycosyl chlorides, themselves synthesized from 3-azido- or 3-fluoro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, followed by 5′-*O*-phosphorylation using an improved procedure.[13] The kinetics of the hydrolysis of the glycosyl nicotinimidium salts (**6**) have been studied as a function of pH.[14] The effect of neighbouring amino- and acetamido-groups on the kinetics and mechanism of the *N*-transamination of *N*-glycosides has been studied.[15] Ring expansions of *e.g.* *N*-acetyl-α-D-glucofuranosylamine to *N*-acetyl-β-D-glucopyranosylamine, occurred in aprotic solvent in the presence of catalytic Lewis acid, under conditions in which sucrose and adenosine were completely hydrolysed, but uridine was extremely resistant.[16] The reagents (**7**) or (**8**) were used to effect the *N*-acylation of unprotected β-D-gluco- and galacto-pyranosylamine and β-lactosylamine in DMF at room temperature, in 65-90% yields avoiding the formation of diglycosylamine byproducts.[17]

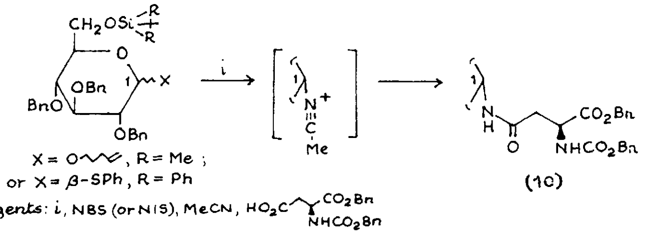
The construction of *N*-linked glycopeptides and related model compounds continues to be investigated. Methodology developed for *O*-glycosidation has been adapted for the synthesis of 4-*N*-glycosyl-asparagines. In these methods, a molecule of acetonitrile is incorporated at the glycosidic centre to yield the β- or α-linked *N*-glycosides, *e.g.* (**9**)[18] or (**10**)[19,20] (Schemes 1 and 2), respectively. The trisaccharide glycopeptides, α-D-Glc*p*(1→6)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1→4)-L-asparagine and -L-asparaginyl-L-proline, models for the nephritogenic rat glomerular basement membrane glycopeptide, were synthesized by the latter procedure[19,20] and by *O*,*O*-diethylcyanophosphate induced acylation of a trisaccharide α-glycosylamine,[21] respectively. Crude glycosylamines, such as β-chitobiosylamine, prepared by the action of saturated ammonium bicarbonate on reducing sugars, can be coupled with *N*-Fmoc-protected asparagine *tert*-butyl ester using DCC-pentafluorophenol as coupling agent in aqueous DMF. After removal of the *tert*-butyl protecting group with acid, the resulting free acid can be used as a component in the solid phase synthesis of glycopeptides.[22] *N*-Linked β-D-glucopyranosyl and -galactopyranosyl neuro-pentapeptides have been synthesized by coupling glycosylamines with active ester derivatives.[23,24]



(9)

Reagents: i, $ZnCl_2$, MeCN ; ii, HCl, H_2O

Scheme 1



X = O∕∕∕, R = Me ;
or X = β-SPh, R = Ph

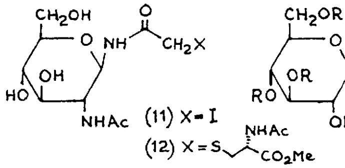
(10)

Reagents: i, NBS (or NIS), MeCN, HO_2C

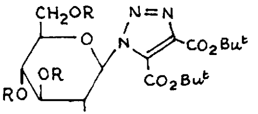
Scheme 2

A novel method for linking sugar and cysteine residues in peptides and proteins utilizes the alkylating agent (**11**) to give derivatives such as (**12**).[25]

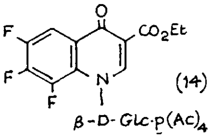
The *N*-glucosyl-triazole (**13**), formed by thermal condensation of the corresponding glucosyl azide with di-*tert*-butyl acetylenedicarboxylate, is hydrolytically stable, and is a useful glycosylating agent when activated by trimethylsilyl triflate.[26] The *N*-glucoside (**14**), a precursor for novel quinoline *N*-glycosides, was constructed from tetra-*O*-acetyl-β-D-glucopyranosylamine.[27] A new, reversible derivatization procedure for reducing oligosaccharides was demonstrated with lacto-*N*-tetraose. Reaction first in aqueous ammonium bicarbonate, then with 9-fluorenylmethyl chloroformate (Fmoc-Cl) yielded the *N*-Fmoc-glycosylamine derivative in 66% yield. It was stable in aqueous solution (pH 7) for at least a month, but could be reconverted into the free sugar in 15% aqueous ammonia. Excellent h.p.l.c. resolution of milk oligosaccharides derivatized by this method was reported.[28]



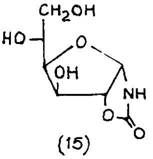
(11) X = I
(12) X = S



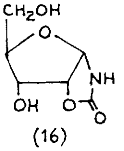
(13) R = Me_3CCO



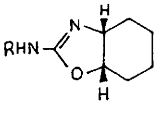
(14)



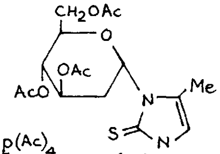
(15)



(16)



(17) R = β-D-Glc·p(Ac)$_4$



(18)

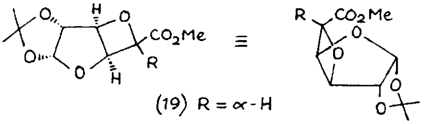
Treatment of pentoses and some hexoses with aqueous potassium cyanate afforded glycosylamine 1,2-(cyclic carbamates). Most products were furanoid, *e.g.* **(15)** and **(16)**, except those from D-mannose and D-lyxose.[29] The cyclic carbamate isolated from the acid catalysed reaction of D-glucose with urea has been shown to be the furanose derivative **(15)** rather than the pyranose isomer reported earlier (Vol.23, p.110).[30] The glucosylamino-oxazoline **(17)** was obtained as a diastereomeric mixture by condensation of *trans*-(±)-2-iodocyclohexyl isocyanate with β-D-glucopyranosylamine, and cyclization of the urea aglycon. Analogous products were obtained from 2-amino-2-deoxy-D-glucose derivatives.[31] A bicyclic 1,6-lactam formed from D-glucuronic acid is covered in Chapter 16.

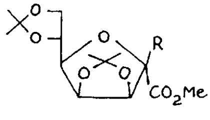
Separable anomeric *O*-acetylated 2-deoxy-D-*arabino*- and D-*lyxo*-hexopyranosyl isothiocyanates, and their 2-brono-2,3-dideoxy-D-*arabino*-analogues, were obtained from the corresponding α-glycosyl acetates (i,Me_3SiBr; ii,AgNCS). The first of these was converted into a thiourea derivatives and cyclized to **(18)**.[32] 2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl isothiocyanate has been prepared from the corresponding ribosyl chloride.[33] 2,3,4,6-Tetra-*O*-benzoyl-β-D-gluco- and galacto-pyranosyl isothiocyanates have been converted into 1-glycosyl-5-oxo-2-thioxotetrahydroimidazoles and 5-aryl-3-glycosylamino-thiazoles *via* *N*-glycosyl-N′-carbonylmethylthiourea intermediates.[34] Further uses of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate as a derivatization reagent in the resolution of enantiomeric amines and amino acids by h.p.l.c. have been reported.[35-37]

Alternative mechanisms for the Maillard (non-enzymic) browning reaction have been considered, particularly direct dehydration of the cyclic forms of Amadori products, since the conventional mechanisms involving 1,2- and 2,3-enolization of open-chain Amadori products do not adequately account for most of the observed products in model systems.[38] The kinetics of formation and degradation of the Amadori product of glucose and proline [*i.e.* *N*-(1-deoxy-fructos-1-yl)proline] were studied with the aid of synthetic material. A three step mechanism was proposed and about 40 reaction products were identified.[39] Many compounds formed from the Maillard reaction of glucose with α-protected lysine have been identified by use of h.p.l.c. and m.s. methods.[40] 5,6-Dihydro-3,5-dihydroxy-1-propyl-4*H*-pyridone was isolated in yields up to 20% from Maillard reactions of *n*-propylamine with 6-*O*-substituted hexoses (*i.e.*, glucose 6-phosphate, isomaltose, and 6-*O*-benzoylgalactose) in aqueous solution at pH 7.[41] The volatile compounds formed on reaction of cysteine or the tripeptide glutathione (γ-Glu-Cys-Gly) with glucose in an aqueous medium at pH 7.5, 180°C for 1 h, have been compared. Sixty two compounds were identified. While 3,5-dimethyl-1,2,4-trithiolane was the major product in the case of cysteine, products characteristic of the thermal degradation of glucose alone, e.g. 5-methylfurfural, were predominant in the case of the tripeptide.[42]

2 Azido- and Azi-sugars

Hepta-*O*-acetyl-β-cellobiosyl, -lactosyl, -maltosyl, and -mellibiosyl azides were synthesized from the corresponding glycosyl acetates (either anomer) using trimethylsilyl azide and stannic chloride. The corresponding, hitherto inaccessible, α-anomeric azides were synthesized from the β-acetates *via* the β-chlorides, in an S_N2 reaction (LiN_3 in HMPT).[43] In an approach to oxetane and furan nucleosides with an anomeric carbon substituent, the β-glycosyl azides (**21**) and (**24**) were synthesized from the *C*-carbomethoxy glycosides (**19**) and (**22**) by bromination [i, $(Me_3Si)_2NLi$; ii, CBr_4] and reaction of the products (**20**) and (**23**), respectively, with sodium azide. The β-anomer of (**19**) yielded both (**20**) and its β-anomer, the latter then giving the α-anomer of (**21**).[44]


(19) R = α-H
(20) R = α-Br
(21) R = β-N₃

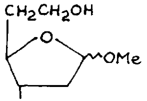

(22) R = α-H (23) R = α-Br
(24) R = β-N₃

2-Azido-2-deoxy-aldoses can be synthesized from the corresponding free amino-sugars by diazo transfer from triflyl azide (prepared *in situ* from Tf_2O and NaN_3). In this way 2-amino-2-deoxy-D-glucose yielded (after acetylation) tetra-*O*-acetyl-2-azido-2-deoxy-α,β-D-glucopyranose in 80% yield.[45] An alternative synthesis of the β-anomer of this latter compound from D-mannose involved reaction of 1,3,4,6-tetra-*O*-acetyl-2-*O*-triflyl-β-D-mannopyranose with sodium azide; the product was converted to the corresponding α-glycosyl chloride (with $ZnCl_2$-Cl_2CHOMe).[46] A new procedure for constructing oligosaccharides containing 2-amino-2-deoxy-D-galactopyranosyl residues utilized anomeric glycosyl *S*-xanthates prepared by azido-xanthation [i, $(NH_4)_2Ce(NO_3)_6$-NaN_3; ii, KSSCOEt] of D-galactal derivatives.[47,48]

2-Azido-1-*O*-acyl and 1-*O*-ethoxycarbonyl-2,3-dideoxyglycopyranoside stereoisomers were obtained by addition of hydrazoic acid to the corresponding hex-2-en-4-uloses followed by reduction, and were utilized in glycosidation reactions.[49]

The one carbon homologue (**25**) of the anti-viral drug AZT was synthesized in 13 steps from D-glucurono-6,3-lactone. The sequence involved radical reductions at C-2 and C-5 and introduction of azide at C-3 with inversion.[50] When the Mitsunobu reaction (Ph_3P-DEAD-HN_3) was applied to the 2,3-didehydro-2-deoxysialic acid derivative (**26**), both the expected 4-azide (**27**) and its epimer (**28**) were obtained. The latter arises from an S_N2' attack of azide to form the glycosyl azide (**29**) which then undergoes [3,3]-sigmatropic rearrangement. Reactions of these 4-azido-derivatives are covered in Chapter 16.[51]

Allyl 2-azido-2-deoxy-glycosides can be efficiently deprotected at O-1 by using [bis-(methyldiphenylphosphine)](1,5-cyclooctadiene)iridium(I) hexafluorophosphate to isomerize the allyl group to a propenyl ether at room temperature, then oxidation (Me_3NO - cat. OsO_4) to cleave the propenyl group. These conditions avoid the formation of cycloaddition byproducts such as (**30**) that were encountered using other deprotection methods. Such cycloadducts can also be formed under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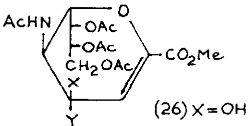
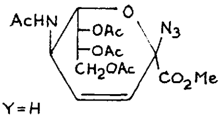

(26) X = OH, Y = H
(27) X = H, Y = N$_3$
(28) X = N$_3$, Y = H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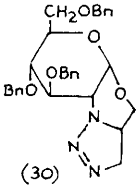
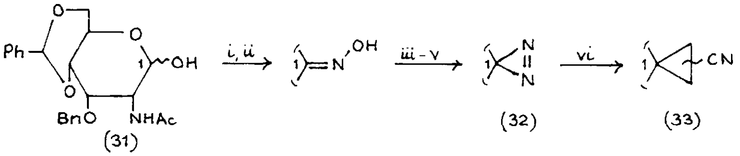

(30)

reflux in benzene.[52] A convenient reagent (PhSH-Pr$^i_2$NEt-MeCN) for removing the nitrate group of 2-azido-2-deoxyglycosyl nitrates (*i.e.* 1-NO$_2$→1-OH), formed by azidonitration of glycal derivatives, has been reported.[53] Azido-sugar and -nucleoside derivatives have been converted into the corresponding amino-analogues by radical reduction (Bu$_3$SnH-AIBN).[54]

Reviews have appeared on the synthesis of glycosylidene diaziridines and their conversion to glycosylidene carbenes, from which a variety of *O*-, *C*- and *P*-glycosides have been synthesized.[55,56] The glycosylidene diazirine **(32)**, derived from 2-acetamido-2-deoxy-D-glucose *via* the allosamine derivative **(31)**, gave the four isomeric spirocyclopropanes **(33)** (Scheme 3), but attempted use of **(32)** for glycosidation (*cf.* Vol. 23, p.16) led only to oxazolidines through participation of the acetamido-group.[57]



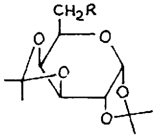
Reagents: i, NH$_2$OH; ii, NaIO$_4$; iii, Tf$_2$O; iv, NH$_3$,MeOH; v, I$_2$,Et$_3$N; vi, Δ, $\diagup\!\!\diagdown$CN

Scheme 3

3 Nitro- and Nitroso-sugars and Nitrones

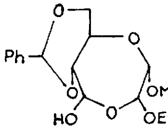
Nitro-sugar chemistry reported in the period from 1970 to 1988 has been reviewed (162 refs),[58] and the preparation and chemistry of nitroaldoses and nitroglycals have been included in a review on new chemistry leading to glycosyl carbanions, oxonium ions, radicals, radical anions and carbenes.[55]

The chain-extended nitro-sugars **(34)** were synthesized by cross-coupling the monosaccharide cobaloxime **(35)** with the anions of nitromethane or nitropropane. Branched-chain sugars produced similarly from secondary cobaloxime derivatives are covered in Chapter 14.[59] Base catalysed addition of nitromethane to the dialdehydo-derivative **(36)**, obtained by periodate oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, yielded mainly four isomeric 3-nitroheptoseptanosides, of which **(37)** and **(38)** were predominant (42 and 36%, respectively).[60] The use of potassium fluoride as catalyst for this reaction was reported to give compound **(38)** as the major product, and a mixture of C-3 epimers **(39)** with methyl nitroacetate in place of nitromethane.[61] Syntheses of glycosyl nitromethanes is covered in Chapter 3, 3-nitroglycals in Chapter 13, and [4+2]cycloadducts of 1,2-dideoxy-1-nitroheptitol peracetates in Chapter 24.



(34) R = CH$_2$NO$_2$ or CH(Et)NO$_2$

(35) R = Co(dmgH)$_2$ py



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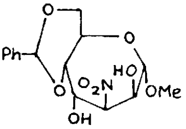

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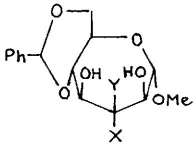
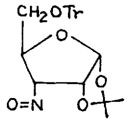


(38) X = NO$_2$, Y = H

(39) X,Y = CO$_2$Me, NO$_2$

C-Nitroso-sugars such as **(40)** were obtained as dimers by oxidation (DDQ in CHCl$_3$) of the corresponding hydroxylamino-sugars.[62]

Various mononitrones, *e.g.* **(41)**, and symmetrical and unsymmetrical dinitrones, e.g. **(42)** and **(43)**, respectively, have been synthesized. The dinitrones could be reduced to their corresponding bis-(*N*-hydroximino)-derivatives. Such sugar hydroxylamines are precursors of free radicals, these being formed on contact with air or by oxidation with lead dioxide, and able to be observed by e.s.r. spectroscopy. In the case of the bis(*N*-hydroximino)-derivatives, only mono-radical species were observed, any di-radicals being present in concentrations insufficient for detection.[63] The nitrones **(44)** and **(45)** were obtained on condensation of the oximes of protected 2-acetamino-2,4-dideoxy-D-*xylo*-hexose and hexuronate derivatives with 4-methoxybenzaldehyde.[64]



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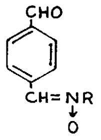
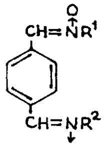
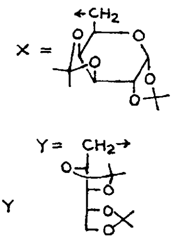


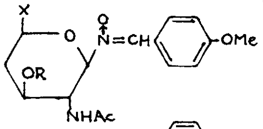
(41) R = X



(42) R^1=R^2=X

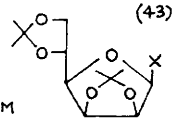
(43) R^1=X, R^2=Y





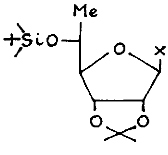
(44) X = CH$_2$OCH$_2$C$_6$H$_4$OMe, R = MOM

(45) X = CO$_2$Me, R = Ac



(46) X = NC

(47) X = CN



(48) X = NC

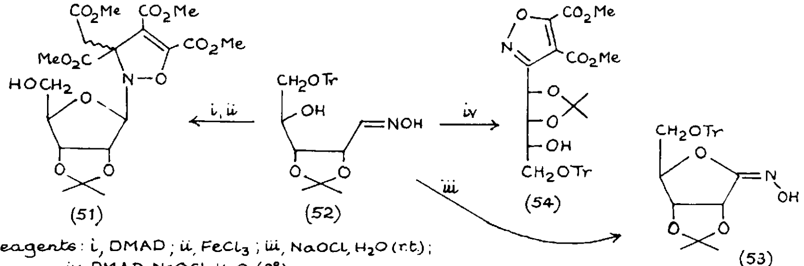
(49) X = NHCHO

(50) X = H

4 Nitriles, Isonitriles, Oximes and Hydroxylamines

A mixture of the β-D-mannofuranosyl isonitrile (**46**; 76%) and nitrile (**47**; 8%) and small proportions of their α-anomers was obtained on treatment of the corresponding glycosyl fluoride with diethylaluminium cyanide. Similar results were obtained with the 1,2:4,6-di-*O*-isopropylidene-D-mannopyranosyl equivalents.[65] In contrast, 2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-α,β-D-*erythro*-pentofuranosyl chloride was reported to yield only the corresponding glycosyl cyanides with the same reagent.[66] The 6-deoxy-D-allofuranosyl isonitrile (**48**) was synthesized from the corresponding glycosyl azide by conversion to the *N*-formyl-glycosylamine (**49**) and dehydration. This isonitrile was transformed into the protected tetrahydrofuran derivative (**50**) by radical reduction (Bu_3SnH-AIBN).[67]

The D-ribose oxime derivative (**52**) was condensed with dimethyl acetylenedicarboxylate (DMAD) to yield the *N*-ribosyl isoxazolidine (**51**) (Scheme 4), from which the aglycone could be released by acid catalysed methanolysis. Oxime (**52**) was oxidized to an acyclic nitrile oxide that was stable at 0°C, but rearranged to the ribono-1,4-lactone oxime (**53**) at room temperature, and that could be condensed with DMAD to give the isoxazole derivative (**54**). Full details on the conversion of oxime (**53**) to spirocyclic sugar isoxazolidines (*cf.* Vol. 24, p.127) have been published,[68] and covered in a symposium paper.[69] The preparation and chemistry of hydroximinolactones and their carbamates, derived from spiro-isoxazolidines, have been included in a review.[55] An isoxazolidine obtained by cycloaddition of a branched-chain sugar enal derivative is covered in Chapter 14.

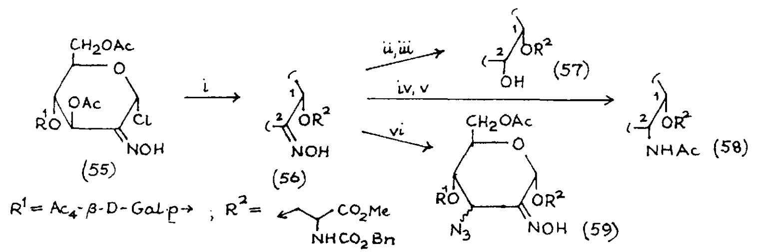


Reagents: i, DMAD; ii, $FeCl_3$; iii, NaOCl, H_2O (r.t.); iv, DMAD, NaOCl, H_2O (0°)

Scheme 4

Lemieux's glycal - nitrosyl chloride based glycosylation procedure has been employed to synthesize the 2-hydroximino-glycosyl chloride (**55**) from lactal, and to convert it into a separable mixture of the L-serine α-glycoside (**56**) and its β-anomer in a 2:1 ratio (Scheme 5). Highly stereoselective reduction procedures were used to transform the α-anomer (**56**) into the glycosides (**57**) and (**58**) of lactose and lactosamine, respectively. However, use of azide led to the 3-azido-epimers (**59**) to indicate a novel route to 3-amino- and 2,3-diamino-compounds. Analogous reductions of the β-anomer of (**56**) provided isomers in which the reducing terminal residues had the D-mannose configuration.[70]

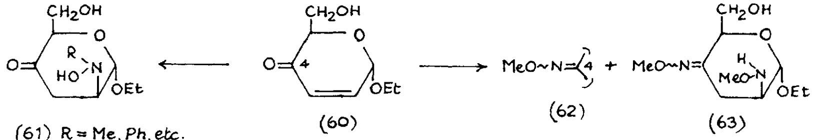
Reaction of the enone (**60**) with a variety of *N*-substituted hydroxylamines gave the conjugate addition products (**61**), whereas the analogous reaction with *O*-methylhydroxylamine gave a mixture of oximino-derivatives (**62**) and (**63**) (Scheme 6). Reduction of uloses (**61**) with sodium borohydride gave predominantly products with the D-*arabino*-configuration;[71] the e.s.r. spectroscopy of free radicals produced on spontaneous oxidation of such products is covered in Chapter 22. The condensation of



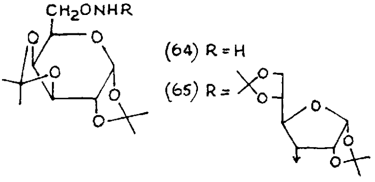
Reagents: i, R^2OH, DMF, $CaSO_4$; ii, CH_2O, H^+; iii, $NaBH_4$; iv, Ac_2O, Py, DMAP; v, $NiCl_2 6H_2O$; $NaBH_4$; vi, NaN_3, EtOH

Scheme 5

the *O*-(galactos-6-yl)hydroxylamine (**64**) (see Vol. 24, p.133) with sugar aldehydes and ketones, followed by reduction ($NaBH_3CH$, pH 2-3), led to blocked disaccharide analogues, e.g. (**65**), bearing an oximino interglycosidic bridge.[72] The synthesis and properties of di- and tri-saccharides related to the calicheamycin and esperamicin antibiotics, that have an *N-O* glycosidic linkage, are covered in Chapters 19 and 21.

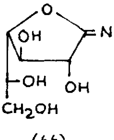


Scheme 6



(64) R = H

(65) R =



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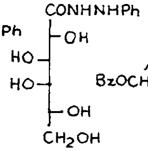

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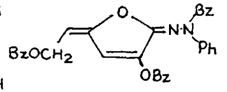
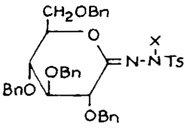


(68)

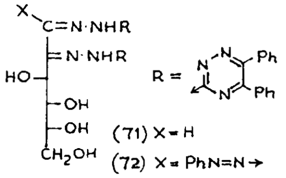
5 Hydrazones, Osazones and Related Heterocycles

Oxidation of D-galactose phenylhydrazone with air (or oxygen) at pH 12-14 in 95% ethanol over 4-5 days yielded the 1,4-lactone hydrazone (**66**) in 49% yield. Similar results were observed with the phenylhydrazones of D-arabinose and D-fucose (Caution: bubbling of air or oxygen in this way can cause explosion). The lactone hydrazone (**66**) can be hydrolysed (dil. HCl, 70°) to the D-galactonoyl hydrazide (**67**), or converted to the unsaturated derivative (**68**) on benzoylation.[73,74] The D-glucono-1,5-lactone *N*-tosylhydrazone derivative (**69**) was obtained from the corresponding D-glucose tosylhydrazone derivative (which exist in a cyclic form) by oxidation (*e.g.*, NBS-DBU). Its sodium salt (**70**) was used as a novel glycosidation reagent under photolytic or thermoditic conditions, where a glycosylidene carbene intermediate is presumed to form. Various other lactone hydrazones were also prepared, sometimes using chromium(VI) oxidants.[75]



(69) X = H

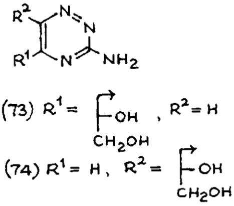
(70) X = Na



(71) X = H

(72) X = PhN=N→

vert

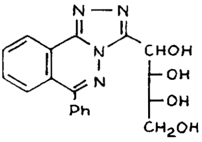


(73) R^1 = , R^2 = H

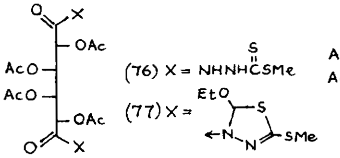
(74) R^1 = H, R^2 =

The osazone (71) was synthesized from either D-glucose or D-fructose, and formed the diazo-derivative (72) on reaction with benzenediazonium chloride. Similar reactions were applied to D-ribose and D-arabinose.[76]

In the study related to the ability of aminoguanidine [$H_2N.NHC(NH)NH_2$] to inhibit the Maillard reaction, the triazine positional isomers (73) and (74) were isolated in modest yields from the condensation of 3-deoxy-D-*glycero*-pentos-2-ulose with aminoguanidine in phosphate buffer at pH 7.[77] The 3-(D-*ribo*-tetritol-1-yl)-1,2,4-triazolo[3,4-*a*]phthalazin derivative (75) was obtained from sequential condensation of D-ribose with 1-hyrazino-4-phenylphthalazine, and cyclization (Pd/C) of the resulting hydrazone. The corresponding hydrazones of D- or L-arabinose, D-lyxose and D-xylose underwent spontaneous autodehydrogenative cyclization to analogues of (75).[78] The bis(heterocyclic) products (77)-(79) were separately obtained (in unspecified yields) from the galactaryl bis(hydrazide) (76) using different cyclization reagents [*i.e.*, $(EtO)_3CH$, $POCl_3$ or $SOCl_2$, respectively].[79]

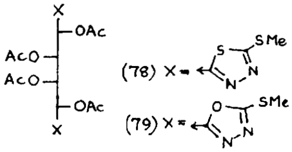


(75)



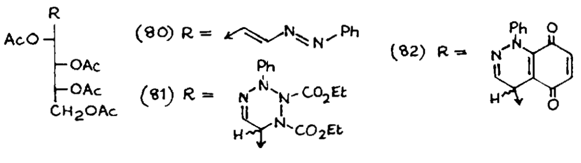
(76) X = NHNHC(S)SMe

(77) X =



(78) X =

(79) X =



(80) R =

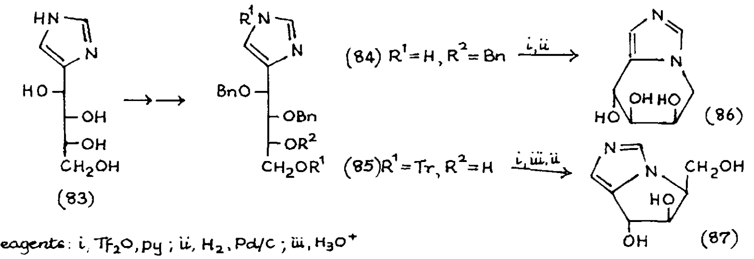
(81) R =

(82) R =

The diazo-diene (80) was obtained on acetylation (Ac_2O-py) of D-mannose phenylhydrazone and underwent [4+2]cycloadditions with diethyl azodicarboxylate to give (81) or hydroquinone to give (82) as epimeric mixtures.[80]

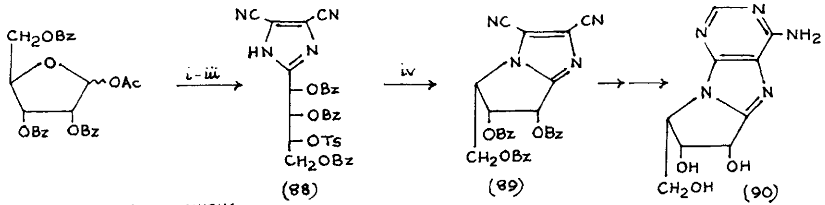
6 Other Heterocycles

Several interesting fused iminoalditol-heterocyclic ring systems have been reported. The imidazole analogues (**86**) and (**87**) of 6-*epi*-castanospermine and 3-*epi*-alexine [referred to as the 3,7a-diepialexine, but C-7a in (**87**) is trigonal], were obtained by cyclization of the protected forms (**84**) and (**85**), respectively, of the D-glucose derived 4-(tetritol-1-yl)-imidazole (**83**) (Scheme 7).[81] The hypermodified purine nucleoside analogue (**90**) was obtained by elaboration of the bicyclic intermediate (**89**) formed on cyclization of the 2-(tetritol-1-yl)-imidazole derivative (**88**) (Scheme 8).[82] The fused tetrazole (**93**), a new β-glucosidase inhibitor, was synthesized from the D-glucose derivative (**91**) *via* the aldononitrile derivative (**92**). The process involves double inversion at C-5 of (**92**), either as shown in Scheme 9, or more satisfactorily *via* an oxidation-reduction sequence[83].



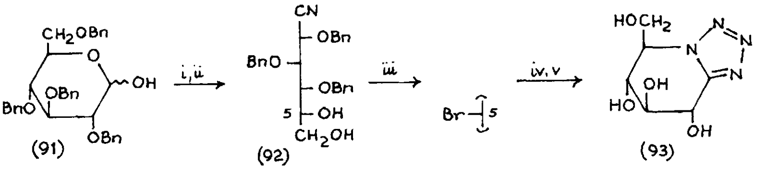
Reagents: i, Tf_2O, py ; ii, H_2, Pd/C ; iii, H_3O^+

Scheme 7



Reagents: i, $Me_3SiNH(NC)C{=}C(CN)NHSiMe_3$, Me_3SiOTf ; ii, NBS, EtOAc ; iii, TsCl, py ; iv, NaH

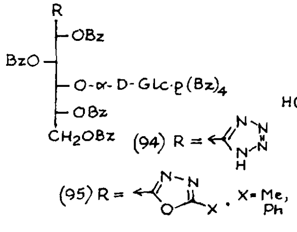
Scheme 8



Reagents: i, NH_2OH ; ii, Ph_3P, CBr_4 ; iii, Ph_3P, Br_2, imidazole ; iv, NaN_3, DMSO ; v, H_2, Pd/C

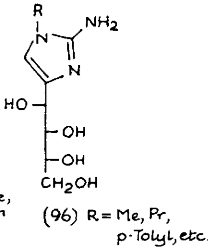
Scheme 9

A variety of alditol-1-yl substituted heterocyclic derivatives have been synthesized. The tetrazole derivative (**94**) was derived from maltose,[84] and converted into the corresponding 1,3,4-oxadiazoles (**95**) on acetylation or benzoylation.[85] Reaction of 1-arylamino- or 1-alkylamino-1-deoxy-D-arabino-hexuloses with cyanamide gave the imidazole derivatives (**96**).[86,87] Fructosazine (**97**) and deoxyfructosazine (**98**) were simultaneously formed by self-condensation of 2-amino-2-deoxy-D-glucose in neutral to basic aqueous solutions, and were shown to have DNA strand breaking activity.[88] Condensation of 2-amino-2-deoxy-D-glucose with aryl isocyanates gave adducts such as (**99**) that exist in solution as (*R*,*S*)-mixtures in which the (*R*)-form predominates.[89]

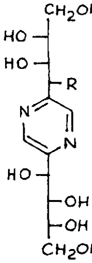


(94) R =

(95) R =

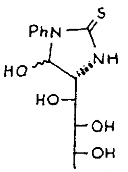


(96) R = Me, Pr, p-Tolyl, etc.



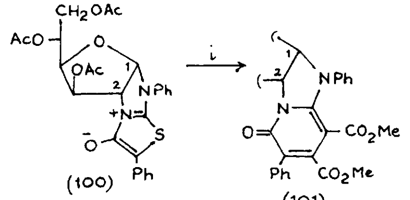
(97) R = OH

(98) R = H



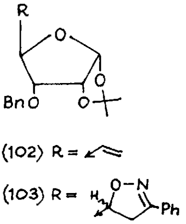
(99)

The synthesis of imidazo[2,1-*b*]thiazolium-3-olate zwitterions such as (**100**) from sugar thiourea derivatives, and their cycloaddition reactions to form imidazo[1,2-*a*]pyridin-4-ones such as (**101**) (Scheme 10) have been detailed.[90]



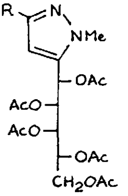
Reagent: i, MeO$_2$CC≡CCO$_2$Me

Scheme 10



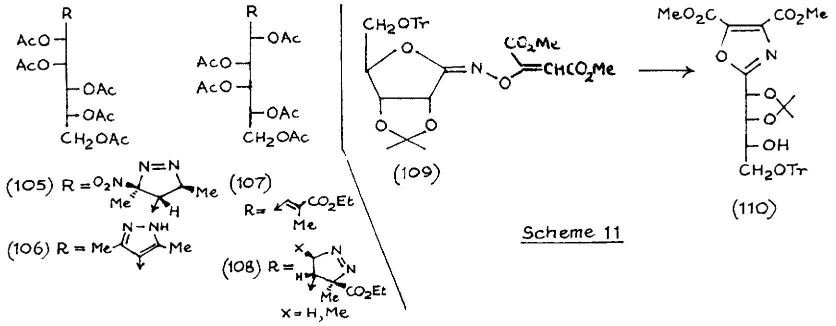
(102) R =

(103) R =



(104) R = Me, Pr^i, Ph, etc

Cycloadditions of nitrile oxides to the D-*ribo*-alkene (**102**) gave near equimolar mixtures of epimeric isoxazoline adducts such as (**103**),[91] whereas related D-*xylo*-alkenes yielded mainly one diastereoisomer[92] (see also Vol. 23, p. 119). (D-*galacto*-Pentitol-1-yl)pyrazole derivatives such as (**104**) resulted from the condensation of 1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol pentaacetate with *N*-phenyl- or *N*-methyl-hydrazones of alkyl or aryl aldehydes.[93] The addition of diazoethane to 1,2,3-trideoxy-2-nitro-oct-2-enitol pentaacetate gave a single isomer (**105**) which was aromatized (HCl) to the pyrazole (**106**).[94] Similarly, addition of diazomethane or diazoethane to unsaturated sugar acid esters such as oct-2-enoate (**107**) yielded single isomeric derivatives such as (**108**).[95]



Scheme 11

Sugar lactone oxime *O*-vinyl ethers such as **(109)** formed oxazole derivatives such as **(110)** on thermolysis (200°, 2 min) (Scheme 11), and a mechanism involving initial radical cleavage of the *N-O* bond was proposed.[96]

A synthesis of lamptoflavin, *i.e.* 5-*O*-ribosyl-riboflavin, is covered in Chapter 18.

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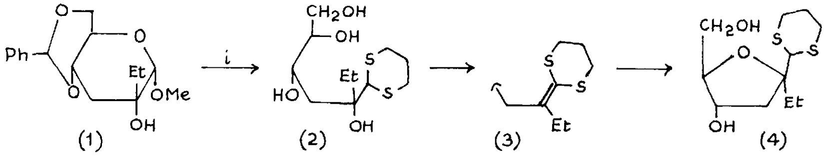
11

Thio- and Seleno-sugars

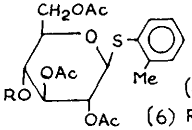
Treatment of the branched 3-deoxy-D-*ribo*-hexopyranose derivative (**1**) with propane-1,3-dithiol and aqueous HCl gave the 2,5-anhydro compound (**4**) in 80% yield (Scheme 1). The reaction is thought to proceed *via* the expected acyclic dithioacetal (**2**) and to involve the well known elimination of a hydroxyl group β to a dithioacetal function, followed by an unprecedented intramolecular H^+-catalysed additon to the β-carbon of the ketene dithioacetal (**3**).[1] The synthesis of KDO by use of bis(ethylthio) intermediates is referred to in Chapter 16.



Reagents: i, $HS(CH_2)_3SH$, HCl.aq

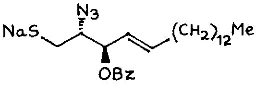
Scheme 1

The preparation of several *o*-toluyl 1-thio-D-glycosides, *e.g.*, the monosaccharide (**5**) and the disaccharides (**6**), by standard methods has been reported.[2] β-Lactosyl 1-thio-ceramide was obtained by condensation of acetobromolactose with the sodium thiolate (**7**), followed by elaboration of the aglycon moiety and deprotection in the usual way.[3] An 8:5:5 mixture of α,α-, β,β,- and α,β-1-thio-trehalose in *ca.* 50% total yield was formed when D-glucose was exposed to H_2S in the presence of anhydrous HF.[4]



(5) R = Ac

(6) R = α-D-Glc*p*(OAc)$_4$ or α-D-Gal*p*(OAc)$_4$



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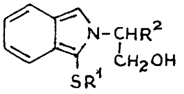


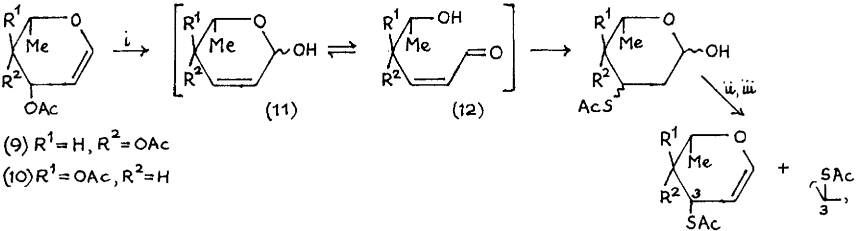
R^1 = β-D-Glc-*p*, β-D-Gal-*p*, or β-D-Man*p*

R^2 = Me, Et, CO_2H, etc

(8)

1-Thio-β-D-glucose, -galactose, and -mannose in combination with *o*-phthaldialdehyde in aqueous base have been employed in the chiral resolution of 2-amino-1-alcohols through formation of diastereomeric indole derivatives of presumed structure (**8**), which were separated by reverse phase h.p.l.c.[5]

Unsaturated phenyl 1-thioglycosides were intermediates in the synthesis of the core trisaccharides of esperamycin which is referred to in Chapter 19. The rearrangement of a thioglycoside on exposure to trimethyl orthobenzoate is covered in Chapter 7.

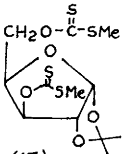


(13) $R^1 = H, R^2 = OAc$ (15)
(14) $R^1 = OAc, R^2 = H$ (16)

Reagents: i, H_2O, AcSH ; ii, Ac_2O, py ; iii, Xylene, Δ

Scheme 2

4-*O*-Acetyl-3-*S*-acetyl-3-thio-L-fucal (**13**) and -L-rhamnal (**14**) and their 3-epimers (**15**) and (**16**) have been prepared from the respective di-*O*-acetates (**9**) and (**10**) by way of hex-2-enopyranoses (**11**) which, being in equilibrium with their acyclic counterparts (**12**), underwent conjugate addition of thioacetic acid, as shown in Scheme 2. Compounds (**13**)-(**16**) were required for the synthesis of new, 3′-modified anthracyclines.[6] Treatment of the bis-xanthate (**17**) with Bu_3SnH and AIBN gave the 3,5-cyclic dithioorthoformate (**18**) instead of the expected deoxygenation product.[7] The mechanism of the S→O migration of thiophosphoryl groups in sugar β-hydroxyphosphorothioates exposed to pyridine is covered in Chapter 7, and 3′-thionucleosides are referred to in Chapter 20.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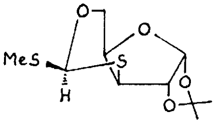
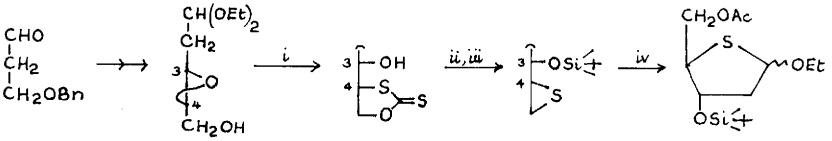

(18)

In the preparation of 4-thiopentofuranoside (**22**) (Scheme 3) from 3-hydroxypropanal, the carbon-chain was first extended and functionalized by Wittig and Sharpless methodology. The reaction of the resulting 3,4-anhydro-2-deoxypentose diethyl acetal (**19**) with CS_2 was accompanied by intramolecular epoxide opening to give the cyclic xanthate (**20**) which, after

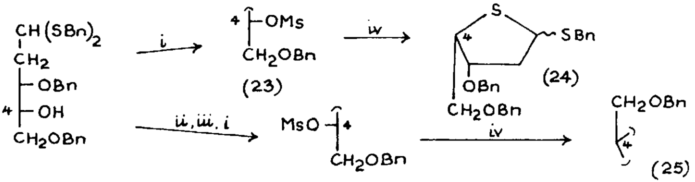


(19) (20) (21) (22)

Reagents: i, CS_2, KH ; ii, $^tBuMe_2SiOTf$, 2,6-Lutidine ; iii, K_2CO_3, MeOH ; iv, NaOAc, HOAc

Scheme 3

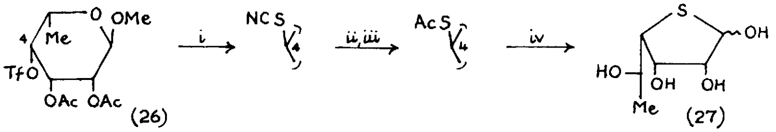
silylation, rearranged to the episulfide (**21**) under the influence of weak aqueous base. The final product (**22**) was formed on opening of the episulfide with NaOAc/HOAc with concomitant attack by the C-4 sulfide at C-1.[8] In the novel synthesis of 1,4-dithio-D-*threo*-pentofuranoside (**24**), illustrated in Scheme 4, ring closure involved intramolecular displacement with inversion of a good leaving group at C-4 of the D-*erythro* precursor (**23**) by a C-1 thioacetal sulfur atom. The D-*erythro* analogue (**25**) of (**24**) was obtained by an extended reaction sequence involving two inversions at C-4.[9,10] The use of thiopentofuranosides (**22**) and (**25**) in the synthesis of 4′-thionucleosides is covered in Chapters 20 and 19, respectively.



Reagents: i, MsCl, py ; ii, DEAD, PPh_3, BzOH ; iii, MeO^-, MeOH; iv, NaI, $BaCO_3$, Me_2CO, Δ

Scheme 4

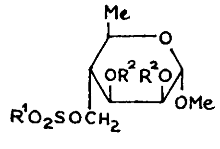
4-Thio-L-rhamnofuranose (**27**) was obtained by triflate displacement at C-4 of the L-*talo*-configurated pyranose derivative (**26**) with KSCN in DMF and subsequent reduction of the thiocyanate group and acetolysis/deacetylation as indicated in Scheme 5.[11] When similar displacements were attempted with derivatives of methyl 6-deoxy-α-D-mannopyranoside, a 2:1 mixture of 4-thiocyano sugars (**32**) and (**33**) was produced from the dihydroxy-*p*-nitrobenzenesulfonate (**28**) in 52% combined yield; however, compounds (**29**)-(**31**) underwent solvolysis and/or decomposition under the reaction conditions.[12]



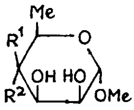
Reagents: i, KSCN, DMF ; ii, Zn, HOAc ; iii, Ac_2O, HOAc, H_2SO_4; iv, MeO^-, MeOH

Scheme 5

A new route to 5-thio-hexopyranosides proceeded by way of monothioacetal derivatives which were formed on treatment of protected methyl glycosides with Me_2BBr followed by thioacetic acid. As an example, the synthesis of perbenzylated methyl 5-thio-L-idopyranoside (**34**) from methyl tetra-*O*-benzyl-β-D-glucopyranoside is shown in Scheme 6. By incorporating

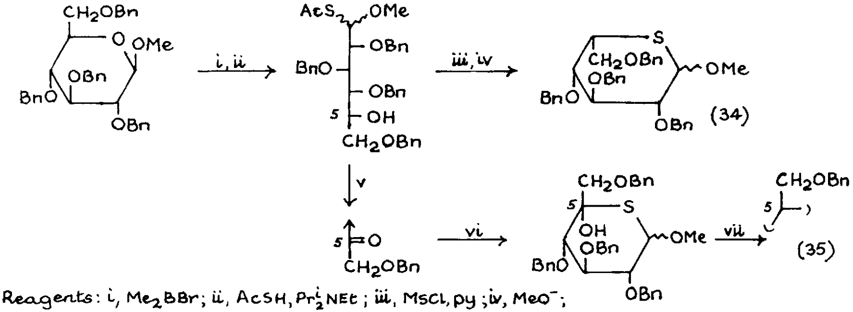


(28) $R^1 =$ -⌬-NO_2, $R^2 = H$
(29) $R^1 =$ " , $R^2 = Bz$
(30) $R^1 =$ p-Ts, $R^2 = H$
(31) $R^1 =$ " , $R^2 = Bz$



(32) $R^1 = SCN$, $R^2 = H$
(33) $R^1 = H$, $R^2 = SCN$

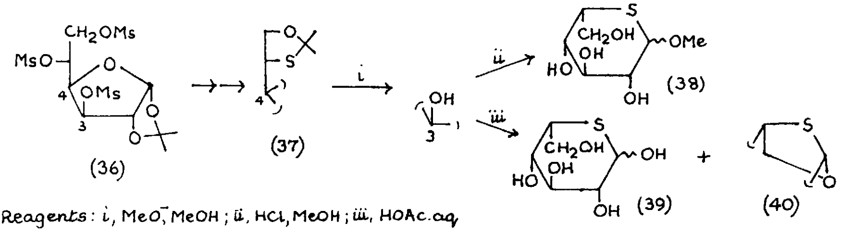
an oxidation and a reduction step before and after the cyclization, respectively, thiosugars with preserved stereochemistry at C-5 [*i.e.*, the D-*gluco* product **(35)** in the above example] were available.[13] Another approach to 5-thio-L-idopyranose and some of its derivatives involved transformation of the D-*gluco*-trimesylate **(36)** in 4 steps *via* the L-*ido* configurated 5,6-episulfide to the 5-thiosugar diacetal **(37)** (Scheme 7). Removal of the remaining mesyl group followed by methanolysis or hydrolysis afforded the methyl glycoside **(38)** or the free thiosugar **(39)**, respectively. A major by-product of the latter reaction was the 1,6-anhydro-thiosugar **(40)**.[14]



Reagents: i, Me_2BBr; ii, AcSH, Pr^i_2NEt; iii, MsCl, py; iv, MeO^-; v, Swern oxidation; vi, $H_2N(CH_2)_2SH$; vii, Et_3SiH, $BF_3.OEt_2$

Scheme 6

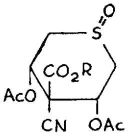
An improved synthesis of methyl 5-thio-D-arabinopyranoside in 5 steps and 28% overall yield from D-arabinose through acyclic intermediates has been reported.[15]



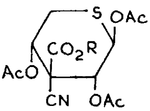
Reagents: i, MeO^-, MeOH; ii, HCl, MeOH; iii, HOAc.aq

Scheme 7

The unusual branched thiosugar derivative **(42)** was produced by Pummerer rearrangement of the functionalized sulfoxide **(41)**, which was formed by condensation of *cis*-2,6-dihydroxy-1,4-oxathiane with L-menthyl cyanoacetate, followed by acetylation and oxidation.[16] The preparation of 5-thiolactose and 3-*O*-fucosyl-5-thiolactose by use of glycosyltransferases is covered in Chapter 3.



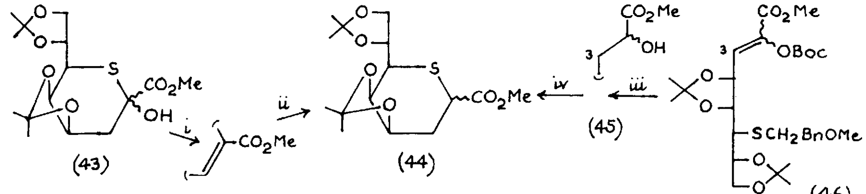
(41)



(42)

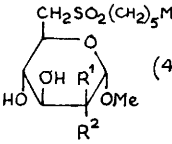
R = L-menthyl

2-Deoxy-6-thio KDO derivatives (**44**) are available, as shown in Scheme 8, either by dehydration/hydrogenation of the known 6-thio KDO diacetonide (**43**) or by reductive hydrolysis of the unsaturated 3-deoxy-6-thio-octonic acid derivative (**46**) [an intermediate in the preparation of (**43**) from D-mannose, see Vol.23, Ch.11, ref.5] with Zn/HOAc and intramolecular displacement of the activated 2-OH group of the saturated intermediate (**45**) by the C-6 sulfur atom.[17] On treatment with tributyl phosphine and diphenyl disulfide at 62°C and 10 kbar, diacetone galactose was quantitatively converted to its 6-phenylthio ether.[18] Displacement of halogen by alkyl thiolate at C-6 of otherwise unprotected methyl α-D-gluco- or -manno-pyranoside and subsequent oxidation with MCPBA gave the new non-ionic surfactants (**47**).[19] 6-Thioglucose 6-phosphate was prepared by reaction of 6-*O*-tosyl-D-glucose with aqueous trisodium thiophosphate, for use in an investigation of its enzymic reactions, in particular the conversion to 5-thioribulose 5-phosphate and 6-thioglucose 1-phosphate.[20]

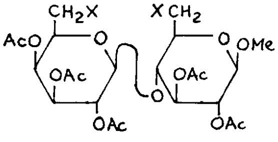


Reagents: i, Ph_2PCl, im, Br_2; ii, Pd/C, H_2; iii, Zn, HOAc; iv, PPh_3, ImI_3

Scheme 8



(47) $R^1=H, R^2=OH$, or $R^1=OH, R^2=H$

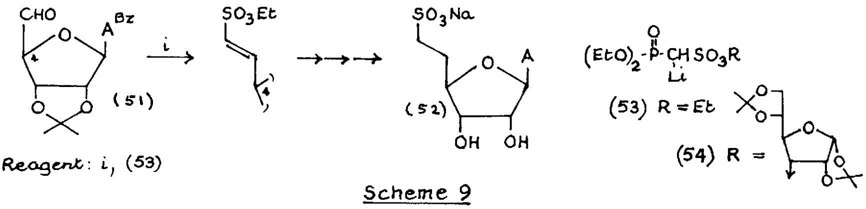


(48) X = Br

(49) X–X = S–S, $S-\overset{S}{\overset{\|}{C}}-S$

(50) X = SAc, SCN, $S-\underset{S}{\underset{\|}{C}}-NMe_2$

As an extension of earlier work on sucrose (see Vol.22, Ch.11, ref.12), various bridged (**49**) and unbridged (**50**) 6,6′-di-*S*-derivatives of methyl β-lactoside have been synthesized by treatment of the dibromide (**48**) with the appropriate sulfur nucleophiles.[21]

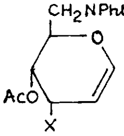


Reagent: i, (53)

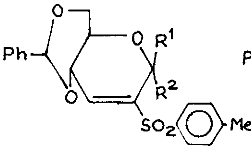
Scheme 9

The key-step in the preparation of adenosyl 5′-sulfonate (**52**) (the sulfonate analogue of adenine), outlined in Scheme 9, was the reaction of the protected adenosine aldehyde (**51**) with the sulfonyl-stabilized α-phosphonate (**53**). By use of the diacetoneallose-derived phosphonate (**54**) in similar procedures, sulfonyl-linked disaccharides and dinucleotides were obtained.[22]

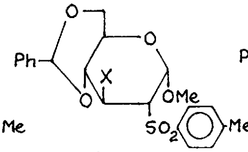
A new, facile procedure for the oxidation of sulfides to sulfones, employing catalytic OsO_4 and tertiary amine *N*-oxides, has been applied to various thiosugars. The chemoselectivity of the method was demonstrated by the high yielding transformation of the unsaturated sulfide (**55**) to the sulfone (**56**) without any sign of double bond hydroxylation.[23] A series of nucleophiles added to the 3-position of the sulfonyl alkene (**57**) to give stereoselectively the D-*gluco* adducts (**59**). Exposure of the analogous phenyl β-glycoside (**58**) to similar conditions, on the other hand, led mainly to D-*arabino* configurated 1-enitol products (**60**).[24]



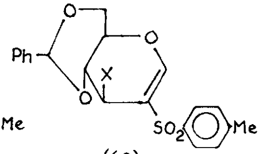
(55) X = SMe
(56) X = SO$_2$Me



(57) R^1 = H, R^2 = OMe
(58) R^1 = OPh, R^2 = H



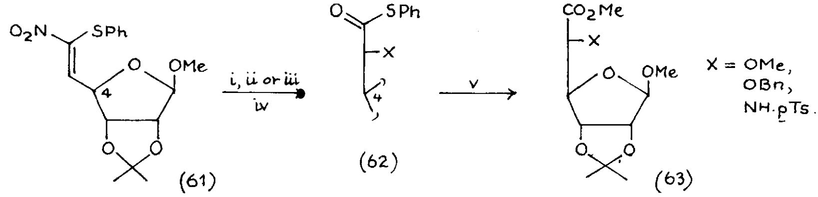
(59)



(60)

X = MeO, O$_2$NCH$_2$, etc.

Michael addition of nucleophiles to the nitro-(phenylthio)alkene (**61**) provided , after ozonolysis of the intermediate nitronates, substituted phenylthiol esters (**62**) with good to excellent diastereoselectivity. They were converted to derivatives (**63**) of methyl L-alluronate by treatment with methanolic mercury(II) acetate.[25]



Reagents: i, MeONa, MeOH, DMF; ii, BnONa, BnOH, DMF; iii, p.TsNH$_2$, Bu^{t}OK, DMF; iv, O_3; v, Hg(OAc)$_2$, MeOH

Scheme 10

Thio derivatives of cyclitols are referred to in Chapter 18, and H,H coupling constants of thiosugars in Chapter 21.

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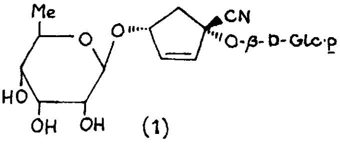
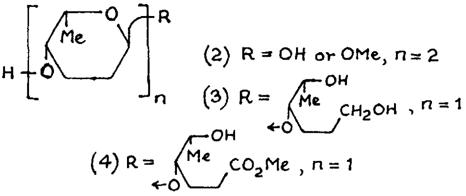
12
Deoxy-sugars

Passitrifasciatin (1), isolated from *Passiflora trifasciata*, has been re-examined and found to contain the rare 6-deoxy-β-D-allopyranosyl residue.[1] The secondary metabolites (2)-(4) of L-rhodinose (*i.e.* 2,3,6-trideoxy-L-*threo*-hexose) were isolated from culture broths of two new *Streptomyces* strains.[2]

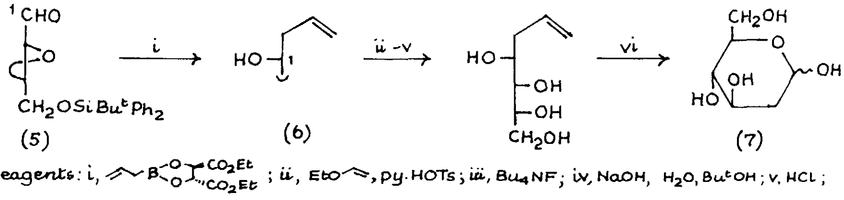


(1)



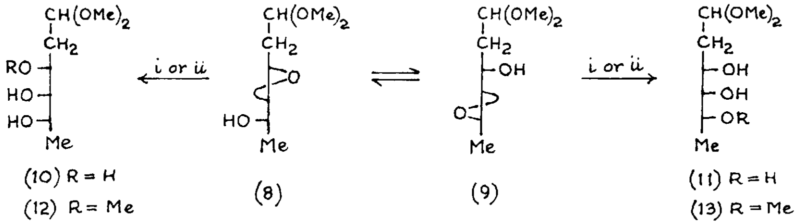
2-Deoxy-D-*glycero*-tetrose was obtained by C-1/C-2 cleavage [$Pb(OAc)_4$] of 3-deoxy-D-*erythro*-pentose, and [1-^{13}C]-3-deoxy-DL-*glycero*-tetrose from acrolein by a sequence of hydration, cyanohydrin-formation, and catalytic reduction reactions. 2-Deoxy-5-*O*-methyl-D-*erythro*-pentose was obtained from the corresponding unmethylated deoxypentose, and its 3-deoxy-analogue by Barton deoxygenation of 1,2-*O*-isopropylidene-5-*O*-methyl-α-D-xylofuranose. The proportions of cyclic and acyclic forms of these and related branded-chain sugars in solution were determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy.[3]

2-Deoxy-D-glucose (7), and similarly 2-deoxy-D-galactose, were synthesized from 2,3-anhydrotetroses, *e.g.* (5), obtained in high optical purity by the Sharpless asymmetric epoxidation procedure (Scheme 1). High stereoselectivity was attained in the addition of a chiral allylboronate to (5), the product (6) and its isomer being formed in the ratio 96:4. In this case the reagent and substrate stereochemistry is "matched". In cases where this was not the case, stereoselectivity was poor.[4] Under alkaline conditions, the epoxyalcohols (8) and (9) equilibrate faster than they undergo ring opening (Scheme 2). In aqueous alkali the enantiomeric digitoxose acetals (10) and (11) were formed, whereas with methoxide ion, the isomeric 2,6-dideoxy-3-*O*-



Reagents: i, ; ii, EtO, py·HOTs; iii, Bu_4NF; iv, NaOH, H_2O, Bu^tOH; v, HCl; vi, O_3, MeOH, then Me_2S.

Scheme 1



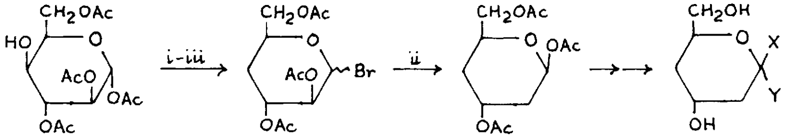
Reagents: i, NaOH, H_2O ; ii, NaOMe, MeOH

Scheme 2

methyl-L-*ribo*-hexose dimethyl acetal (**12**) and its 5-*O*-methyl-D-isomer (**13**) were formed in the ratio 32:68. In each case, the epoxide is attacked by the external nucleophile at the carbon remote from the hydroxy-substituent. Identical results were obtained in the enantiomeric series.[5]

Radical reduction of thioacylated sugars continues to be widely applied for the synthesis of deoxy-sugars, and several important advances in methodology have been reported. Organotin residues can be difficult to remove from products obtained using tributyltin hydride as reagent. Phenylsilane ($PhSiH_3$),[6] triethylsilane (Et_3SiH),[7] and tris(trimethylsilyl)silane,[8] in combination with AIBN or benzoyl peroxide as radical initiator, can be used instead of this reagent, resulting in simplified work-up procedures. Efficient conversions (ca. 70% overall) of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose to its 6-deoxy-derivative have involved *N*-hydroxysuccinimide-assisted 6-*O*-(2,4,6-trichlorophenoxy)thiocarbonylation or 6-*O*-(4-fluorophenoxy)thiocarbonylation followed by radical reduction (with Bu_3SnH-AIBN or $PhSiH_3$-Bz_2O_2).[9] The synthons (**17**) and (**18**) for the β-hydroxy-δ-lactone moiety of mevinic acid were synthesized from penta-*O*-acetyl-β-D-glucose *via* the easily obtained 1,2,3,6-tetra-*O*-acetyl-α-D-idose (**14**) (Scheme 3). Conventional 4-deoxygenation led to (**15**), then the use of Giese's C-1 to C-2 radical rearrangement (*cf.* Vol. 22, p. 129) gave the 2,4-dideoxy-derivative (**16**) (60%), accompanied by a 1,4-dideoxy-derivative (40%) resulting from direct reduction at C-1.[10] Methyl 3,6-anhydro-2,4-dideoxy-β-D-*threo*-hexopyranoside (**19**) was obtained by double radical reduction (Bu_3SnH) of the β-*galacto*-derivative (**20**); similar reactions of the α-*gluco*- or α-*manno*-isomers were not successful. It was proposed that in these latter cases the initial C-2 radical is intramolecularly trapped to form intermediate (**21**), resulting in a complex mixture from which the stannylthiomethyl ether (**22**) was isolated (in 48% yield in the case of α-*gluco* starting material).[11] (*R*)-2,2-Dimethyl-1,3,6-trioxaspiro[4,5]decane (**23**) and its hydroxy-analogues (**24**) and (**25**) were synthesized from 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranoside by multistep sequences involving either radical reductions of xanthate derivatives, or Corey-Winter elimination of a 4,5-thionocarbonate derivative [with $(MeO)_3P$] followed by hydrogenation.[12] A 2-acetamido-2,4-dideoxy-D-*xylo*-hexose derivative was obtained by radical reduction (Bu_3SnH) of a 4-xanthate ester, while a related methyl 2-acetamide-2,4-dideoxy-D-

xylo-hexuronate was obtained from methyl (benzyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-α-D-glucopyranosiduronate) by 4,5-elimination of acetic acid [with DBU or preferably MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, which gives particularly high yields] and reduction (H_2-Pd/C).[13] Alternative syntheses of acetamidodideoxyhexoses are covered in Chapter 9.

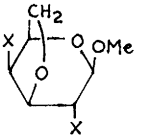


(14) (15) (16) (17) X,Y = O

(18) X,Y = H,OMe

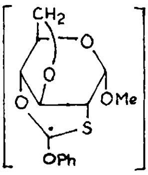
Reagents: i, PhOCSCl, DMAP ; ii, Bu_3SnH, AIBN ; iii, HBr, HOAc

Scheme 3



(19) X = H

(20) X = $\underset{S}{\overset{\|}{OC}}OPh$



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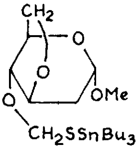

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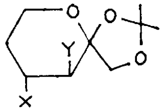
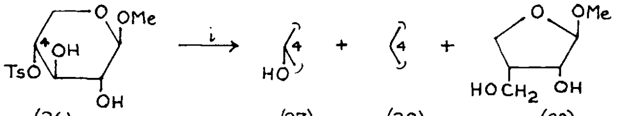


(23) X = Y = H

(24) X = OH, Y = H

(25) X = H, Y = OH

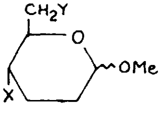
A large scale preparation of 2-deoxy-D-*erythro*-pentose in *ca.* 14% from D-glucose involved the alkaline degradation of 3-*O*-tosyl-D-glucose.[14] Reaction of glycopyranoside monotosylates with lithium aluminium hydride results in detosylation *via* O-S bond cleavage, and/or deoxygenation, and/or ring-contraction to branched-chain furanosides. In the case of methyl 4-*O*-tosyl-β-D-xylopyranoside (**26**) the products of all three reaction pathways *i.e.* (**27**) - (**29**), were obtained on 25, 41 and 17% yield, respectively (Scheme 4). Deoxygenation is the exclusive reaction in the case of primary tosylates.[15] A separable mixture of methyl α- and β-D-amicetopyranosides (**30**) was obtained in five steps from methyl 2,3-dideoxy-5,6-di-*O*-isopropylidene-D-gluconate (readily available from D-gluconolactone: *Recl. Trav. Chim. Pays-*



(26) (27) (28) (29)

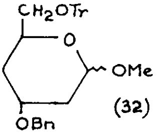
Reagent: i, LAH, THF

Scheme 4



(30) X = OH, Y = H

(31) X = H, Y = OH



(32)

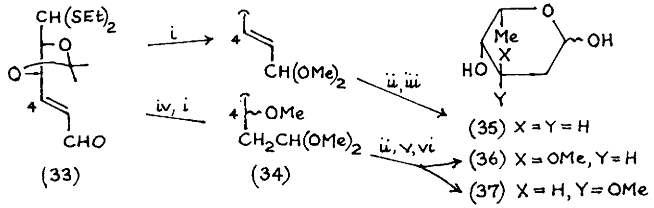
Bas., 1989, *108*, 330), the final step involving the treatment of a glycopyranoside 4,6-ditosylate with lithium aluminium hydride to effect O-4 detosylation and C-6 deoxygenation. A separable mixture of the anomeric 2,3,4-trideoxyglycosides (**31**) was obtained from the same starting material by synthesis (Ph_3P-CBr_4-Im) and reduction (H_2 -Pd/C) of an acyclic C-4 bromide.[16]

The 2,4-dideoxy-D-*erythro*-hexopyranoside (**32**) was prepared in 7 steps and 30% overall yield from D-glucose, though details of the methodology were not revealed in the available abstract.[17]

4-Deoxy-L-fucose and its methyl α-glycoside was synthesized from a 1,2,3-*O*-protected L-fucose derivatives by a conventional sequence involving displacement with inversion of a 4-triflate by iodide, and catalytic reduction (see also ref. 25 this chapter).[18] The anomeric 2-deoxy- and 2,6-dideoxy-D-*arabino*-hexopyranosyl fluorides were prepared either by reduction (Bu_3SnH) of the corresponding 2- or 2,6-di-(bromodeoxy)-hexosyl fluorides, or from 2-deoxy-D-*arabino*-hexopyranosyl derivatives.[19] 2-Deoxy-sugar glycosides can be obtained by the iodoglycosidation of glycals, followed by reductive removal of the 2-iodo-substituent; examples can be found in Chapter 3. Synthesis of 2,6-dideoxy-3-*C*-branched-chain sugars by desulphurization of 2,6-anhydro-2-thio-derivatives is covered in Chapter 14.

L-Fucose has been converted into the liquid crystalline materials methyl 2-*O*-dodecanoyl-α-L-fucopyranoside, and octyl and dodecyl β-L-fucofuranosides, the last two being separated from mixtures containing the pyranoside isomers. These compounds represent a novel organizational type of liquid crystalline material, for which the concept "monolayer with frustrated chain end" was suggested. The frustration arises from the presence of the $CH_3(6)$ group in the hydrophyllic centre of the molecule[20].

The L-arabinose derived enal (**33**) (*cf.* Vol. 24, p. 112) was a common starting material in syntheses of the trideoxy-sugar L-rhodinose (**35**)[21] and the epimeric dideoxy-sugars L-diginose (**36**) and L-sarmentose (**37**)[22] (Scheme 5). The epimeric intermediates (**34**) were separated and independently converted into (**36**) and (**37**). The D-enantiomers of (**36**) and (**37**) were similarly prepared from D-arabinose. Methyl α,β-D-ribofuranoside was converted to 1-*O*-acetyl-5-*O*-benzoyl-2,3-dideoxy-α,β-D-*erythro*-pentofuranose by radical deoxygenation (Bu_3SnH) of a 2,3-*O*-

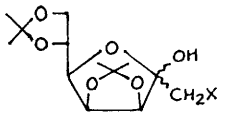


Reagents: i, $Me_2C(OMe)_2$, MeOH, H^+; ii, Raney Ni, EtOH; iii, H_2O, HOAc; iv, NaOMe, MeOH; v, H_2SO_4, MeOH; vi, H_3O^+

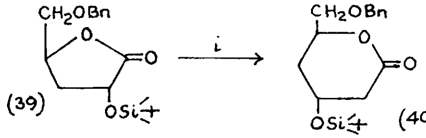
Scheme 5

thionocarbonate and catalytic reduction (H_2-PtO_2) of the resulting 2,3-dideoxy-hex-2-enoside derivative.[23]

1-Deoxy- and 1-chloro-1-deoxy-ketoses, *e.g.* **(38)**, resulted from the reactions of *O*-protected aldonolactones with trimethylsilylmethyl anions ($LiCH_2SiMe_3$ or $LiCH(Cl)SiMe_3$, respectively) followed by protodesilylation which occurred during chromatography on silica gel.[24] The 2,4-dideoxy-D-*erythro*-hexono-1,5-lactone derivative **(40)**, a key chiral synthon for the lactone portion in mevinic acids (see also ref. 10 this chapter), was obtained in 11 steps from D-xylose. The sequence involved 3-deoxygenation of a xylofuranose 3-xanthate derivative under the conditions of radical reduction (Bu_3SnH), and a rather unusual homologation of lactone **(39)** as shown in Scheme 6.[25] 2-, 3-, and 4-Deoxy-derivatives of L-rhamnose have been synthesized.



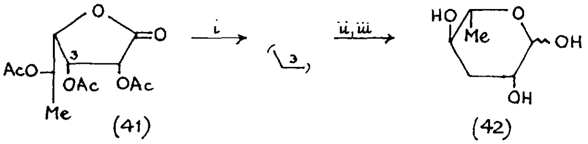
(38) X = H or Cl



Reagents: i, $LiCHBr_2$, then HCl, Et_2O

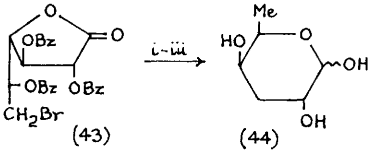
Scheme 6

The 2-deoxy-derivative was obtained from the known 2,6-dideoxy-L-*arabino*-hexono-1,4-lactone, while the 4-deoxy-derivative was obtained by radical reduction of an *O*-protected L-rhamnose 4-xanthate derivative. The 3-deoxy-derivative **(42)** was obtained from L-rhamnose *via* a mixture of acetylated L-rhamnono-1,4-lactone **(41)** and its 1,5-lactone isomer, utilizing hydrogenolytic conditions that effect β-elimination of acetic acid and stereoselective reduction of the resulting 3-deoxy-hex-2-enonolactone (Scheme 7). 2- and 4-Deoxy-L-rhamnose exist mainly in the pyranose form in solution, whereas 3-deoxy-L-rhamnose **(38)** forms a mixture of pyranose and furanose forms in the ratio 2:1.[26] Similar reactions have been used to convert benzoylated



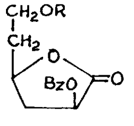
Reagents: i, H_2, Pd/C, Et_3N ; ii, HCl, MeOH ; iii, disiamylborane

Scheme 7

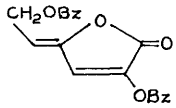


Reagents: i, H_2, Pd/C, Et_3N ; ii, disiamylborane ; iii, MeONa, MeOH

Scheme 8



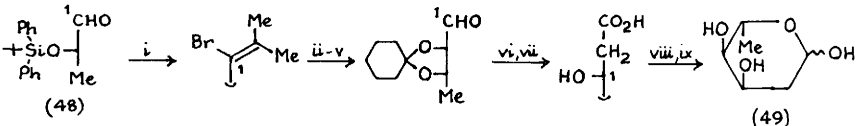
± (45) R = Bz
(46) R = β-D-Gal-*f*(Bz)$_4$



(47)

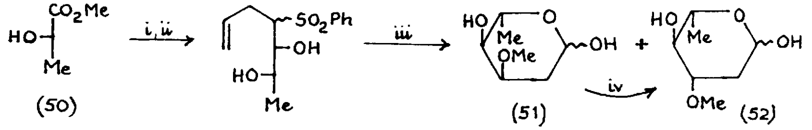
6-bromo-D-galactono-1,4-lactone (**43**) into abequose (**44**) (Scheme 8) and into the methyl and ethyl β-D-abequofuranoside tribenzoates,[27] D-glucono-, D-galactono- or D-mannono-1,4-lactones into the racemic 3,5-dideoxy-hexonolactone (**45**) *via* the same diene (**47**), and 6-*O*-(β-D-galactofuranosyl)-D-galactono-1,4-lactone heptabenzoate into a separable mixture of the galactosylated 3,5-dideoxy-D-*threo*-hexonolactone (**46**) and its L-*threo*-diastereomer.[28] Electro-oxidative reduction of 3-deoxy-D-*ribo*- and D-*arabino*-hexonic acids in dilute sulphuric acid in the presence of cerium(IV) ions gave 2-deoxy-D-*erythro*-pentose in *ca.* 60% yield, equivalent results being reported in the L-series.[29] Preparations of 5-deoxy-D-ribono-1,4-lactone and 5-deoxy-D-ribose from D-ribono-1,4-lactone in 5 and 6 steps, respectively, have been described.[30]

Chiral non-carbohydrate starting materials have been used in syntheses of several deoxy-sugars. L-Digitoxose (2,6-dideoxy-L-*ribo*-hexose) (**49**) was synthesized from the ethyl (*S*)-lactate-derived aldehyde (**48**) in 9 steps (Scheme 9). The required one and two carbon chain elongations were achieved using a formyl anion equivalent (step i) and a chiral acetate anion (step vi), respectively.[31] L-Oleandrose (2,6-dideoxy-3-*O*-methyl-L-*arabino*-hexose) (**52**) and its C-3 epimer (**51**), were obtained as a 3:2 mixture, in a 3 step synthesis starting from methyl (*S*)-lactate (**50**) (Scheme 10). Under methoxide ion catalysis, compound (**51**) isomerized to (**52**) in 60% yield.[32] A total synthesis of the glycosylated macrolide antibiotic avermectin B1a utilized the bis-oleandrose glycosylating agent (**56**), which was synthesized from an (*S*)-lactaldehyde-derived allylic alcohol (**53**) *via* the monomer (**55**) (Scheme 11). The preparation of (**55**) was not particularly efficient since epoxidation of alkene (**54**) (step v) and a subsequent Michael addition (step vii) gave rise to mixtures, each containing two isomers.[33] Syntheses of the four isomeric 2-acetamido-2,4-dideoxy-D-hexopyranoses from (*S*)-malic acid or D-glucose are covered in Chapter 9. Enantioselective syntheses of the four 2,4-dideoxyhexose stereoisomers have been



Reagents: i, $Br_2C{=}CMe_2$, Bu^tLi; ii, Bu^tLi, then H_3O; iii, $Bu_4NF.3H_2O$; iv, $HC(OEt)_3$, $(CH_2)_5C{=}O$, TsOH; v, O_3, then Me_2S; vi $CH_3CO_2CH(Ph)CPh_2OH$, $LiNPr^i_2$; vii, KOH, MeOH; viii, CF_3CO_2H, H_2O; ix, disiamylborane, then H_2O.

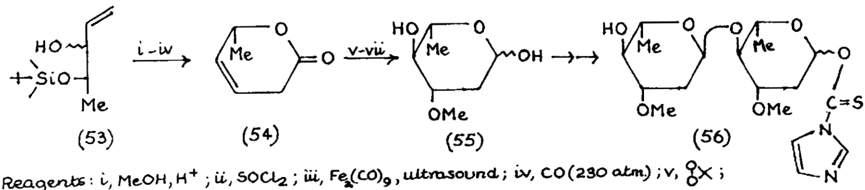
Scheme 9



Reagents: i, $CH_2{=}CHCH_2SO_2Ph$, BuLi; ii, $Zn(BH_4)_2$; iii, O_3, MeOH, then Me_2S, DBU; iv, DBU, MeOH

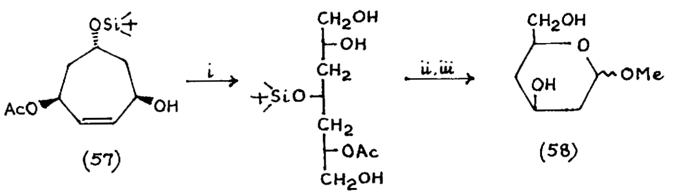
Scheme 10

achieved from either the cycloheptene-3,5,7-triol (57) or its C-5 epimer, these being produced in chiral form by lipase-catalysed hydrolysis of diesterified precursors. The procedure is exemplified for the D-*threo*-isomer (58) in Scheme 12.[34]



Reagents: i, MeOH, H^+ ; ii, $SOCl_2$; iii, $Fe_2(CO)_9$, ultrasound; iv, CO (230 atm.) ; v, ;
vi, Bu^i_2AlH ; vii, MeOH, Et_3N

Scheme 11



Reagents: i, O_3, then Me_2S, then $NaBH_4$; ii, $NaIO_4$; iii, MeOH, Resin (H^+)

Scheme 12

The strategy for constructing enantiomerically pure sugar derivatives, particularly 4-deoxy-, 2,4-dideoxy- and 3-amino-3,4-dideoxy-sugars, from dihydropyrans *via* readily separated lactate or mandelate 2,3,4-trideoxy-2-enopyranoside diastereomers (*cf.* Vol. 23, p. 132) has been reviewed.[35] A three-step preparation of 5-acetoxy-2,3-dideoxypentopyranosyl chloride (presumably racemic) from tetrahydrofurfuryl alcohol has been reported.[36]

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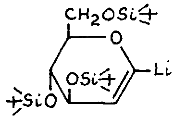
13

Unsaturated Derivatives

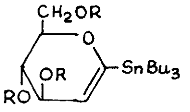
1 Glycals

A paper on the lone pair interactions in the chemistry of monosaccharides has appeared.[1]

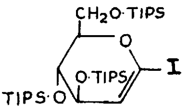
Friesen *et al.* have shown that metallation of 3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-D-glucal with *tert*-butyllithium gives the presumed lithio-species (1) together with some products derived from α-silylcarbanions.[2] Exclusive preparation of (1) was however achieved by the use of TIPS or TBDMS protecting groups, and on reaction with tributyltin chloride it gave (2). In an extension to this work, the iodo-derivative (3) was prepared by treating (2, R=TIPS) with iodine in dichloromethane and used as a useful intermediate in the preparation of *C*-aryl glucals by palladium-catalysed coupling with a variety of metallated aromatics.[3] (See also Vol. 24, p.46, Vol. 23, p.136 and Vol. 20, p.132 for the preparation of 1-alkylated derivatives from 1-tributylstannyl compounds or 1-lithiated glycals).



(1)

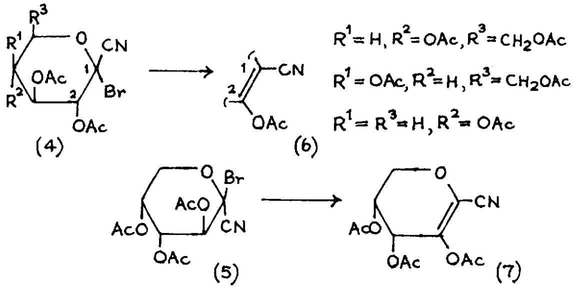


(2) R = TIPS, $SiBu^tPh_2$

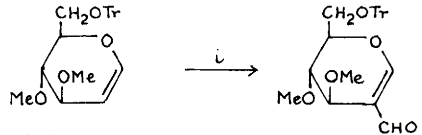


(3)

In an attempt to displace bromide from compounds (4) and (5) with cyanide ion, the 1-cyanohydroxyglycal esters (6) and (7) resulted.[4]



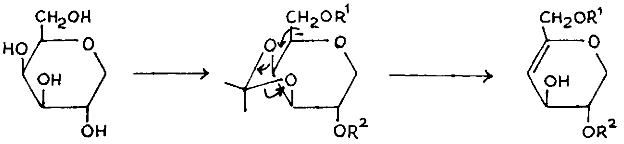
A route to *C*-2-formylglycals by use of the Vilsmeier-Haack reaction has been reported (Scheme 1).[5] Other examples are given, but, in one case, involving a compound with a 4,6-*O*-isopropylidene protecting group, the reaction failed. For a different approach to the preparation of *C*-2-formylglycals see Vol. 22, p.138.



Reagents : i, $POCl_3$, DMF, Py

Scheme 1

Treatment of 1,5-anhydrogalactitol with 2,2-dimethoxypropane and camphorsulfonic acid gave a mixture of (8), 40% and (9), 50% (Scheme 2).[6] Treatment of (8) with potassium *tert*-butoxide gave glycal (10) which was deprotected under acidic conditions to (11). Alternatively, deprotecting a mixture of (8) and (9) with methanolic acetic acid, followed by benzylation, and treatment with potassium *tert*-butoxide afforded glycal (12). These glycals are suitable intermediates for the synthesis of α-L-tagatopyranosides (see also Chapter 2).

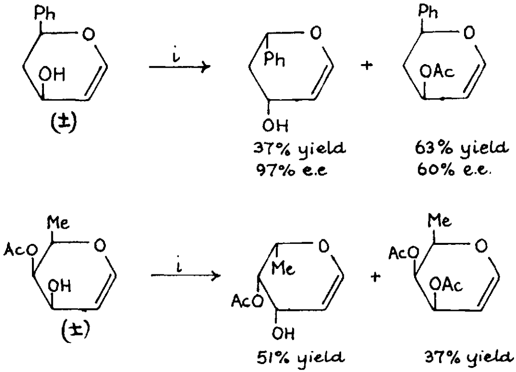


(8) $R^1 = R^2 = C(OMe)Me_2$
(9) $R^1 = C(OMe)Me_2, R^2 = H$

(10) $R^1 = R^2 = C(OMe)Me_2$
(11) $R^1 = R^2 = H$
(12) $R^1 = R^2 = Bn$

Scheme 2

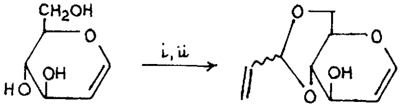
Enzymatic mediated kinetic *O*-acetylation of synthetic racemic glycals with a free OH group at C-3 has been achieved using lipase PS 30 and vinyl acetate (Scheme 3).[7] Several other examples are given.



Reagents : i, Lipase, vinyl OAc

Scheme 3

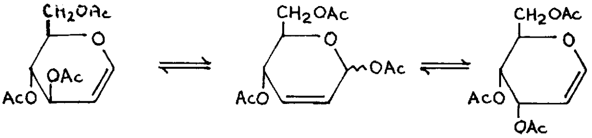
A new method for the protection of carbohydrate groups in carbohydrates involves the use of propenylidene acetals (Scheme 4).[8] The protecting group can be removed using Wilkinson's catalyst in ethanol, sometimes with the addition of one equivalent of trifluoroacetic acid. Benzoyl groups are labile under these conditions, but in their presence 1% sulfuric acid in dioxane can be used.



Reagents : i, Bu_2SnO ; ii, $CH_2=CHCH(OAc)_2$, $(Ph_3P)_4Pd$

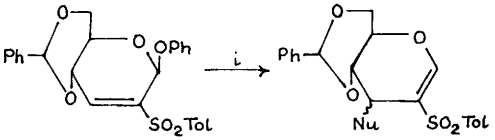
Scheme 4

Tri-*O*-acetyl-D-glucal can be reversibly epimerized at C-3 using various metal chlorides ($NiCl_2$, $CuCl_2$, $CoCl_2$, $MnCl_2$) in acetic anhydride and gives a mixture which includes a 2,3-unsaturated isomer (Scheme 5).[9]



Scheme 5

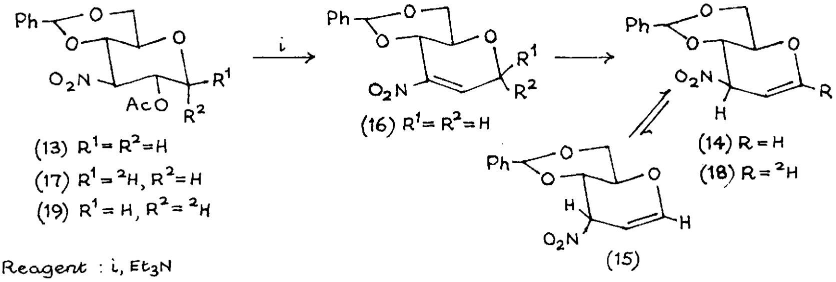
The addition of nucleophiles to 2-*C*-*p*-toluenesulfonyl-2-enopyranosides results in the formation of substituted glycals (Scheme 6).[10] The use of MeO^-, $^-CH_2NO_2$, ^-OH and $^-BH_4$ gave the D-*arabino*-configurated products, whilst the use of benzoic or acetic acid in pyridine with benzoic or acetic anhydride (to act as scavenger for phenol) gave the D-*ribo*-configurated products. (See Vol. 22, p.139 for similar examples.)



Reagents : i, Nu^- (see text)

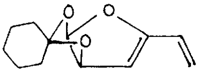
Scheme 6

A paper concerned with the effect of the anomeric effect on C-H acidity has appeared (Scheme 7).[11] Initially it was observed that elimination of acetic acid from the nitroanhydroglucitol (13) with triethylamine was accompanied by a double bond migration to give an equilibrium mixture of (14) and (15) *via* the 3-nitro-2-enitol (16). Subjecting the deuterated derivative (17) to a similar reaction gave the expected deuterated compound (18) but containing approximately 25% of non-deuterated compound (14), suggesting the anomeric effect may be operating. On the other hand, subjecting deuterated nitroglucitol (19) to the same reaction gave exclusively (18). It was concluded from these experiments that the *quasi*-equatorial hydrogen atom in the intermediate 3-nitro-2-enitol derivatives was abstracted slightly more readily than the *quasi*-axial one, but the difference was smaller than the isotope effect. The conclusion was further supported by AM1 calculations.



Scheme 7

3,4-Di-*O*-acetyl-L-fucal and -L-rhamnal derivatives have been used as starting materials for the preparation of 3-thioglycals (Chapter 11). Selective deacetylation of peracetylated glycals is described in Chapter 7. The synthesis of the 4-*O*-(β-D-galactopyranosyl) derivative of D-glucal using a β-1,4-galactosyltransferase is described in Chapter 3. The transformation of the "*quasi*-glycal" (20) into intermediates for a proposed synthesis of clerodanes is mentioned in Chapter 24, and glycal (21) has been used as starting material for the preparation of *O*-glycosides by a method involving a radical decarboxylation (Chapter 3). Transformation and use of 2,3-didehydro-2-deoxysialic acids is outlined in Chapter 16.



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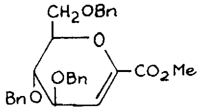
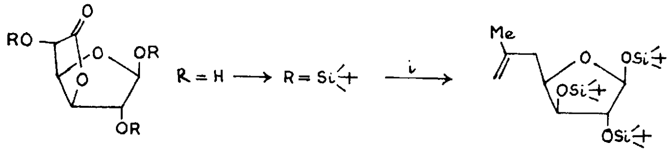


(21)

2 Other Unsaturated Derivatives

A two step synthesis of 6,7-dideoxy-6-*C*-methyl-β-D-*xylo*-heptofuran-6-enose derivative (22) from D-glucurone (Scheme 8) has been described.[12] A proposed mechanism for the reaction is put forward.

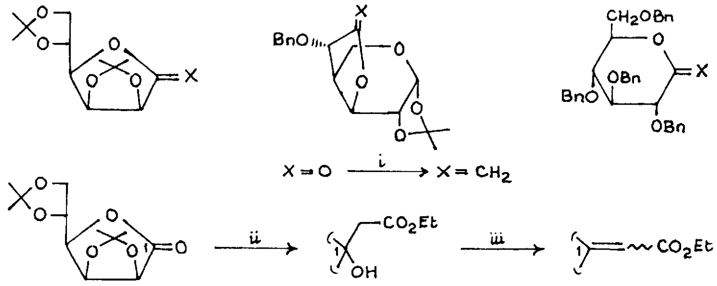
A paper describing the methylenation of aldonolactones using dicyclopentadienyldimethyl titanium as a more stable alternative to the Tebbe reagent has been presented (Scheme 9).[13] Also described is the use of the zinc-silver/graphite reagent for effecting a Reformatsky-like reaction on aldonolactones with ethyl bromoacetate followed by β-elimination.



Reagent: i, $Cp_2Ti{=}CH_2$

(22)

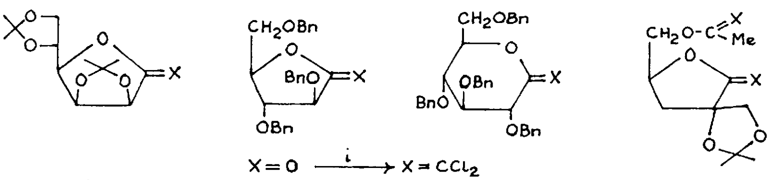
Scheme 8



Reagents: i, $Cp_2Ti(Me)_2$; ii, Zn-Ag, graphite, $BrCH_2CO_2Et$; iii, MsCl, Et_3N

Scheme 9

The transformation of aldonolactones into the corresponding dichloromethylene derivatives on reaction with triphenylphosphine-carbon tetrachloride reagent has been described (Scheme 10).[14] This reagent is of more general applicability than the bis(dimethylamino)phosphine-carbon tetrachloride reported earlier (Vol. 18, p.34). Ester carbonyl groups are also dichloromethylated.

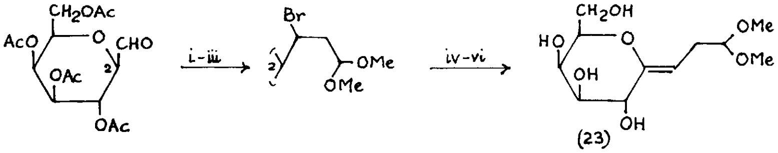


Reagents: i, Ph_3P, CCl_4

Scheme 10

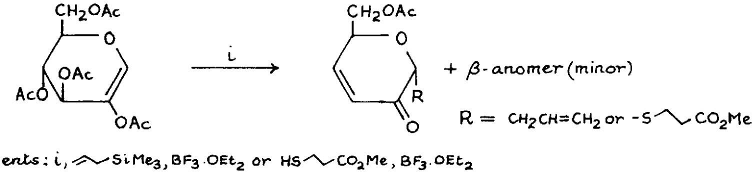
The preparation of 4,8-anhydro-2,3-dideoxy-D-*galacto*-non-3-enose dimethylacetal (23) as a probe for determining the steric course of protonation by a glycoside hydrolase has been described (Scheme 11).[15]

The treatment of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal with allyl trimethylsilane or methyl-3-mercaptopropanoate under Lewis acid catalysis gave α:β mixtures (α-form predominating) of the 4-enopyran-2-uloses (Scheme 12).[16]



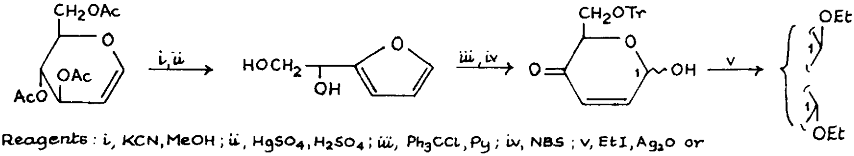
Reagents: i, $Ph_3P{=}CHCHO$; ii, HBr, HOAc; iii, MeOH, $CuSO_4$, H_2SO_4; iv, separate isomers; v, v, AgF (major isomer); vi, MeO^-, MeOH

Scheme 11



Scheme 12

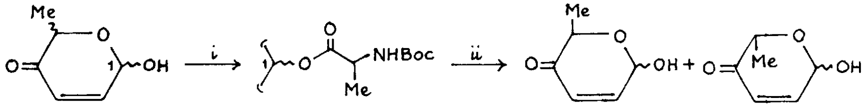
A novel approach to the preparation of hex-2-enos-4-uloses from glycals which proceeds *via* furanoid intermediates has been described (Scheme 13).[17]



Reagents: i, KCN, MeOH; ii, $HgSO_4$, H_2SO_4; iii, Ph_3CCl, Py; iv, NBS; v, EtI, Ag_2O or $ClCO_2Et$, Et_3N, followed by $HClO_4$, EtOH

Scheme 13

A simple and effective procedure for the resolution of 2,3,6-D,L-trideoxy-hex-2-enopyran-4-uloses *via* diasteromeric *O*-*tert*-butoxycarbonyl-L-alanyl esters has been described (Scheme 14).[18] Other examples are given.

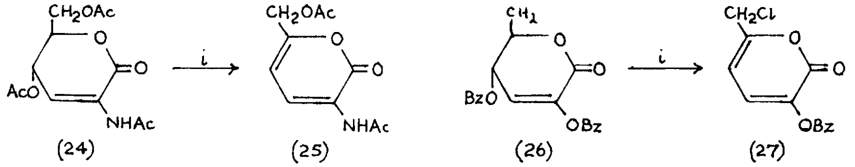


Reagents: i, Boc-L-Ala-OH, DCC, DMAP; ii, Chromatography, then 98% HCO_2H

Scheme 14

The conversion of sugar-derived 5,6-dihydro-2-pyrones by tin(IV) chloride into 3-acyloxy and 3-acylamido-2-pyrones has appeared (Scheme 15).[19] For example (24) gave (25). On prolonged reaction time pyrone (26) gave an almost quantitative yield of halogenated pyrone (27).

The conjugate reduction of some enone and pyrone systems is mentioned in

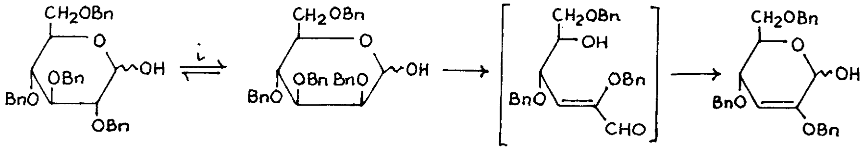


Reagents : i, $SnCl_4$, CH_2Cl_2

Scheme 15

Chapters 15 and 16; the preparation of N-containing enones is mentioned in Chapter 9; the use of levoglucosenone in the preparation of altrose is reported in Chapter 2; and the preparation of some enone-*C*-glycosides can be found in Chapter 3.

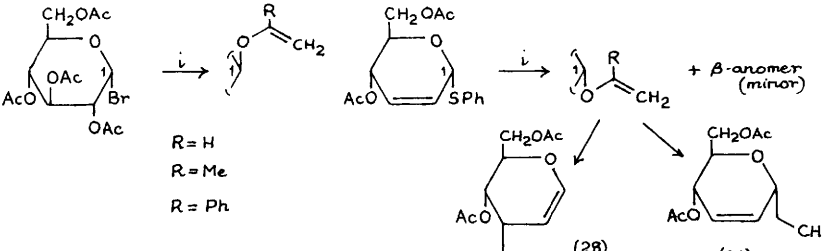
The action of alkali on *O*-benzylated aldoses has been reported (Scheme 16).[20] A similar reaction takes place with 2,3,5-tri-*O*-benzyl-D-arabinofuranose.



Reagent : i, Me_2CHONa

Scheme 16

The reaction of acetobromoglucose with bis(acylmethyl)mercurys gives rise to vinyl and 1'-substituted vinyl β-D-glycosides (Scheme 17).[21] 2,3-Unsaturated phenyl thioglycosides also undergo a similar reaction to give a mixture of α- and β- glycosides. These products on treatment with zinc bromide rearrange to give *C*-glycosides (see Chapter 3), and on heating undergo a Claisen rearrangement to give rise to unsaturated branched-chain glycals such as (28) and (29).

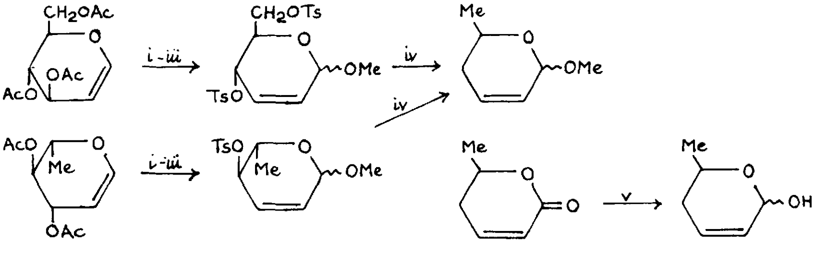


Reagent : i, $Hg(CH_2COR)_2$

Scheme 17

A report on three reductive syntheses directed towards the preparation of desosamine has been reported (Scheme 18).[22] Thus tri-*O*-acetyl-D-glucal can be converted *via* the di-tosylate derivative shown into the D-form of methoxy-2-methyl-6-dihydro-4,5-

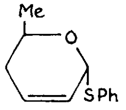
α-[2H] pyran whilst the L-form can be obtained from L-rhamnal in a similar way. Racemic paraascorbic acid (δ-hexenolactone) can also be reduced directly to the hydroxy dihydropyran derivative.



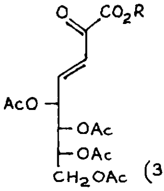
Reagents: i, MeOH, $BF_3.OEt_2$; ii, NaOMe, MeOH; iii, TsCl, Py; iv, $LiBEt_3H$; v, BBN or K Selectride

Scheme 18

The use of the unsaturated thioglycoside (30) as a starting material for the preparation of spiro-sugars is described in Chapter 24. The preparation of α,β-unsaturated acyclic derivatives such as (31) from C-glycosides is mentioned in Chapter 16.



(30)



(31) R = Me, H

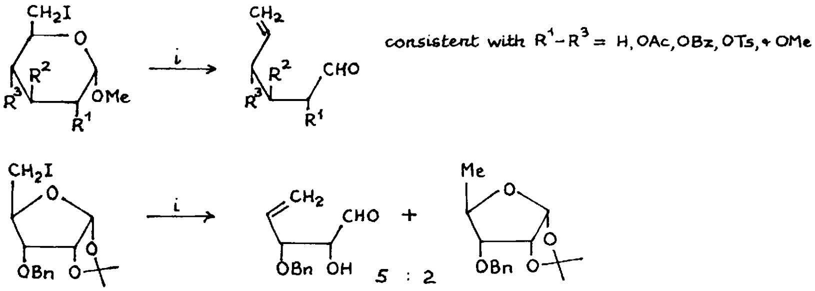
For the preparation of 2,3-unsaturated nitrogen-containing sugars as potential precursors of lincosamine see Chapter 9. The preparation of methyl 2,3,4,5-tetradeoxy-D-*arabino*-nonoate by Wittig reaction with $Ph_3P{=}CHCH{=}CHCO_2Me$ on free arabinose, followed by catalytic hydrogenation, is reported in Chapter 2.

The reductive dealkoxyhalogenation of some 6-iodopyranoses and 5-iodofuranoses using zinc-silver/graphite complex has been described (Scheme 19).[23] In the latter series some alternative reactions are observed (see also Vol. 24, p.160).

The preparation of alkenes from *vic* diols by reaction of the dixanthates with diphenylsilane has been reported (Scheme 20).[24] Several examples were given and the reaction is especially applicable in the nucleoside series.

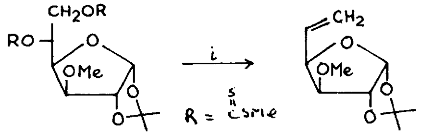
Also reported by the same authors is the use of triethylsilane-dibenzoyl peroxide for preparing alkenes by the deoxygenation of dixanthates.[25]

The synthesis of alkene (32) in four steps from D-glucose has been achieved and attempts at synthesizing cyclic alkenes from L-rhamnose and L-lyxose derivatives are also reported.[26]



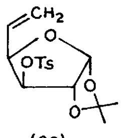
Reagents: i, Zn/Ag, graphite

Scheme 19



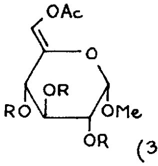
Reagent: i, Ph_2SiH_2

Scheme 20



(32)

The synthesis of D-*myo*-inositol derivatives by a biomimetic route from enol acetate (33) is described in Chapter 18 as is the synthesis of cyclitols from 5,6-unsaturated pyranosides.



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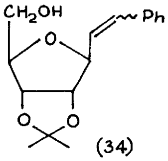
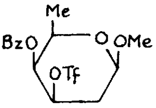


(34)

The preparation of *C*-glycosides like (34) is covered in Chapter 3. The fragmentation of triflate (35) to yield unsaturated compounds (36) and (37) is described in Chapter 7.



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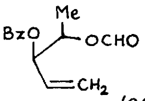

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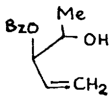

(37)

The conversion of some aldonolactones into unsaturated lactones is mentioned in

Chapter 16. The preparation of *C*-glycosides from 2,3-unsaturated glycosyl carbonates is described in Chapter 3.

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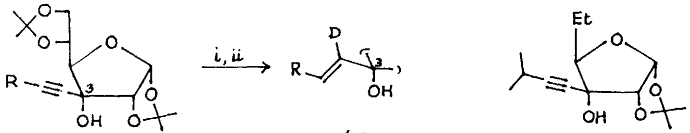
14

Branched-chain Sugars

A review on the synthesis and reactivity of sugars with two branches at C-3 has appeared,[1] as well as another on the synthesis of rare carbohydrates which includes the application of "naked sugars" to the synthesis of branched, long chain carbohydrates amongst the topics covered.[2]

1 Compounds with an R-C-O Branch

The reasons behind the facile regio- and stereo-selective reduction of the propargylic alcohol moiety in (1) to give compound (2) with lithium aluminium hydride (Vol. 16, p.267, Scheme 12) have been investigated by reaction of homologues (3) and (4) and a variety of simpler analogues (Scheme 1).[3] The probable effect of the sugar oxygen atoms on the reduction was investigated by semi-empirical MO calculations.



(1) R = H

(2)

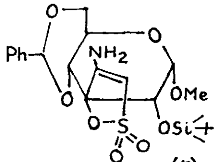
(4)

(3) R = Me, Pr^i

Reagents: i, LAH ; ii, D_2O

Scheme 1

A paper describing further examples of the base treatment of *O*-mesylcyanohydrins to produce spiro-sulfonates such as (5) and (6) has appeared.[4] (See Vol. 22, p.145 for preliminary work in this area.)



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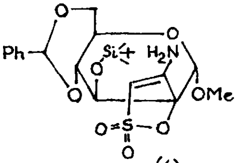
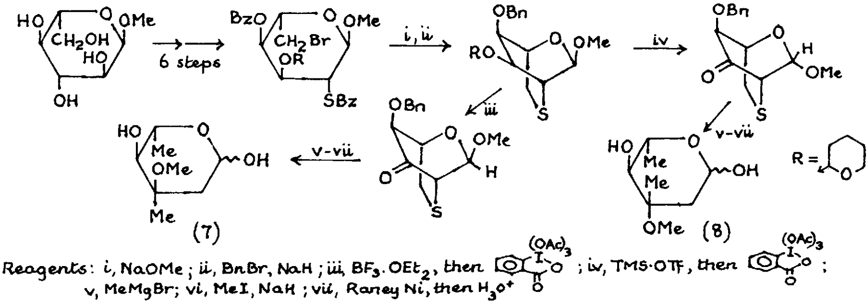


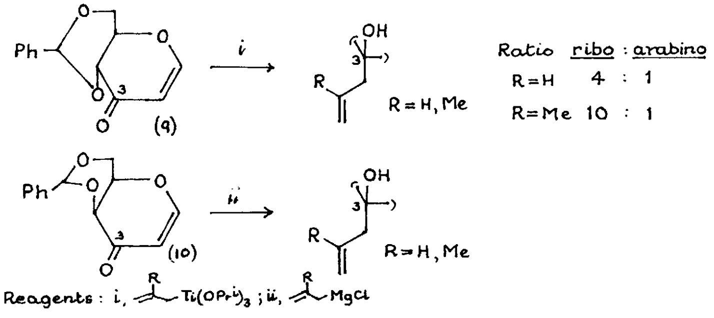
(6)

The syntheses of L-cladinose (7) and its C-3 epimer (8) have been achieved by the desulfurization of 2,6-anhydro-2-thiopyranoside derivatives (Scheme 2).[5] A full paper on this work together with other related 2,6-dideoxy sugars has also appeared.[6]

The reaction of hex-1-enopyran-3-ulose derivatives with organometallic reagents to give branched-chain sugars with reasonable π-facial selectivity has been disclosed (Scheme 3).[7] Thus the use of titanium reagents on the D-*erythro*-compound (9) gave reasonable α-attack (better than with simpler alkyl anion reagents). On the other hand the D-*threo*-derivative (10) gave exclusive α-attack when used with Grignard reagents.



Scheme 2

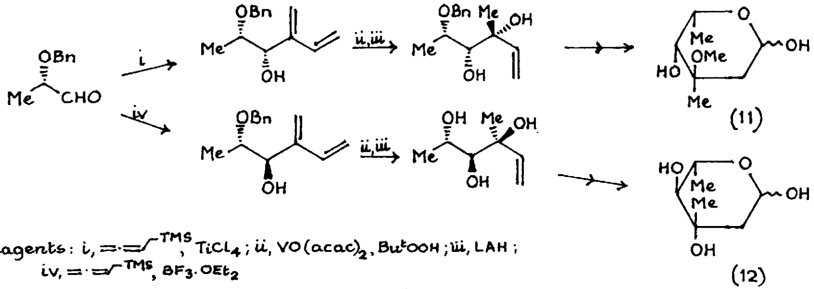


Scheme 3

The stereo- and enantio-controlled synthesis of L-arcanose (11) and L-olivomycose (12) by a Lewis acid-mediated reaction of 1-TMS-2,3-butadiene with S-benzyl lactaldehyde has been disclosed (Scheme 4).[8] The nucleophilic addition which led to the former sugar is concluded to have gone by way of a chelated transition state; the major product in the latter case was produced by way of a non-chelated transition state.

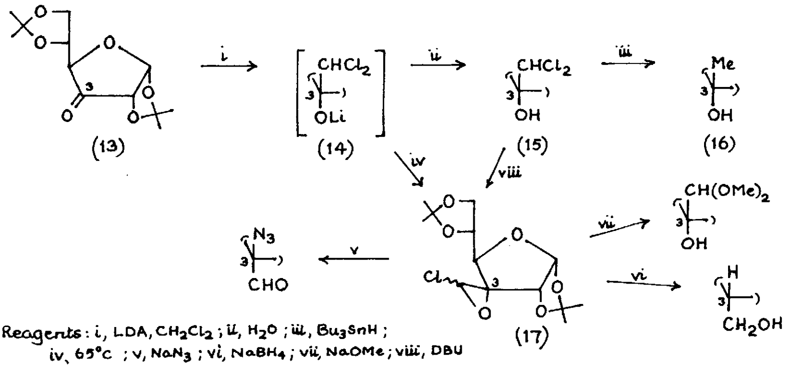
The use of dichloromethyllithium for the synthesis of functionalized branched-chain sugars has been reported (Scheme 5).[9] For example, ketone (13) reacts with the reagent to give the *O*-lithiated derivative (14) which on hydrolysis and reduction, affords compounds (15) and (16). Alternatively, heating (14) gives the spiro-chloroepoxide (17). Compound (17) reacts with nucleophiles such as azide or hydride with complete regiospecificity and S_N2 reaction at the β-carbon with respect to chlorine as shown in the Scheme. Reaction with methoxide anion occurs at the α-carbon.

Treatment of the 4-oxo-N-acetylneuraminic acid derivative (18) with



Reagents: i, $=\cdot=/^{TMS}$, $TiCl_4$; ii, $VO(acac)_2$, Bu^tOOH; iii, LAH; iv, $=\cdot=/^{TMS}$, $BF_3.OEt_2$

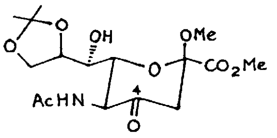
Scheme 4



Reagents: i, LDA, CH_2Cl_2; ii, H_2O; iii, Bu_3SnH; iv, 65°C; v, NaN_3; vi, $NaBH_4$; vii, NaOMe; viii, DBU

Scheme 5

tribenzyloxymethylzirconium gave exclusively compound (20), whereas reaction using tetramethylzinc led to a 3:2 mixture of (20) plus its C-4 epimer.[10] Reaction of (18) with methylene diiodide and zirconocene dichloride gave the methylene compound (20) which on catalytic hydrogenation furnished (19) plus its C-4 epimer. The products, as free acids, were inhibitors of CMP-sialate synthase.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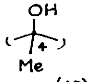
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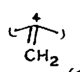
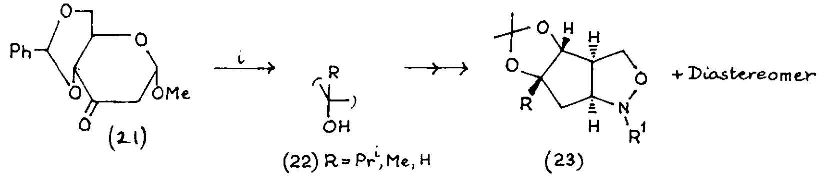

(20)

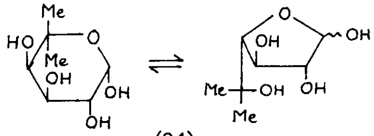
The reaction of various organometallic reagents with the ketone (21) leading to the branched-chain sugars (22) has been described (Scheme 6).[11] The products were used to prepare cyclopentane fused isoxazolidines (23) by a nitrone-alkene cycloaddition process (see Chapter 18).



Reagents: i, Pr^{i}MgBr, or MeLi, or L-Selectride

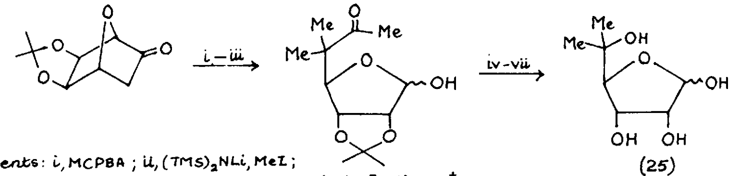
Scheme 6

Further application of P. Vogel's "naked sugar" chemistry to the preparation of 5-*C*-branched-chain sugars has appeared.[12] Thus the L-*arabino*-hexose (24) has been synthesized by a method similar to that used to prepare 5-*C*-methyl-α,β-D-talose (see Vol. 23, p.146). Compound (24) exists as a 37:25:38 mixture of α-furanose:β-furanose:α-pyranose.



(24)

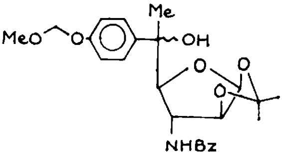
The synthesis of 6-deoxy-5-*C*-methyl-D-*ribo*-hexose (25) has been described (Scheme 7).[13] The furanose form of the product is preferred in solution (*ca* 80%).



Reagents: i, MCPBA ; ii, $(TMS)_2NLi$, MeI ;
iii, $TMSCH_2Li$; iv, Ac_2O, Py ; v, TFA ; vi, MeO^- ; vii, H_3O^+

Scheme 7

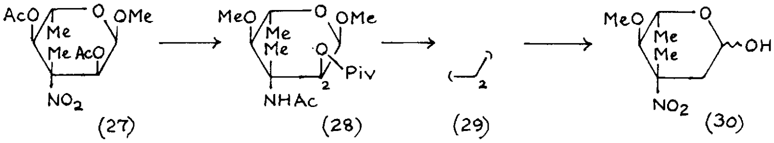
The use of branched-chain sugars (26) in the synthesis of delicorubicin is mentioned in Chapter 19.



(26)

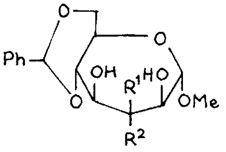
2 Compounds with an R-C-N Branch

The synthesis of evernitrose (30) by an improved procedure has been achieved (Scheme 8).[14] Thus oxidation of methyl-α-L-rhamnopyranoside with sodium periodate and subsequent treatment with nitroethane followed by acetylation afforded (27). This was converted into acetamide (28) which was deoxygenated by photolysis in HMPA-H_2O to give (29) which was further transformed in a number of steps into (30).



Scheme 8

Reaction of the product from periodate oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with methyl nitroacetate and potassium fluoride catalysis gave the heptoseptanoside compounds (31) and (32).[15]

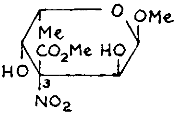


(31) $R^1 = NO_2$, $R^2 = CO_2Me$

(32) $R^1 = CO_2Me$, $R^2 = NO_2$

The periodate oxidation product of methyl α-L-rhamnopyranoside was also treated with methyl nitroacetate under fluoride catalysis to give an improved yield of (33).[16] Hydrogenation (Pt/H_2) gave amine (34). When the same oxidation product was treated with cyanoacetamide the product (35) was formed and further converted to (36) and (37).

The synthesis of evernitrose glycosides is mentioned in Chapter 3. See also Scheme 5, preceding section, for the preparation of a compound with an R-C-N branch.



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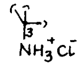

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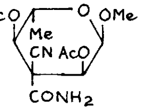

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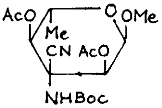

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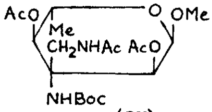
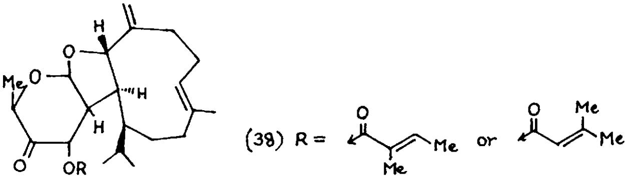


(37)

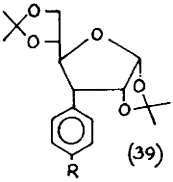
3 Compounds with an R-C-H Branch

The absolute configuration of the glycoside moiety of pittosporatobirasides (38) isolated from *Pittosporum tobira* flowers has been determined by the exciton chirality method applied to the dibenzoate ester of the ketone reduced product.[17]



(38)

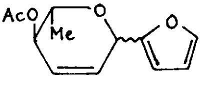
The preparation of compound (39) has been reported; the product having R=NO_2 has anticonvulsant properties.[18]



(39) R = NO_2, CO_2Et, NEt_2

The reaction of furan with 3,4-di-*O*-acetyl-L-rhamnal gave epimeric (40) and 1-*C*-(2-furyl)-hex-2-enopyranose (41).[19] Compound (40) could be converted into 2-deoxyglycosides, e.g. (42), and to 3'-deamino-3'-*C*-(2-furyl) daunorubicins.

(40)



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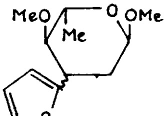
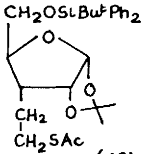


(42)

The synthesis of branched-chain thio-sugars (43) and (44) from 1,2-*O*-isopropylidene-D-xylofuranose has been described.[20] Acetolysis at 0° with camphorsulfonic acid and acetic anhydride of (43) led mostly to the di-substituted thiolane (45) together with some compound (46), whereas at 70° only (46) was formed.



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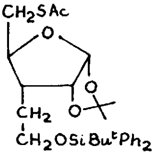

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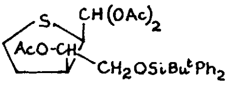

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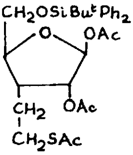
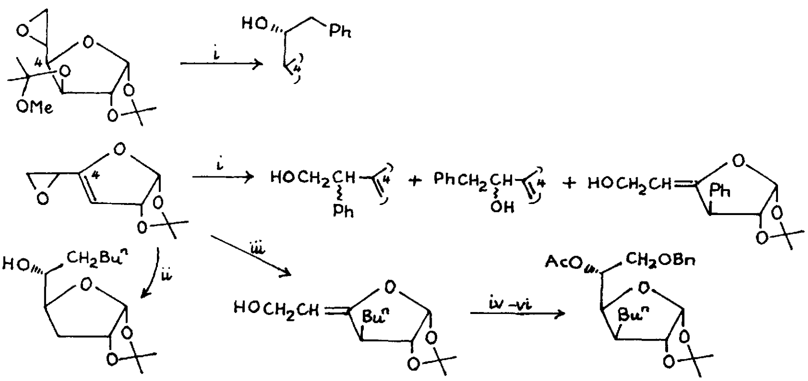


(46)

A route to derivatives of 1-*O*-acetyl-L-deoxy-2-hydroxymethyl-D-*erythro*-oxetanose has been described.[21] The route is essentially the same as that described in Vol.

24, p.168 and represents a more expeditious route over previously reported work (Vol. 22, p.150).

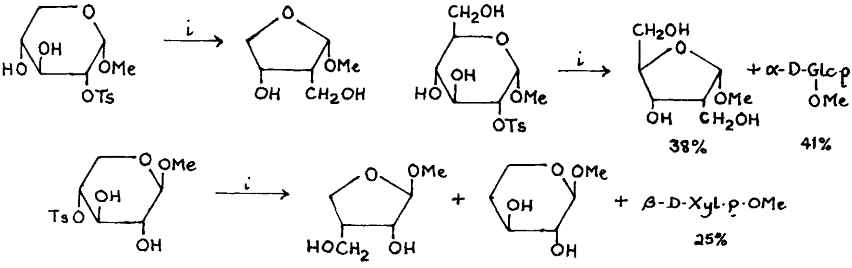
The products of reaction of some organo-copperlithium reagents with terminal epoxides is depicted in Scheme 9.[22]



Reagents: i, $Ph_2Cu(CN)Li_2$; ii, $Bu^n_2Cu(CN)Li_2$; iii, $Bu^nCu(CN)Li$; iv, NaH, BnBr; v, $BH_3.Me_2S$; vi, Ac_2O

Scheme 9

The reaction of glycopyranoside monotosylates with lithium aluminium hydride has been reported to result in ring contraction and give branched furanosides (Scheme 10).[23] The rearrangement occurs in only one of two possible directions for 2- or 4-tosylates.



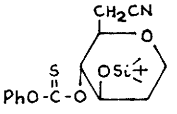
Reagent: i, LAH

Scheme 10

Full details of an earlier paper (Vol. 23, p.151, Scheme 3) on facial-selective carbohydrate-based aldol reactions between methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose and various aldehydes have been reported.[24]

Photolysis of the phenylthionocarbonate (47) (available in 8 steps from tri-*O*-

acetyl-D-glucal) in the presence of allyltributyltin gave rise to the branched-chain compound (48) which is useful as an intermediate in the synthesis of novel prostanoids.[25]



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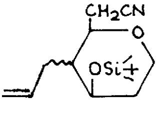
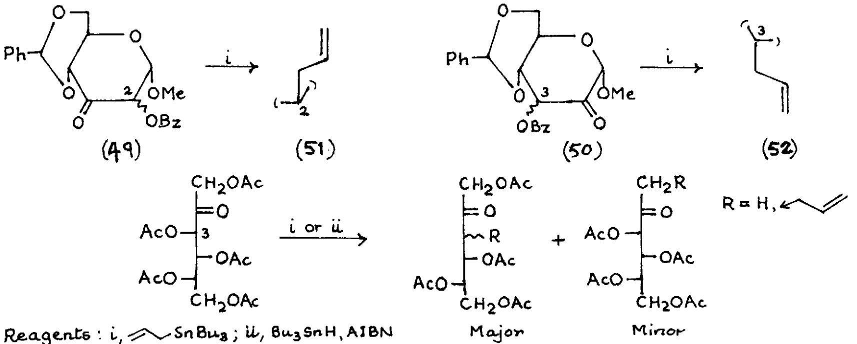


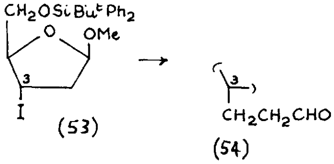
(48)

Acyloxy groups α to a ketonic group can be replaced by hydrogen or allyl under free radical conditions (Scheme 11).[26] Thus either the C-2 epimeric compounds (49) or C-3 epimeric compounds (50) afforded the axial *C*-allyl products (51) and (52) respectively. (Compound (52) has also been prepared in a different way in Scheme 24, this Chapter.) Compound (52) could readily be epimerized to its C-3 equatorial product on treatment with acid resin in ethanol. The reactions were also applicable to L-sorbose pentaacetate.

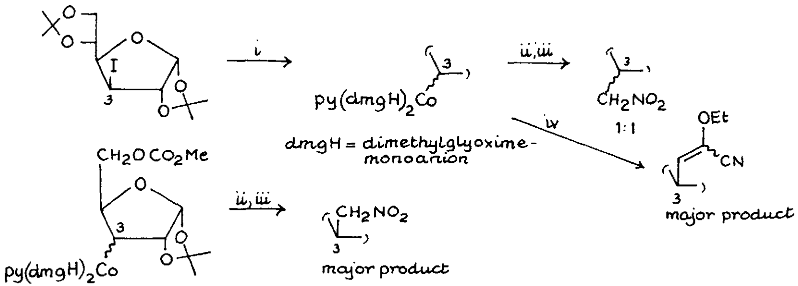


Scheme 11

The conversion of the iodide (53) into branch-chain product (54) by treatment with tributyltin hydride in the presence of acrolein has been reported and the product used as an intermediate in the preparation of 3'-branched nucleoside analogues.[27]



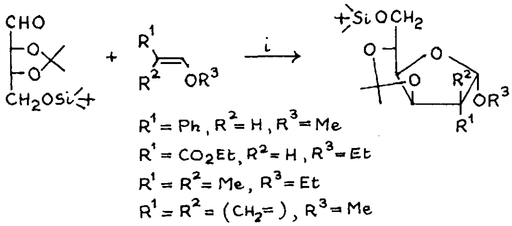
The reaction of monosaccharide cobaloximes with nitroalkyl anions to afford branch-chain sugars has been reported (Scheme 12).[28] (See Vol. 22, p.161 for a similar chain extension at C-6.)



Reagents: i, py(dmgH)$_2$Co$^-$Na$^+$; ii, Na$^+$CH$_2$NO$_2^-$, hν; iii, AcOH; iv, $=\!<^{CN}_{OEt}$, hν

Scheme 12

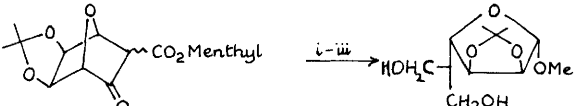
The reaction of alkenyl ethers with aldehydo-D-erythrose derivatives mediated by boron trifluoride etherate gave rise to branched-hexosides depicted in Scheme 13.[29]



Reagent: i, $BF_3.OEt_2$

Scheme 13

The synthesis of a new type of branched-chain sugar with the β-D-*ribo*-configuration from the bicyclic compound (55) has been reported (Scheme 14).[30]



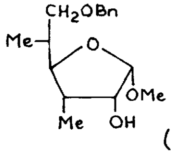
(65)

Reagents: i, MCPBA; ii, $Me_2C(OMe)_2$, MsOH; iii, LAH

Scheme 14

As part of a review on the use of metallated 2-alkenyl carbamates as chiral homoenolate reagents for asymmetric synthesis, the preparation of the α-D-*allo* cofigurated methyl-branched 3,6-dideoxy compound (56) as well as the β-D-*talo* derivative (57) have been reported starting from R-benzyl lactaldehyde.[31] For the preparation of the α-L-*allo* and the β-L-*talo* compounds see Vol. 21, p.144.

The preparation of the most unusual polymer (58) has been achieved by the



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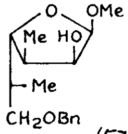
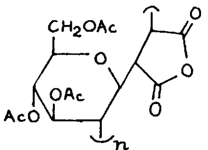


(57)

copolymerization of tri-*O*-acetyl-D-glucal and maleic anhydride.[32] Hydrolysis under different conditions led to the polymeric dicarboxylic acid derivatives (59) and (60).



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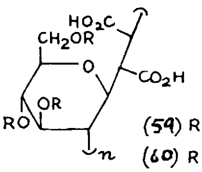
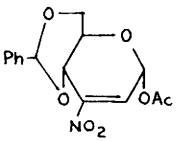


(59) R = Ac

(60) R = H

Treatment of the unsaturated nitro-sugar (61) with 2,4-pentanedione under basic conditions afforded cyclized product (62) and *gluco* adduct (63)–the ratio of products being dependent on the solvent and base.[33] Products (64) and (65) were also observed under certain conditions.



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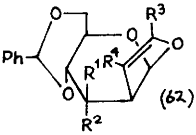
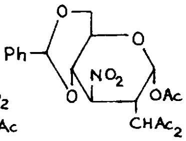


(62) R^1=H, R^2= NO_2, R^3=Me, R^4= Ac

(64) R^1= NO_2, R^2= H, R^3= Me, R^4=Ac



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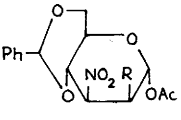
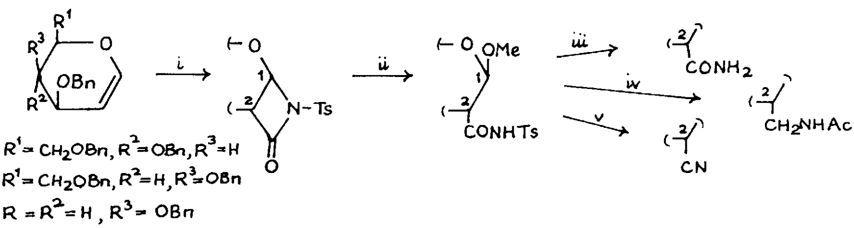


(65) R=$CHAc_2$

The reaction of glycals with tosyl isocyanate gives unstable adducts which can be

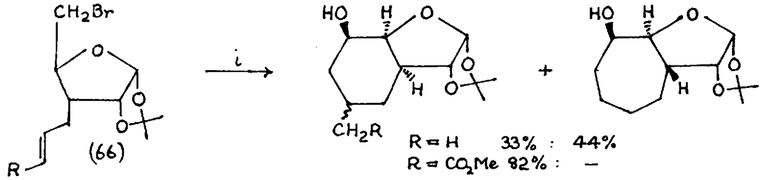


Reagents: i, TsNCO ; ii, MeOH ; iii, Na, NH_3(l) ; iv, LAH, then Ac_2O ; v, $SOCl_2$, py

Scheme 15

methanolyzed to afford methyl glycosides with C-2 branching (Scheme 15).[34] They can then be used to prepare other derivatives as shown.

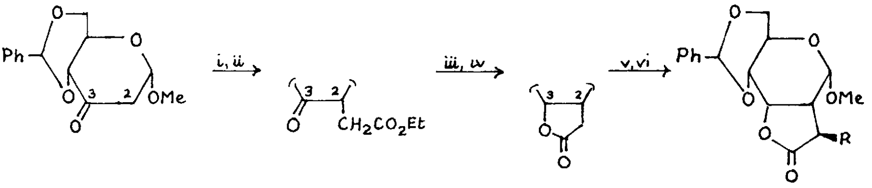
The radical cyclizations of diacetoneglucose-derived halo-alkenes for example (66) to give cyclohexane and cycloheptane annulated furanoses has been described (Scheme 16).[35] A paper by two of the same authors describing similar work has also appeared.[36]



Reagents : i, Bu_3SnH, AIBN

Scheme 16

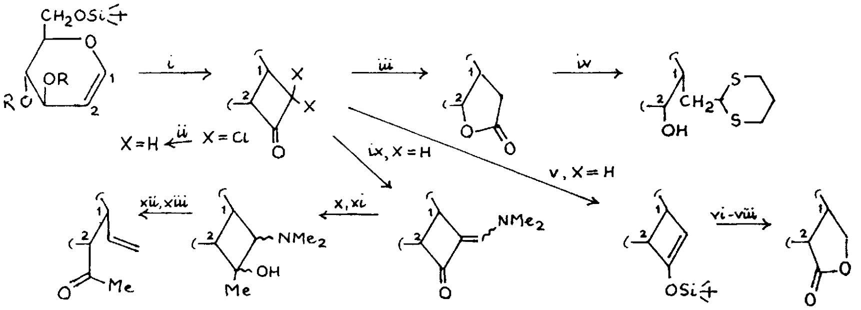
The synthesis of homochiral trisubstituted γ-butyrolactones has been described (Scheme 17).[37]



Reagents: i, $KN(TMS)_2$; ii, ICH_2CO_2Et; iii, $NaBH_4$; iv, NaH; v, $LiN(TMS)_2$; vi, RX R = , n-hexyl, Me

Scheme 17

The cycloaddition products derived from glycals and dichloroketene have been



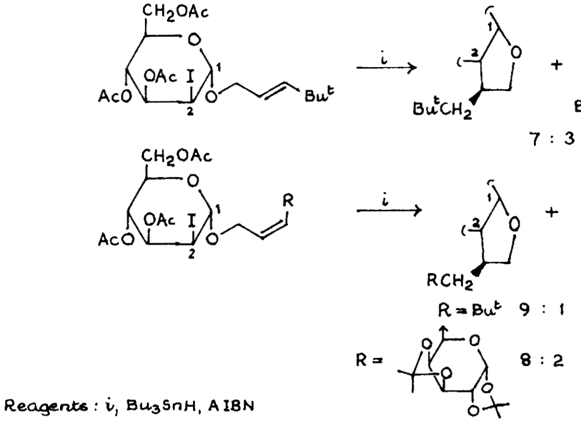
Reagents: i, CCl_3COCl, Zn, ultrasound; ii, Bu_3SnH; iii, MCPBA; iv, 3 steps; v, LDA, then TBDMS·OTf; vi, O_3; vii, $NaBH_4$; viii, NH_4Cl, py, TsCl; ix, $Bu^tOCH(NMe_2)_2$; x; Bu^i_2AlH; xi, MeMgCl; xii, MeI; xiii, DBU

Scheme 18

used to prepare an extensive range of branched-chain *C*-glycosides (Scheme 18).[38]

Further examples of the 1,3-dipolar cycloaddition of nitrones to sugar enlactones have been reported.[39] In these examples the chemistry of nitrones derived from formaldehyde and acetaldehyde is discussed. (See Vol. 21, p.143 for similar work.) The paper also makes some corrections to the configurational assignments of the cycloadducts which had earlier been incorrectly interpreted.

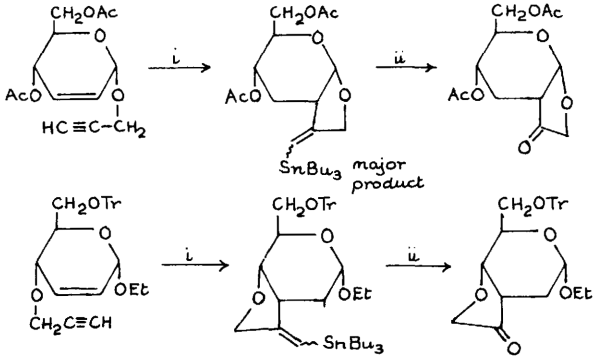
A study has been reported on the stereoselectivity of the 5-*exo* radical cyclization reaction of some allylic 2-deoxy-2-iodoglucopyranosides (Scheme 19).[40]



Reagents : i, Bu_3SnH, AIBN

Scheme 19

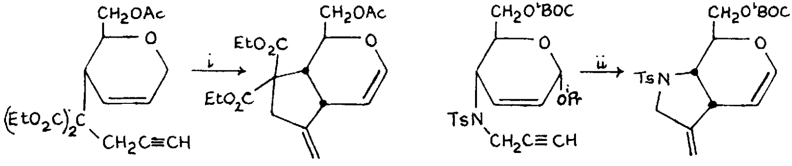
A radical cyclization-oxidation strategy has been developed to produce branched-chain derivatives from allyl propargyl ethers and acetals (Scheme 20).[41] (See Vol. 23, p.149 for a preliminary account.)



Reagents: i, Bu_3SnH, AIBN ; ii, O_3

Scheme 20

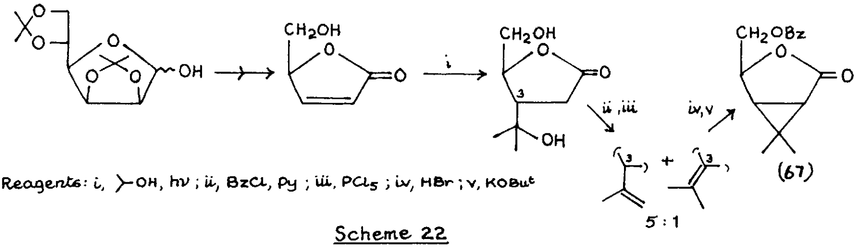
A stereoselective palladium-catalyzed cyclization to cyclopentanes and heterocyclic analogues has been disclosed (Scheme 21).[42]



Reagents : i, $Pd(dba)_3$, Ph_3P, AcOH ; ii, $Pd(Ph_3P)_4$, AcOH

Scheme 21

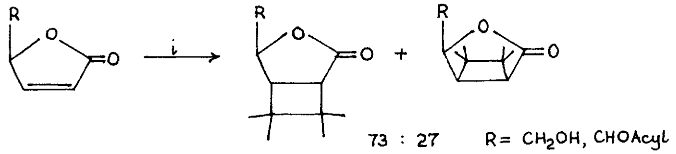
A new route to intermediates useful for the synthesis of *cis* chrysanthemic acid has been reported (Scheme 22).[43] The enantiomer of compound (67) was also described.



Reagents: i, >—OH, hν ; ii, BzCl, Py ; iii, PCl_5 ; iv, HBr ; v, $KOBu^t$

Scheme 22

A paper disclosing details of the stereoselective [2+2]photocycloaddition of chiral 2(5H)furanones to alkenes has appeared (Scheme 23).[44]

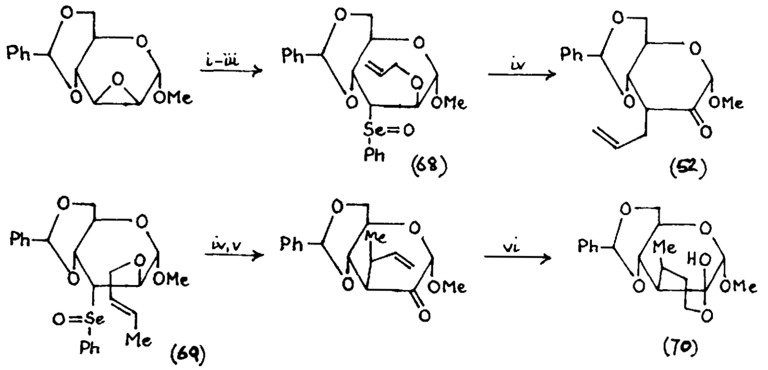


Reagents : i, $\rangle\!=\!\langle$, hν

Scheme 23

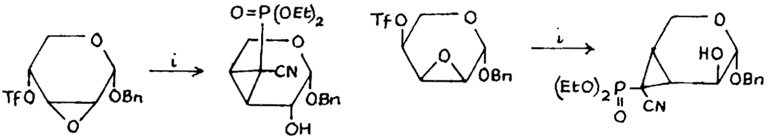
A new approach to the preparation of α-branched-chain sugars by the Claisen rearrangement of hexenopyranoside allyl ethers has been reported (Scheme 24).[45] Thus compound (68), on heating produces the axially substituted *C*-alkyl derivative (52) which can be epimerized to the equatorially substituted product with base. The rearrangement proceeds through a chair-like transition state as proved by the conversion of the E-crotyl ether derivative (69) to the tricyclic product (70). (See Scheme 11 for a different preparation of (52).)

The synthesis of some cyclopropylcyano phosphonate pyranosides has been described (Scheme 25).[46] (See Vol. 24, p.167 and Vol.22, p.150 for a similar preparation of cyclopropyl cyanides.)



Reagents: i, PhSe⁻; ii, NaH, $\sim$Br; iii, MCPBA; iv, Δ, xylene; v, SiO_2 (epim. ax→eq); vi, hydroboration-oxidation.

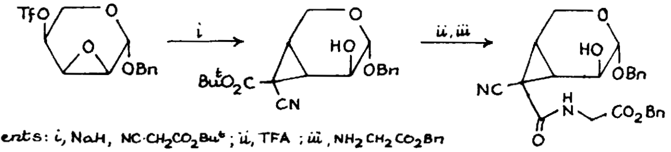
Scheme 24



Reagent: i, $NCCH_2P(O)(OEt)_2$

Scheme 25

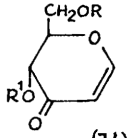
In a similar fashion the same authors have described the synthesis of disubstituted cyclopropa[c]pyranosides (Scheme 26).[47] Several examples are given.



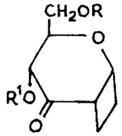
Reagents: i, NaH, $NC{\cdot}CH_2CO_2Bu^t$; ii, TFA; iii, $NH_2CH_2CO_2Bn$

Scheme 26

The photochemical cycloaddition of acetylene to anhydrodeoxyhexenulose (71) gave, after hydrogenation, the cyclobutane derivative (72).[48]



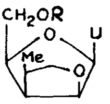
(71)



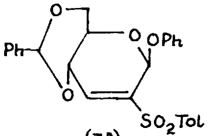
(72)

R = R^1 = CMe_2
R = CPh_3, Ac; R^1 = Ac

The preparation of some fused [3.3.0] furanoside nucleosides such as (73) is mentioned in Chapter 20 and that of branched-chain (-)-canadenosolide from D-glucose is mentioned in Chapter 24. The preparation of 3,5-disubstituted carbohydrates from 3-*C*-methyl aldoses by Claisen rearrangement is described in Chapter 2. The addition of nitromethane anion to unsaturated derivative (74) is described in Chapter 13.



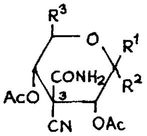
(73)



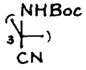
(74)

4 Compounds with a R-C-R, R-$\overset{\triangledown}{\text{C}}$-R or C=R Branch

Branched derivatives of the type (75) have been transformed into *N*-protected 3-amino-3-cyano-3-deoxy derivatives of the type (76) by a Hofmann rearrangement.[49] The cyano group was also reduced to the aminomethyl group.

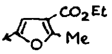


(75)



(76)

R^1 = H, OMe, or

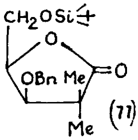


R^2 = H, OMe

R^3 = H, CH_2OAc

The preparation of 3-cyano-3-deoxyheptoseptanosides further branched at C-3 has been reported.[50]

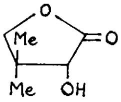
The protection of the branched-chain furanolactone (77) from a glyceric acid derivative has been reported.[51]

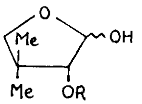


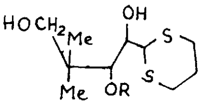
(77)

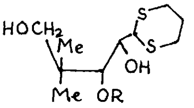
The conversion of (R)-pantolactone (78) into the corresponding free sugar derivative (79) which has been used as starting material for the addition of 2-lithio-1,3-dithiane to afford pentose products (80) and (81) has been described.[52]

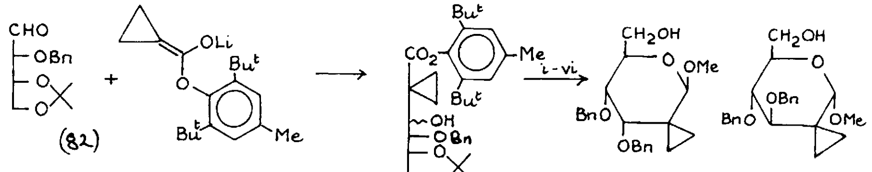
The preparation of 2-spiro-cyclopropylhexoses as potential glycosidase inhibitors has been achieved by treating the *erythro* sugar (82) as indicated in Scheme 27.[53] (See


(78)


(79) R = H, Si$<\!+$


(80)


(81)

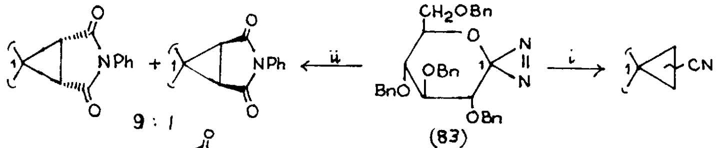


Reagents: i, BnBr, NaH ; ii, LAH ; iii, separate isomers ; iv, PCC ; v, AcOH ; vi, PPTS

Scheme 27

also Vol. 23, p.153.)

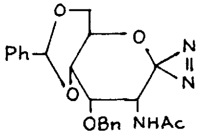
The diazirine (83) (see Vol. 23, p.16 and 114) reacts (by way of the glycosylidene carbene) on heating with acrylonitrile to give all four isomeric glycosyl cyanocyclopropanes (Scheme 28).[54] Trapping of the intermediate carbene with *N*-phenylmaleimide, dimethyl maleate and dimethyl fumarate are also described.



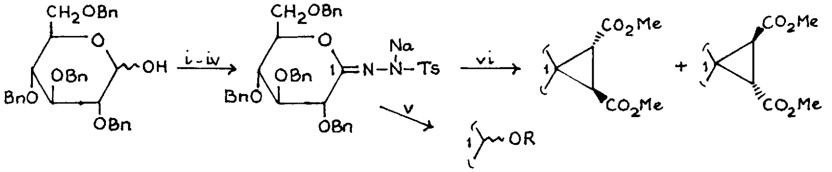
Reagents: i, $\diagup\!\!\diagdown$CN, Δ ; ii, N-phenylmaleimide (NPh), Δ

Scheme 28

The preparation of the *allo*-configurated diazirine (84) derived from N-acetyl glucosamine has also been described.[55] It reacts with acrylonitrile in a similar way to (83) to give all four isomeric cyclopropane derivatives. Attempts to convert (84) into an *O*-glycoside using isopropanol failed with only the oxazolidine being isolated following NHAc participation.


(84)

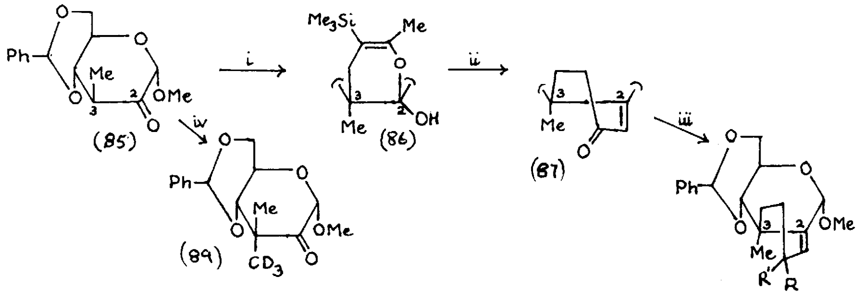
The use of glyconolactone tosylhydrazones as precursors of glycosylidene carbenes has been achieved (Scheme 29).[56] Treatment of the sodium salt of the tosylhydrazone with dimethyl fumarate or alcohol under the action of light gave the cyclopropane and *O*-glycoside, respectively. Reaction also occurs with *N*-phenylmaleimide and acrylonitrile.



Reagents: i, TsNHNH$_2$; ii, NBS; iii, DBU; iv, NaH; v, ROH, hν; vi, MeO$_2$CCH=CHCO$_2$Me, hν

Scheme 29

The application of the Robinson annulation to a carbohydrate derivative has been disclosed (Scheme 30).[57] Thus trapping of the enolate derived from ketone (85) with 3-trimethylsilylbut-3-en-2-one gives compound (86) which can be converted to the Robinson product (87) with base. Compound (87) was reduced with a variety of reducing agents to compounds (88). On the other hand trapping of the enolate derived from (85) with deuterated methyl iodide led to axially substituted product (89) instead.



(88) R^1 = OH, R = H
R^1 = H, R = OH

Reagents: i, LTMP, 3(TMS)but-3-en-2-one; ii, KOH; iii, H$^-$; iv, LTMP, CD$_3$I

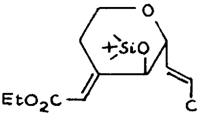
Scheme 30

Syntheses of 3-deoxy-3,3-di-*C*-methyl-D,L-*glycero*-tetrose, 3-*C*-methyl-D,L-erythrose and -threose have been achieved.[58]

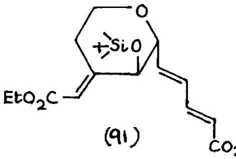
The preparation of aza-sugars branched at C-5 is covered in Chapter 9.

The synthesis of the macrocyclic diester part of the trichothecene satratoxin has been described.[59] The branched-chain sugars (90)-(92) were prepared amongst others.

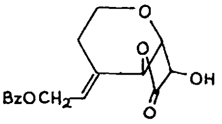
The preparations of the α-methylene δ-lactone derivatives in the *gluco* and *galacto* (93) series have been described.[60] (See also Vol. 20, p.147 for earlier work).



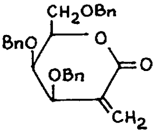
(90)



(91)



(92)



(93)

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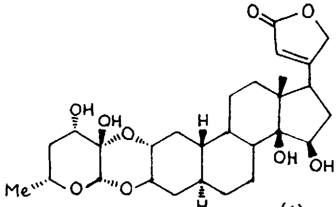
15

Aldosuloses, Dialdoses, and Diuloses

1 Aldosuloses

A doubly linked 4,6-dideoxy-D-*threo*-hexos-2-ulose residue was identified in the cardenolide glycoside (**1**) isolated from *Asclepias curassavica* stems,[1] and a branched hexos-4-ulose derivative isolated from *Pittosporum tobira* flowers is covered in Chapter 14. Oxidation (MCPBA/MeOH) of unsaturated derivative (**2**) (obtained by base treatment of methyl 3,4-*O*-isopropylidene-2,6-di-*O*-methyl-β-D-galactopyranoside) afforded L-*arabino*-hexos-5-ulose derivative (**3**) and then (**4**) after acid hydrolysis.[2] The hexopyranosid-3-uloses (**5**) have been prepared by oxidation (CrO_3/Ac_2O/pyridine) of the corresponding 3-alcohols.[3]



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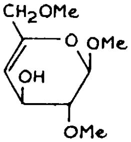

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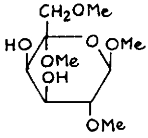

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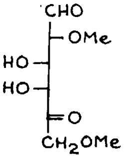

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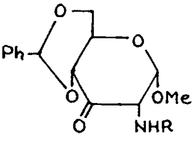

(5) R = H, Bz, Cbz

Hydrogenation (Pd/C) of D-*erythro*- and D-*threo*-pentos-2-ulose has afforded the corresponding 2-pentulose. The 1-^{13}C and 2-^{13}C derivatives were also prepared.[4] Isomaltulose has been shown to suffer oxidative cleavage at a higher rate than those of other disaccharides presumably consequent upon the ease of formation of the enediolate.[5] A modified oxidation procedure for the degradation of permethylated oligosaccharides involving the generation of hexos-2-ulose moieties has been described.[6] A Claisen rearrangement of hex-2-enopyranoside allyl ethers to give 3-*C*-allyl-hexos-2-ulose derivatives is mentioned in Chapter 14.

In a study of the hydration of the carbonyl groups of 2-*C*-halo-2-deoxy-α- or β-D-*ribo*- or *xylo*-hexopyranosid-3-ulose derivatives, only the *xylo*-β-anomer was found to be hydrated.[7]

Treatment of hexopyranosid-2-ulose derivatives with DAST produced the gem-difluorides only if both neighbouring groups were either axial or equatorial.[8] The stereoselective aldol coupling of 2-deoxy-hexopyranosid-3-uloses with various carbohydrate aldehydes is covered in Chapter 14. The chemoselective reduction of enones in the presence of allyl ethers by the conjugate addition of thiophenol followed by radical desulfurization with Bu_3SnH has been achieved.[9]

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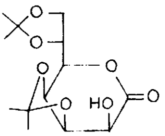
16
Sugar Acids and Lactones

1 Aldonic, Aldaric and Saccharinic Acids

A convenient and high-yielding method for the synthesis of crystalline sodium D-arabinonate involves oxidation of D-glucose with oxygen in alkaline methanol-water mixtures.[1] Conditions have been optimised for the catalytic hydrogenation of D-*xylo*-5-hexulosonic acid so as to give a 3:1 preponderance of L-idonic acid over D-gluconic acid in a very efficient reaction.[2]

Large-scale Kiliani reaction of di-*O*-isopropylidene-D-mannofuranose gives access to the D-*glycero*-D-*talo*-heptonolactone (1) and the D-*glycero*-D-*galacto*-isomer in a ratio of 2.5:1. On acid hydrolysis with TFA, (1) formed the 1,4-lactone, which could be converted into its 2,3:6,7-di-*O*-isopropylidene derivative. Similar Kiliani reaction applied to 2,3:5,6-di-*O*-isopropylidene-L-gulose gave approximately equal amounts of the L-*glycero*-D-*talo*- and L-*glycero*-D-*galacto*- products (2) and (3),[3] whilst reaction of 2,3:5,6-di-*O*-isopropylidene-D-allose gave the D-*glycero*-D-*altro*-heptonolactone derivative almost exclusively, but in only modest yield. 2,3-*O*-Isopropylidene-D-ribofuranose and its 5-azido-5-deoxyderivative also gave products with the D-*altro*- configuration, again in rather poor yield.[4]



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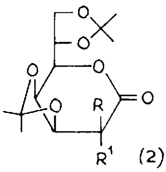
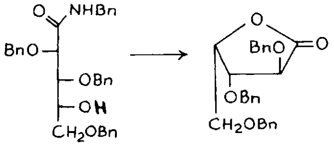


	R	R¹
(2)	OH	H
(3)	H	OH

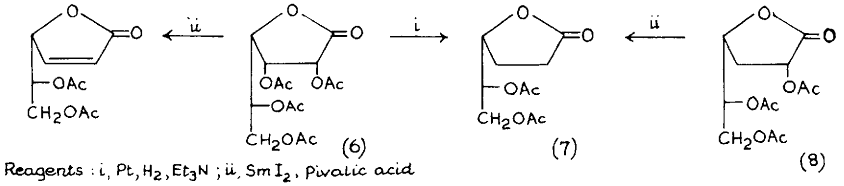


(4) (5)

When the amide (4) was treated under Mitsunobu conditions, cyclization occurred through oxygen to give the L-xylono-1,4-lactone derivative (5).[5] A convenient large-scale synthesis of D-ribono-1,4-lactone from D-ribose has been described,[6] and 5-*O*-glucopyranosylarabinonic acid can be obtained selectively by oxidative removal of C-1 from isomaltulose.[7]

Rate constants for the hydrolysis of D-glucono-1,5-lactone, and for the reverse reaction, have been determined.[8]

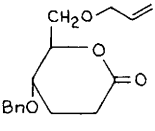
Hydrogenation of peracetylated aldono-γ-lactones over *platinum* catalysts in the presence of triethylamine gives the 2,3-dideoxy derivatives, as in the formation of (7) from (6) (Scheme 1); 3-deoxy-2,3-enes are considered to be intermediates.[9] When acetylated 3-deoxy-aldono-1,4-lactones such as (8) (formed by hydrogenation of the peracetylated lactone



Reagents : i, Pt, H_2, Et_3N ; ii, SmI_2, Pivalic acid

Scheme 1

over *palladium hydroxide* in the presence of triethylamine) are treated with samarium diiodide, the same 2,3-dideoxy derivatives are produced. If the oxygen substituent is still present at C-3, as in (6), SmI_2 gives a 2,3-dideoxy-2,3-didehydroderivative (Scheme 1).[10] 2,3-Dideoxy-δ-lactones such as (9) have been prepared from the corresponding enones by conjugate addition of thiophenol followed by reduction with tributylstannane.[11] Lewis-acid-catalysed reaction between isopropylidene-D-glyceraldehyde and 1-ethoxy-1-trimethylsilyloxyethene led, after acidic hydrolysis, to 2-deoxy-D-ribono-1,4-lactone,[12] and a route to convert D-ribono-1,4-lactone into its 5-deoxy analogue has been described.[13] When the (*R*)-hydroxyester (10), produced by microbiological reduction of the ketoester, was treated with osmium tetroxide, the two products (11) and (12) of *cis*-dihydroxylation were isolated in a ratio of 3:2 after lactonization and acetylation. Use of methylrhenium trioxide-H_2O_2 gave a 1:1 mixture of the two lactones derived



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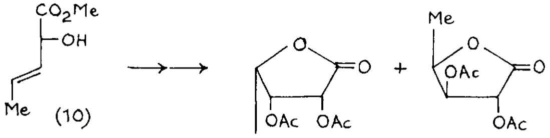

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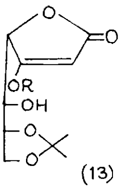

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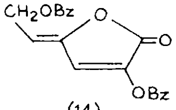
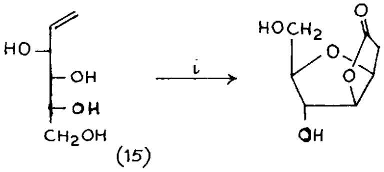


(14)

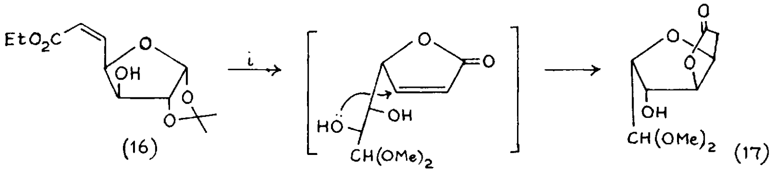
by *trans*-dihydroxylation.[14] Products of type (13) can be obtained stereoselectively by aldol condensation between tetronic acid derivatives and isopropylidene-D-glyceraldehyde; in the case of (13, R=Bn), hydrogenation over Rh/Al_2O_3 proceeded stereoselectively to give a 2-deoxy-D-*gluco*-heptonolactone derivative.[15] Dienone (14) was obtained by treatment of tetra-*O*-benzoyl-D-glucono-, -D-galactono- or -D-mannono-1,4-lactones with triethylamine, and on hydrogenation, (14) gave 2,6-di-*O*-benzoyl-3,5-dideoxy-D,L-*threo*-hexono-1,4-lactone.[16]

A route to 3,5-anhydro-2-deoxy-1,4-glyconolactones by Pd(II)-catalysed oxycarbonylation is illustrated by the case of the alkene (15) derived from D-mannitol (Scheme 2).[17] *Cis*-alkenes such as (16) can be obtained from 5-*aldehydo*-pentose derivatives by application of Wittig reactions in methanol. When treated with acidic methanol, (16) gives the 3,6-anhydro-2-deoxyheptonolactone derivative (17), with the proposed intermediate being shown (Scheme 3); three other similar cases were reported.[18]



Reagents: i, CO, $PdCl_2$, $CuCl_2$, NaOAc, AcOH

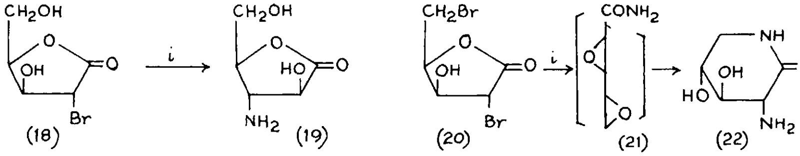
Scheme 2



Reagents: i, MeOH, H^+

Scheme 3

Interaction of bromolactone (18) with liquid ammonia led to 3-amino-3-deoxy-D-arabinono-1,4-lactone (19), via a 2,3-D-*lyxo*-epoxide (Scheme 4), and the dibromide (20) gave lactam (22), with diepoxide (21) as an intermediate. Evidence was adduced for the sequence of events in these reactions from experiments with aqueous ammonia.[19] Some 2-deoxy-2-



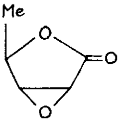
Reagent: i, NH_3, Liq

Scheme 4

alkylamino-D-gluconic acids with surfactant properties have been prepared by oxidation of the corresponding glucopyranoses with mercuric oxide.[20] 1,2-*O*-Isopropylidene α-D-xylofuranose has been deoxygenated at C-5 by reduction of the tosylate, and then converted separately into the D-*ribo*-epoxide (23) and the analogous D-*lyxo*-compound.[21]

Reaction of the δ-lactone with the amine led to *N*-(undecen-10-yl) lactobionamide, which could be polymerised; the micellar properties of both monomer and polymer were studied.[22] Two groups have described the preparation of diacetylenic aldonamides, which aggregate into supramolecular tubular assemblies on heating in boiling water and then cooling.[23,24] A series of arylhydrazides of gluconic acid having broad antibacterial activity have been reported.[25] A paper referring to 4-amino-4-deoxy-L-ribono-1,4-lactam is mentioned in Chapter 9.

A number of muropeptides have been conjugated to 2-deoxy-β-KDO to give compounds such as (24); these were designed to act as prodrugs of 2-deoxy-β-KDO which could permeate into bacterial cells.[26] A range of analogues of 2-deoxy-Neu5Ac have been made which have methyl and *exo*-methylene groups at C-4, as in (25); a protected 4-oxo compound was used as a key intermediate.[27] The oxazoline (26) was prepared by treating peracetylated Neu5Ac methyl ester with TMSOTf, and then used to make a number of analogues of 2,3-didehydro-2-deoxysialic acid (Neu5Ac2en) modified at C-4.[28] The C-5 modified structures (27, R=OH, N_3) have also been described, along with a better route to the sialidase inhibitor (27, $R=NHCOCF_3$)[29] and the 8-azido-8-deoxy-analogue of Neu5Ac2en has been prepared.[30] *C*-Glycosides of Neu5Ac and of 2-deoxy-D-*arabino*-heptulosonic acid are mentioned in Chapter 3, 2,6-dideoxy-6-thio-derivatives of KDO in Chapter 11, and the phosphonic acid analogue of Neu5Ac2en in Chapter 17.



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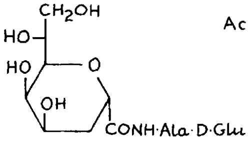

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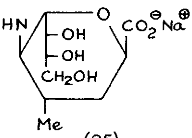

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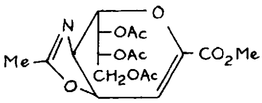

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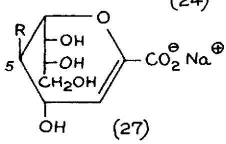
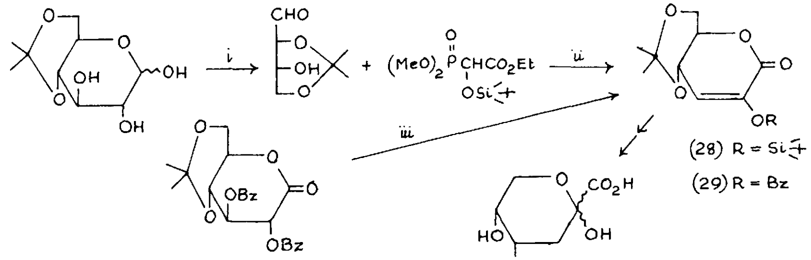


(27)

Molecular modelling studies have been carried out on *N*,*N*''-dimethyl- and *N*,*N*'-dihexyl xylaradiamide, which are simple models for the functionalised nylon poly(hexamethylenexylamide).[31] A preparation of α-D-glucosaccharinic acid from D-glucose has been reported.[32]

2 Ulosonic Acids

Ramage and co-workers have given full details of their Wittig approach to 2-ulosonic acids (see Vol. 22, p.161) and have extended this route to the synthesis of 3-deoxy-D-*erythro*-2-hexulosonic acid (KDG, 30), albeit in low yield in this case.[33] A French group have developed two routes to KDG (30) (Scheme 5) involving, respectively, a Wittig synthesis of (28)[34] or β-elimination from a gluconolactone derivative to yield (29);[35] the second approach could be modified to make 5- and 6-*O*-methyl ethers of (30).



(28) R = Si$\overset{|}{\underset{|}{}}$+

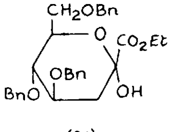
(29) R = Bz

(30)

Reagents: i, $NaIO_4$; ii, $(TMS)_2NLi$; iii, Et_3N, CH_2Cl_2

Scheme 5

The derivative (31) of 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH) has been prepared by interaction of the cyclic sulfate of 2,3,5-tri-*O*-benzyl-D-arabinitol with the lithium derivative of 2-carboethoxy-1,3-dithiane (an approach used for KDO synthesis; Vol. 21, p.161-2),[36] and the D-*gluco*-heptulosonic and derivative (32) is accessible by hydroxylation of the 2,3-ene.[37] The chloroglycidate (33) gives the bromoderivative (34) of DAH on treatment with $MgBr_2$ or PhMgBr, and a similar reaction was also observed from a precursor of L-*gulo*-configuration.[38]



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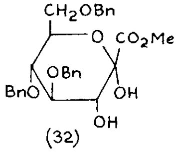

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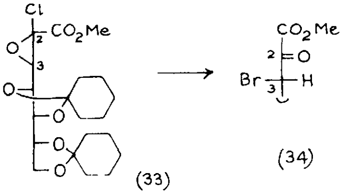

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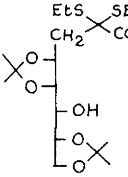
(34)

Martin and Zinke have given a full account of their synthesis of KDO in which the molecule is assembled around a furan template (see Vol. 23, p.162-3).[39] The dithioacetal (35) of KDO (see also Vol. 23, p.161-2) can be subjected to iodonium-ion induced cyclisation to give access to, depending on the conditions, the thioglycoside (36) or the alkene (37); (36) can be used to make β-glycosides of KDO, whilst (37), when activated with phenylselenenyl triflate, acts as a precursor to α-glycosides.[40] Other references to glycosides of KDO are mentioned in Chapter 3. A thioacetal derivative of KDO has also been made by reaction of 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-D-mannitol with $(EtS)_2CHCO_2H$ in the presence of BuLi, and this adduct was then converted to KDO itself.[41] In a new '$C_6 + C_2$' approach to KDO, intermediate (38) was made by a Wittig reaction.[42] A full account has been given of Dondoni's route to KDO using the enolate of 2-acetylthiazole (see Vol. 24),[43] and in related work, the Wittig product (39) underwent stereoselective Michael addition with benzyloxy anion to give the precursor (40) of D-*gluco*-KDO.[44] *C*-Glycosides such as (41) can be ring-opened to give acyclic unsaturated ketoesters by treatment with Me_2BBr; the product (42) is a known precursor of KDO.[45]



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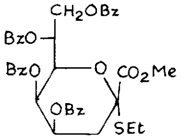

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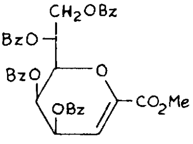

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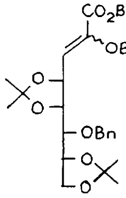

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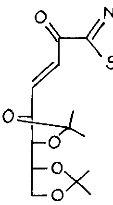

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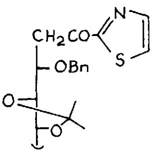

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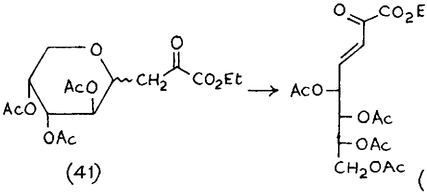
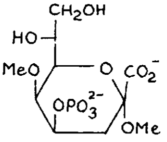


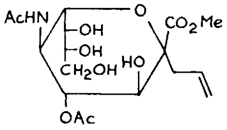
(41)
(42)

The 4-and 5-phosphates of KDO have been prepared as their *O*-allyl glycosides by phosphorylation of the 7,8-*O*-isopropylidene methyl ester and separation of the two regioisomers.[46] Various methyl glycosides of KDO phosphorylated at O-4 and alkylated at O-5, as in the case of (43), have been made to assist in the identification of KDO derivatives isolated naturally. When the glycosidic link is hydrolysed, such compounds undergo elimination of phosphate, and, if possible, subsequent Michael-type intramolecular cyclization.[47]

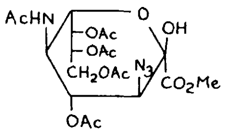
A large-scale preparation of sialic acid from egg chalaza and yolk membrane has been documented.[48] The synthesis of Neu5Ac, both by chain extension of other sugars and by *de novo* methods, has been reviewed,[49] and an enzymatic 2-step synthesis of Neu5Ac by epimerization of *N*-acetylglucosamine and subsequent condensation with pyruvate, using an enzyme membrane reactor, has been described.[50] Engineered mutants of subtilisin can be used to prepare the 6-*O*-acetyl and 6-*O*-L-lactyl-esters of *N*-acetylmannosamine, and these esters can subsequently be condensed with pyruvate using sialic acid aldolose to give 9-*O*-acyl derivatives of sialic



(43)

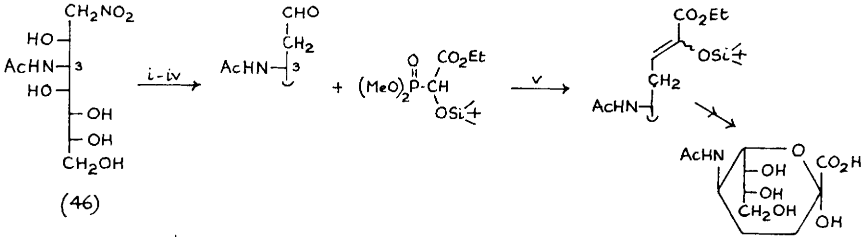


(44)



(45)

acid.[51] The *C*-allyl glycoside (44) can be prepared from the glycosyl bromide (Vol. 21, p.17) by free-radical reaction with allyl tributylstannane. The same paper also describes the 3-azido-derivative (45) of Neu5Ac, and its C-3 epimer, made by azidonitration of the 2,3-ene.[52] Some other references to *C*-glycosides of Neu5Ac are given in Chapter 3. A new synthesis of 4-deoxy-Neu5Ac (47) proceeds from the known Henry product (46) from *N*-acetylmannosamine, as outlined in Scheme 6,[53] and the truncated form (48) of Neu5Ac has been prepared from D-glucono-1,5-lactone, nitrogen being introduced with inversion of configuration at C-5 of an open-chain derivative.[54]

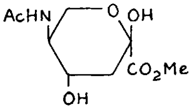


(46) (47)

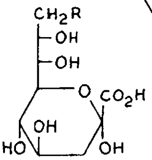
Reagents: i, Ac_2O, H^+; ii, $NaHCO_3$, Δ, toluene; iii, $NaBH_4$; iv, KOH, $KMnO_4$, MeOH; v, $(TMS)_2NLi$

Scheme 6

In a study of the thermal and photochemical degradation of sodium *N*-acetylneuraminate, it was found that the main product formed thermally was the 4,8-anhydrocompound previously observed (see Vol. 23, p. 164); under alkaline conditions, the 3,7-anhydrooctonic acid (49) was also produced,

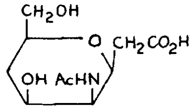


(48)

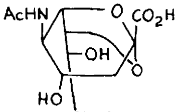


(51) R = OH

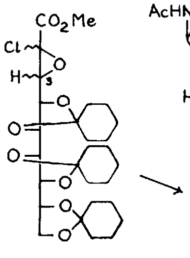
(52) R = H



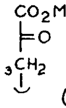
(49)



(50)



(53)



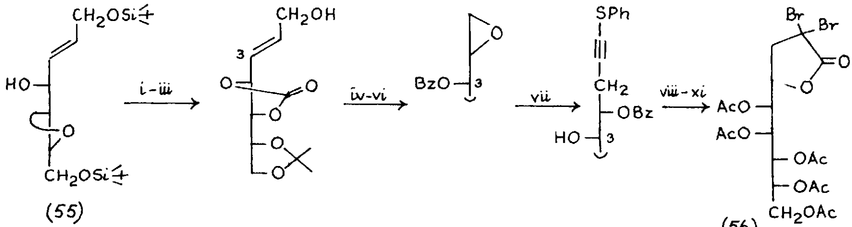
(54)

whilst in acid the 2,7-anhydrocompound (50) was also a product. Photochemically, the decarbonylation product 4-acetamido-2,4-dideoxy-D-*glycero*-D-*galacto*-octonic acid was formed.[55] The 2,7-anhydrocompound (50) has been synthesised by an intramolecular glycosidation reaction,[56] and the same material has been identified as the product formed from various sialyl glycosides and -glycoproteins by the action of a novel sialidase from a species of leech.[57]

A decarboxy analogue of Neu5Ac and some imino-derivatives are mentioned in Chapter 9, and work on the use of n.m.r. methods to determine configuration of Neu5Ac derivatives at C-2 is covered in Chapter 21.

When L-mannose was condensed with pyruvate under the catalysis of Neu5Ac aldolase, the L-enantiomer (51) of KDN was formed. Thus the same relative configuration between C-4 and C-5 is established by the enzyme independent of the absolute configuration of the sugar substrate. In the same way, L-rhamnose gave 9-deoxy-L-KDN (52).[58] Zhdanov's group has prepared the chloroglycidate (53) by Darzens-type reaction of the *aldehydo*-heptose derivative and converted it to the KDN ester-acetal (54) by reductive ring opening using $MgI_2/NaHSO_3$.[59] A *de novo* synthesis of the KDN equivalent (56) originates from the chiral epoxyalcohol (55), produced by Sharpless epoxidation of the divinyl carbinol (Scheme 7).[60] Some KDN-containing analogues of lipid A are mentioned in Chapter 9, and nucleosides of KDN in Chapter 20.

A paper on the synthesis of enolised 2,4-diulosonic esters from chain-extension of sugars is covered in Chapter 2.



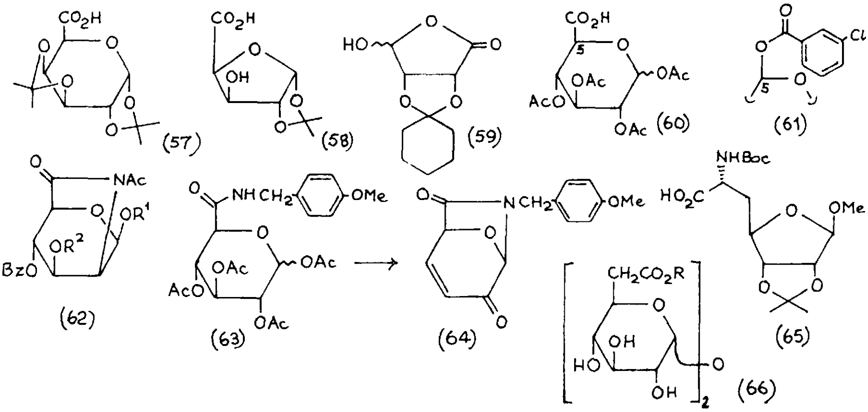
Reagents: i, PhNCO; ii, MeOH,HCl; iii, Me_2CO, H^+; iv, OsO_4, NMMO, collidine, HOTs; v, Ph_3P, DEAD; vi, BzCl; vii, LiC≡CSPh, then $BF_3.Et_2O$; viii, Br_2, NaOMe,MeOH; ix, DBU,MeOH; x, H^+(resin); xi, Ac_2O, Py

Scheme 7

3 Uronic Acids

1-*O*-Pivaloyl-β-D-glucopyranuronic acid has been prepared in order to identify it as a metabolite of pivaloyloxyalkyl-containing prodrugs, the acid grouping being introduced by catalytic oxidation.[61] Electrochemical oxidation of some carbohydrate primary alcohols at a nickel hydroxide electrode in alkaline solution has been developed as a route to uronic acids. Examples include the formation of (57) from the galactose derivative, and of (58) from 1,2-*O*-isopropylidene-D-glucofuranose, where oxidative cleavage of the side-chain diol occurs. This latter example indicates that isolated secondary alcohol groups are not affected; lactols give lactones under these conditions.[62] 1-^{13}C-D-Penturonic acids have been prepared by catalytic oxidation of the labelled methyl D-pentofuranosides;[63] the use of these compounds in nmr studies is discussed in Chapter 21.

The L-erythuronic acid derivative (59) has been prepared by periodate treatment of 2,3-*O*-cyclohexylidene-D-ribono-1,4-lactone,[64] and oxidative decarboxylation of uronic acids using MCPBA/DCC, as in the conversion of (60) to (61), has been described; diacyl peroxides are probable intermediates.[65]



Bicyclic uronolactams of type (62), including a disaccharide case, can be made by oxidation of the corresponding *N*-acetylmannosamine derivatives with PDC and Ac_2O,[66] whilst treatment of the D-glucuronamide (63) with triflic acid in chlorobenzene gave the 1,6-lactam (64); a reasonable mechanism was proposed for the formation of this product, which is of potential use in making chiral polyamides.[67] The derivative (65) of 6-amino-5,6-dideoxy-D-*ribo*-heptofuranuronic acid, which has similarity to the sugar units in some chain-extended nucleosides, can be made by displacing a triflate at C-5 in a ribose unit using R.M. Williams' chiral glycine enolate.[68] Work on 6-amino-6-deoxy-D-*glycero*-D-*talo*-heptopyranuronic acid derivatives is discussed in Chapter 9.

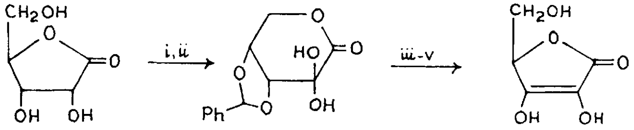
UDP-Glucuronic acid has been prepared enzymically from UDPG on a gram scale.[69]

Esters of type (66), with R as various long-chain aliphatic groups, have been made from the corresponding dicarboxylic acid, the preparation of which from trehalose was reported last year. These esters (66) can be regarded as analogues of cord factor, in which the ester units have been regioinverted.[70]

^{13}C-Nmr methods have been used to determine the pK_a values of both α- and β-D-glucuronic acid, and of the carboxy groups of heparin.[71] The reduction of Cr(VI) by D-galacturonic acid has been studied; the reduction only occurs in the presence of metal ions such as Cu(II) or Cr(III) itself, the metals forming stable complexes in which opening of the sugar ring leads to the formation of a reducing aldehyde group.[72]

4 Ascorbic Acids

'D-Erythroascorbic acid' (67) can be made from D-ribono-1,4-lactone as indicated in Scheme 8. In this work, the ribonolactone was prepared from D-glucose by oxidation to give calcium D-arabinonate, which isomerised to the D-ribonate using $Ca(OH)_2$ at 137°, and the overall yield of (67) from glucose was 20%.[73]



Reagents: i, PhCHO, H$^+$; ii, MnO$_2$; iii, H$^+$(resin), MeOH; iv, NaOMe, MeOH; v, H$^+$(resin)

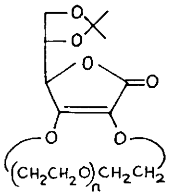
(67)

Scheme 8

A new synthesis of L-ascorbic acid involves anodic oxidation of 1,3:2,4-diacetals of D-glucitol leading to 3,5:4,6-diacetals of 2-keto-L-gulonic acid, which give L-ascorbic acid directly on hydrolysis.[74] The Na, K and Ca salts of ascorbic acid have been prepared by treating the acid with metal carbonates, bicarbonates or hydroxides in the absence of solvent.[75]

The discovery and chemistry of the non-reducing, chemically stable 2-*O*-α-D-glucopyranosyl-L-ascorbic acid has been reviewed,[76] and a new synthesis of it has been described in which L-ascorbate and α-cyclodextrin interact in the presence of a cyclomaltodextrin glucanotransferase from *Bacillus stearothermophilus*. Other products with higher maltooligosaccharides linked to *O*-2 of the ascorbate were also formed, but glucoamylase could be used to convert these to more 2-*O*-α-glucopyranosyl-L-ascorbic acid.[77]

Treatment of 5,6-*O*-isopropylidene-L-ascorbic acid with alkyl halides and $NaHCO_3$ in DMSO gave alkylation only at O-3; the products were then hydrolysed to give 3-*O*-alkyl-ascorbic acids as free radical scavengers.[78] The crown ether type of derivatives (68) of isopropylidene-L-ascorbic acid could be made by interaction with the appropriate ditosylate and K_2CO_3 in DMF; the reaction was unsuccessful in the case of (68, n=2).[79] The mechanism by which 3-*O*-dodecylcarboxymethyl-ascorbic acid inhibits lipid peroxidation, and hence is a protectant for biomembranes, has been studied. It appears to act as a chain-breaking antioxidant by intercepting hydroxyl radicals, and is present in the lipid layer due to its hydrophobic moiety.[80]



(68) n = 1,3,4

The conformations of neutral L-ascorbic acid[81] and its anion[82] in both their unhydrated and hydrated states have been investigated by conformational free-energy calculations.

Ascorbic acid can be oxidised photochemically by molecular oxygen in the presence of ruthenium complexes to give dehydroascorbic acid.[83] Various bis(aroylhydrazones) of this compound have been prepared.[84] The kinetics and mechanism of oxidation of ascorbic acid by Fe(III) ions[85] and by hexacyanoiron(III)[86] in acidic media have been studied, and a polarographic investigation of the oxidation by molecular oxygen has been reported, including an examination of the catalytic effect of Cu(II) ions and the retardant effect of Sn(II) and Al(III) species.[87] The dielectric behaviour and intermolecular association between ascorbic acid and ethanol have been studied.[88]

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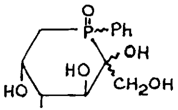
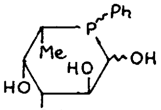
17

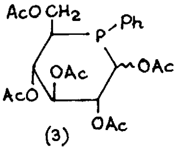
Inorganic Derivatives

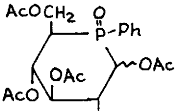
1 Carbon-bonded Phosphorus Derivatives

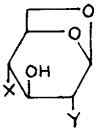
The phenylphosphinyl D-fructopyranose 4-ether (1) has been prepared from D-fructose,[1] and the analogue (2) of L-fucose has also been reported.[2] The same group has also prepared the "P in the ring" glucose derivatives (3) and (4),[3] as well as 2,4-dideoxy-4-methoxyphosphinyl-D-*erythro*-pentofuranose triacetate.[4]


(1)

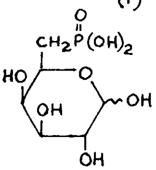

(2)


(3)


(4)


(9) X = Ph_2P, PhS, $Ph_2P{=}O$

Y = Ph_2P, PhS, Cl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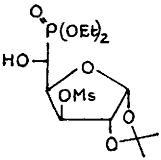
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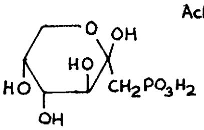
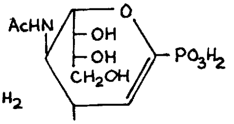
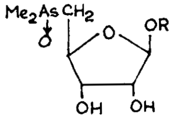

(7)


(8)

The synthesis of glycosyl phosphonates from glycosyl acetates or trichloroacetimidates has been reviewed.[5] The phosphonate analogue (5) of galactose-6-phosphate has been synthesized; the key step being an Arbuzov reaction on 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.[6] 1,2-*O*-Isopropylidene-3-*O*-methanesulfonyl-α-D-xylopentodialdofuranose has been converted into the diethoxyphosphonyl derivative (6) and its crystal structure has been determined.[7] The 1-deoxy-1-phosphonic acid derivative (7) of D-fructose has been reported,[8] as well as the phosphonic acid analogue (8) of the sialidase inhibitor *N*-acetyl-2,3-didehydro-2-deoxyneuraminic acid.[9] Some carbohydrate-derived phosphines and bis-phosphines (9) have been prepared and evaluated (without much success) as ligands for use in asymmetric homogeneous hydrogenation.[10]

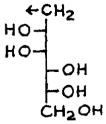
2 Other Carbon-bonded Derivatives

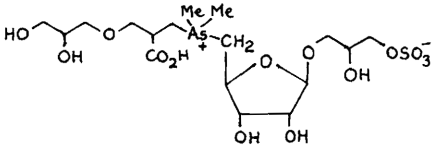
Three novel arsenic containing ribosides (**10**) - (**12**) together with several other known derivatives have been isolated from *Sargassum lacerifolium*.[11] Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-triphenylstannyl-α-D-altropyranoside reacts readily with halogens with phenyl-tin bond cleavage.[12]



(10) R = Me

(11) R =

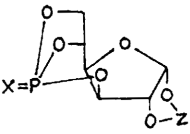




(12)

3 Oxygen-bonded Derivatives

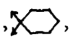
The metal ion complexes of carbohydrates have been reviewed,[13] as well as the possible quantitative determination of mannitol by chelation with transition metal ions.[14] The synthesis and chemical properties of bicyclophosphate derivatives (**13**) have been reported as well as their selective hydrolyses into (**14**).[15,16] Methyl α-D-glucopyranoside is efficiently oxaphosphoranylated by $(EtO)_2PPh_3$ to afford two unstable isomeric dioxaphospholanes (see Vol. 24, p. 74).[17] Glucose 6-phosphate analogues bearing at C-6 a thiophosphate or thiophosphoramidate group have been studied as potential hexokinase inhibitors,[18] and the complexation properties of D-*myo*-inositol 1,2,6-trisphosphate towards Li^+, Na^+, Rb^+, and Cs^+ cations were studied at 25°C in 0.1 M Bu_4NBr.[19] The cationic Rh(I) chelate of phenyl 4,6-*O*-benzylidene-2,3-*O*-bisdiphenylphosphino-β-D-glucopyranoside has been immobilized on sulfonated ion exchangers allowing the formation of highly active and enantioselective heterogeneous catalysts.[20,21]



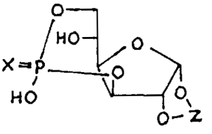
(13)

X = O, S, Se

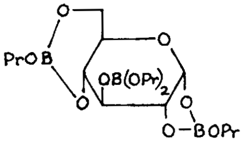
$Z = CMe_2$,



$CHCCl_3$



(14)



(15)

Diethylborinyl esters of 4,6-*O*-alkylidene-D-glucose compounds have been utilized during the regioselective reductive cleavage of the alkylidene group.[22] Heating glucose in tripropylborate has given dipropylboryl ester derivatives which can be converted into cyclic borate esters such as (**15**).[23] Potentiometric and spectroscopic studies of the binding of Cu(II) ions by aminodeoxy derivatives of 1,6-anhydro-β-D-glucopyranose have shown that they were less effective than the parent aminodeoxy sugars.[24] Lactobionic acid has been shown to be a very efficient chelating agent for metal ions,[25] and complexes formed between various aldonic or uronic acids and ferric ions in aqueous solution have been studied.[26] The site-selective interaction of metal ions with saccharides and their application to selective oxidation of monosaccharides using Cu(II) and Fe(II) in aqueous DMSO has been investigated.[27] Six new well-defined stable Cu(II) complexes of nitrogenous sugar derivatives have been prepared,[28] and a number of *N*-substituted ethylenediamine Ni(II) compounds have been prepared and the relative rates of the C-2 epimerization of aldohexoses in their presence have been studied.[29] The interaction of L-ascorbic acid with Al(III), La(III), and Pb(II) ions in aqueous solution and in the solid state has been investigated.[30]

The tungstate and molybdate complexes of D-*glycero*-D-*galacto*-heptitol, D-galactitol, and D-mannitol have been shown by ^{13}C n.m.r. to have similar structures that involve four vicinal OH groups,[31] while the tetradentate molybdate complexes of some aldoses and alditols have been shown to have characteristic ^{95}Mo n.m.r. spectra depending on the conformation of the sugar.[32] The coordination of Cp_2MoCl_2 with some nucleosides is discussed in Chapter 20.

The interaction between lanthanide shift reagents containing β-diketones and several methyl 2,3-anhydro-4,6-*O*-benzylidene-D-hexopyranosides has shown that the carbohydrate may be bound to the reagents in either monodentate or chelated manner.[33] The separation of xylitol and L-arabitol on cation exchange resin in the La^{3+} form is mentioned in Chapter 23. The n.m.r. shifts induced by complexation between per-*O*-methylated aldopyranoses and metal cations (mostly Eu^{3+}) have been studied and an order of stability of the complexes has been deduced.[34] Treatment of (dppe)$PtCl_2$ with 2 equiv. of $KOSiMe_3$ and a slight excess of 1,2:5,6-di-*O*-isopropylidenemannitol has afforded the (dppe) Pt (glycolate) complex.[35]

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18

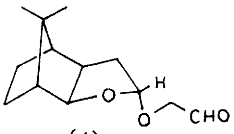
Alditols and Cyclitols

1 Alditols

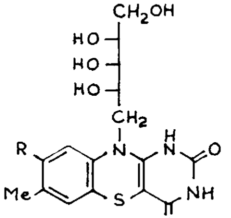
1.1 Acyclic Alditols. - A simple method has been described for transforming Fischer projections into zig-zag forms.[1] Dipole-dipole interactions of D-sorbitol in water and methanol solution have been studied, and evidence for solute-solvent interactions presented.[2] The preparation of 1,4-di-*O*-benzyl-L-threitol from L-tartaric acid in 4 steps has been reported.[3] A study of optical rotations of (S)-propane-1,2-diol, D-*threo*-butane-2,3-diol as well as some alditols and some deoxyalditols in aqueous and non-aqueous solution has been reported;[4] D-glucitol, for example, is dextrorotary in DMSO or HMPT but levorotary in water or pyridine. The dependence of rotation on the solvent is considered in detail. The mass spectra of some per-*O*-benzoylalditols have been described.[5]

The trimerization of acetal-protected glycolaldehyde (1) (see Vol. 23, p.177 for similar work) under strongly basic conditions, affording allose with low asymmetric induction as the main product, has been described.[6] The products were characterized by comparison of their *O*-methyl or *O*-trityl alditol derivatives with reference sugars of defined configuration.

The syntheses of lampteroflavin[7] (see also Vol. 24, p.199 and Vol. 22, p.177) and of 8 electron-donor-substituted-5-thia- and 5-deaza-riboflavin derivatives (2) and (3) have been reported.[8]

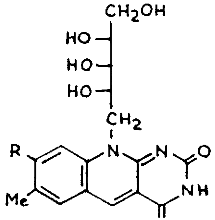


(1)



(2)

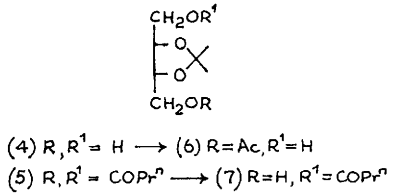
$R = OMe, NMe_2$

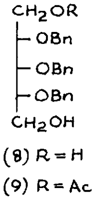


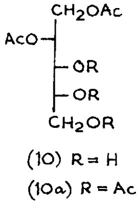
(3)

The syntheses of optically active esters of 2,3-*O*-isopropylidene-erythritol using SAM II lipase has been described.[9] Thus treatment of (4) with the lipase in the presence of vinyl acetate afforded monoacetate (6) in 95% ee. Whereas treatment of (5) with lipase only gave compound (7) in 97% ee.

Similarly the biocatalytic desymmetrization of pentitol derivatives using a crude lipase extract from *Candida cylindracaei* and vinyl acetate has been reported.[10] For



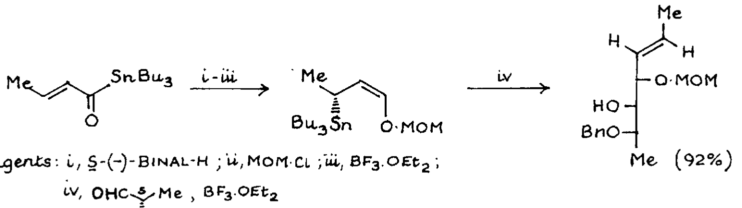




example the ribitol derivative (8) can be transformed into mono-acylated derivative (9) in > 95% ee. A high ee was also observed for the corresponding D-arabitol compound. In the case of xylitol and L-arabitol derivatives low selectivity was observed and it was concluded that the stereochemical arrangements of the substituents determined if the reaction was processed rapidly or slowly.

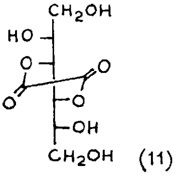
The preparation of D-arabitol derivatives (10) and (10a) by way of an aldol reaction between glyceraldehyde and tetronic acids has appeared.[11]

The preparation of alditol derivatives by the additions of enantioenriched (γ-alkoxyallyl) stannanes to α-alkoxyaldehydes has been reported (Scheme 1).[12]

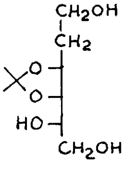


Scheme 1

1,2:5,6-Di-*O*-isopropylidene-D-mannitol has been transformed into the cyclic oxalate derivative (11) in a two-step process.[13] The 2-deoxy-L-*ribo*-hexitol derivative (12) has been prepared from 2,3-di-*O*-benzyl-L-glyceraldehyde as an intermediate in the preparation of a thienamycin synthon.[14]



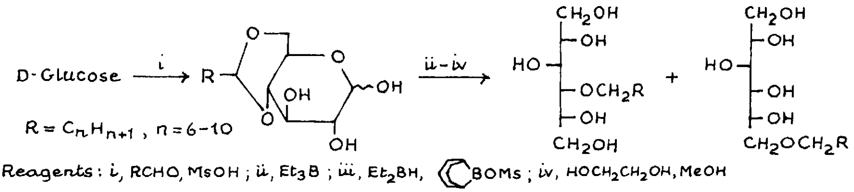
(11)



(12)

The preparation of amphiphilic carbohydrate-based mesogens that exhibit smectic

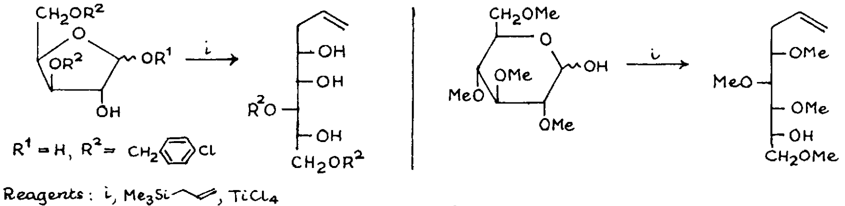
A liquid crystalline phases has been achieved (Scheme 2).[15]



Reagents: i, RCHO, MsOH; ii, Et_3B; iii, Et_2BH, BOMs; iv, $HOCH_2CH_2OH$, MeOH

Scheme 2

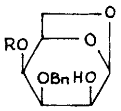
Glycosides and hemi-acetals can be *C*-alkylated with cleavage of the endocyclic C-O bond to give acyclic products by use of titanium tetrachloride catalysis (Scheme 3).[16]



Reagents: i, Me_3Si, $TiCl_4$

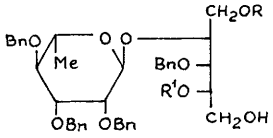
Scheme 3

The preparation of some glycosylated ribitols as useful building blocks for the synthesis of certain teichoic acids has been described.[17] The 1,6-anhydro-β-D-talopyranose (13), a key intermediate, is readily accessible from 1,6-anhydro-2,3-*O*-(S)-benzylidene-β-D-mannopyranose. Thus coupling of (13) with *S*-ethyl-2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside affords the L-ribitol derivative (14) after further processing. Also the 4-*O*-allyl derivative (15) is a suitable precursor of glycoside (16).



(13) R = Bn

(15) R =



(14) R = , $R^1 = Bn$

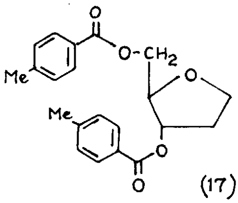
(16) R = Bn, $R^1 =$

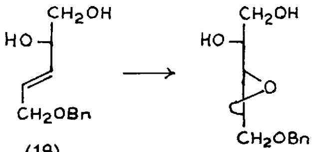
A review of the possible quantitative detection of mannitol by chelation with transition metal ions is mentioned in Chapter 17, the conformation of alditols in aqueous and non-aqueous solution is reported in Chapter 21, the cryoprotective effect of mannitol and D-glucitol on the denaturation of the enzyme catalase during the freeze drying process is covered in Chapter 2, the separation of alditols by ion exchange chromatography is mentioned in Chapter 23 and the isolation from two new *Streptomyces* strains of some secondary metabolites of L-rhodanose is covered in

Chapter 12.

1.2 Anhydro-Alditols. - The synthesis of a whole range of 1,5- and 1,4-anhydro-alditols and their inhibitory effects against glycosidases have been reported.[18] The preparation of 2,5-anhydro-3-deoxy-D-*arabino*-hexitol by hydrogenation of 2,5:3,4-dianhydro-D-allitol over Pearlman's catalyst has been described.[19] The selective chlorination of pentitols to afford 1,5-dichloro-1,5-dideoxy derivatives as well as mono- and di-chloro-1,4-anhydro derivatives has been reported.[20]

The preparation of the 1,4-anhydroalditol (17) from 1-chloro-2-deoxy-3,5-di-*p*-toluyl-D-*erythro*-pentosyl chloride as part of a programme towards the synthesis of "abasic" 2'-deoxy-ribonucleoside analogues which could readily be turned into the corresponding 5'-*O*-dimethoxytrityl-3'-*O*-β-cyanoethyl-*N,N*-di-isopropylamino-phosphoramidate monomers has been reported. These latter compounds can be transformed into homo-oligodeoxy-ribonucleotides and oligodeoxyribonucleotides.[21]

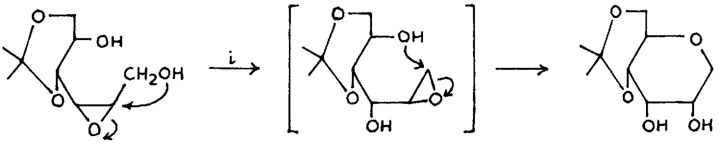

(17)


(18) (19)

The incorporation of deuterium into 1,5-anhydro-D-glucitol to afford [1-$^2H_1$], [3-$^2H_1$], [1-$^2H_2$], [6-$^2H_2$] and [5,6-$^2H_3$] derivatives has been reported.[22] (See Vol. 18, p.167 for an earlier communication).

The preparation of *syn*-epoxide (19) from alkene (18) by Sharpless epoxidation proceeds with inversion of the selectivity expected by the empirical rule established for simple allylic alcohols.[23]

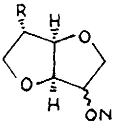
The preparation of 1,5-anhydro-4,6-*O*-isopropylidene-D-allitol by way of an unexpected 6-*endo* ring opening of an epoxide has been described (Scheme 4).[24]


Reagents: i, NaOH, Bu^{t}OH, Δ

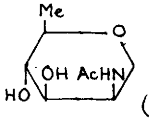
Scheme 4

A study on the formation of furan derivatives from polyols by heterogeneous catalysis over metals has been described. The use of Raney copper catalyst modified by mixing with aqueous solutions of metal (Ir, Rh, Ru, Pd, Pt, Au) will convert , for example, D-glucitol into 1,4:3,6-dianhydro-D-glucitol.[25]

The preparation of monodeoxydianhydrohexitol nitrates such as (20) have been reported as potential cardiovascular agents.[26]



(20) R = H,Cl



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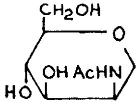


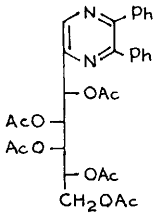
(22)

The preparation of some 2-acetamido-1,5-anhydro-2-deoxy-mannitol derivatives like (21) or (22) as potential inhibitors of sialic acid biosynthesis have been described.[27]

The conversion of xylitol into 1,3:4,6-dianhydro-xylitol using anionic ruthenium iodocarbonyl complexes has appeared.[28]

The transformation of β-glucofuranosyl isonitriles into 1,4-anhydroallitol derivatives is covered in Chapter 10, and the dehydration of some hexitols affording complex mixtures of 1,4-, 3,6-, 1,5- and 1,6-monoanhydrohexitols as well as 1,5:3,6-dianhydro products is described in Chapter 5.

1.3 Amino- and Imino-Alditols.- The synthesis of 1,2-diamino-dideoxy-D-*glycero*-L-*manno*- and D-*glycero*-L-*gluco*-heptitol and their conversion into the same pyrazine (23) on reaction with benzil followed by acetylation and oxidation has been reported.[29]

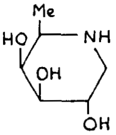


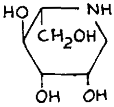
(23)

Glucose has been shown to be the biosynthetic precursor of deoxynojirimycin and deoxymannnojirimycin in *Streptomyces subrutilus*.[30]

The reaction of dihydroxyacetone phosphate (DHAP) with racemic or (R)-3-azido-2-hydroxypropanol under the influence of rhamnulose-1-phosphate aldolase or fuculose-1-phosphate aldolase afforded azidoketose intermediates which were converted by way of palladium-mediated reductive amination into a number of novel compounds including 1,6-dideoxy-D-galactojirimycin (24), 1,6-dideoxy-L-altojirimycin (25), 1-deoxy-D-talojirimycin (26), 1-deoxy-L-mannojirimycin (27) and 1-deoxy-L-rhamnojirimycin (28).[31]

Under similar conditions but using fructose-1,6-diphosphate aldolase, pyrrolidine


(24)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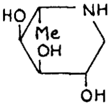
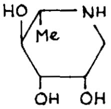
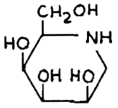
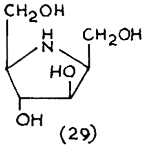
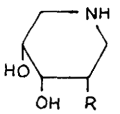

(25)

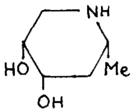

(28)


(26)

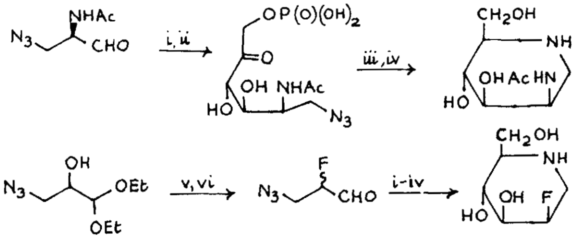

(29)

(29), is formed, which is the 5-epimer of the natural product 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) and a potent inhibitor of several glycosidases. The preparation of the novel iminoalditols (30) and (31) in a similar manner using 2-deoxyribose-5-phosphate aldolase has also been described.[32]


(30) R = H, Me


(31)

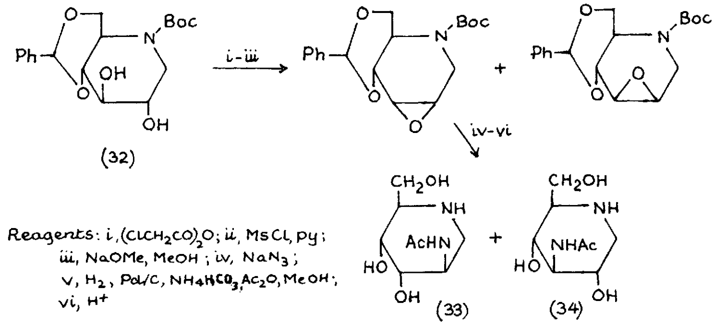
The preparation of some 2-acetamido and 2-fluoro-2-deoxy-1,5-iminoalditols as glucosidase inhibitors has been reported (Scheme 5). A molecular modelling study was also performed in order to understand the structure-inhibition relationship of some monosaccharide-based *exo*-glycosidase inhibitors.[33]


Reagents: i, Fructose-1,6-diphosphate aldolase; ii, DHAP; iii, Phosphatase; iv, H_2, Pd/C; v, DAST; vi, H^+

Scheme 5

The use of rabbit muscle aldolase in the preparation of 1,4-dideoxy-1,4-imino-D-mannitol (DMDP) has been described.[34] For similar enzyme-catalysed reactions see Vol. 24, p.194, Vol. 23, p.180 and Vol. 22, p.180.

Deoxynojirimycin has been used as starting material for the preparation of a range of *N*-acetylamino-1,5-dideoxy-1,5-imino alditols.[35] Thus the former was converted into the partially protected derivative (32) by standard procedures and further elaborated into the key epoxides as shown in Scheme 6. Conversion of one of these epoxides, for example, leads to the imino alditols (33) and (34) as shown.



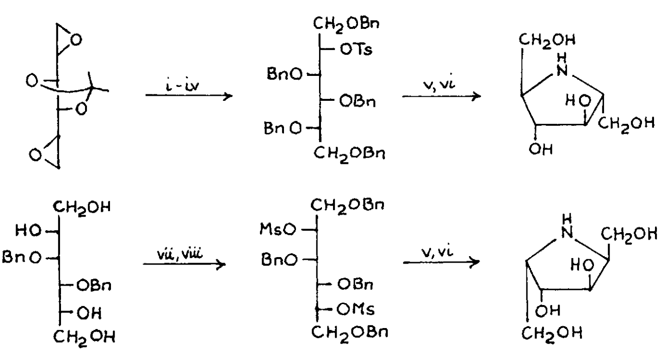
Reagents: i, $(ClCH_2CO)_2O$; ii, MsCl, py; iii, NaOMe, MeOH; iv, NaN_3; v, H_2, Pd/C, NH_4HCO_3, Ac_2O, MeOH; vi, H^+

Scheme 6

A short practical synthesis of 1-deoxynojirimycin from L-sorbose that requires only one protection-deprotection step has been reported.[36]

The selective functionalization of the C-2 hydroxyl group of *N*-carbobenzyloxy-4,6-*O*-benzylidine-1-deoxynojirimycin by use of dibutyl stannylene derivatization of the C-2 and C-3 hydroxyl groups has been achieved.[37] By this method the 2-*O*-benzoyl and 2-*O*-tosyl derivatives were made.

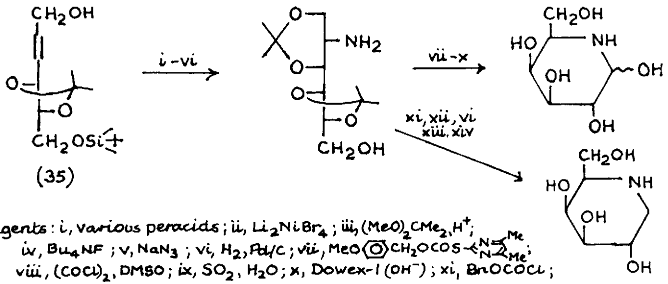
The synthesis of 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) and 2,5-dideoxy-2,5-imino-L-iditol from D-mannitol by way of the known 1,2:5,6-dianhydro-3,4-*O*-isopropylidine-L-iditol or 3,4-di-*O*-benzyl-D-mannitol is outlined in Scheme 7.[38]



Reagents: i, NaH, BnOH; ii, TsCl, DMAP; iii, TFA, H_2O; iv, $CCl_3C(OBn)=NH$, CF_3SO_3H; v, $BnNH_2$; vi, H_2, Pd, AcOH; vii, Bu_2SnO, BnBr; viii, MsCl, Et_3N

Scheme 7

The preparation of galactostatin and 1-deoxygalactostatin from the known allylic alcohol (35) (*J. Org. Chem.*, 1987, *52*, 3337) has been achieved (Scheme 8).[39]

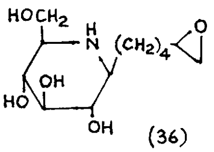


(35)

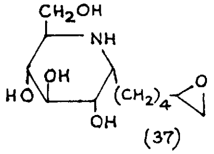
Reagents: i, various peracids; ii, Li$_2$NiBr$_4$; iii, (MeO)$_2$CMe$_2$,H$^+$; iv, Bu$_4$NF; v, NaN$_3$; vi, H$_2$,Pd/C; vii, $MeOC_6H_4CH_2OCOS\text{-}C_4HN_2Me_2$; viii, (COCl)$_2$, DMSO; ix, SO$_2$, H$_2$O; x, Dowex-1 (OH$^-$); xi, BnOCOCl; xii, MsCl,Et$_3$N; xiii, Et$_3$N; xiv, HCl.

Scheme 8

The preparation of 1-(ω-epoxyalkyl)-1-deoxynojirimycins (36) and (37) has been achieved from 2,3,4-tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-hex-5-enose.[40]

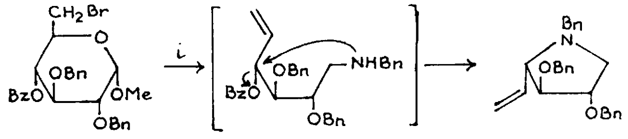


(36)



(37)

A short homochiral synthesis of substituted vinyl pyrrolidines by a reductive ring opening-reductive amination sequence, followed by spontaneous displacement of benzoate has been reported (Scheme 9).[41]



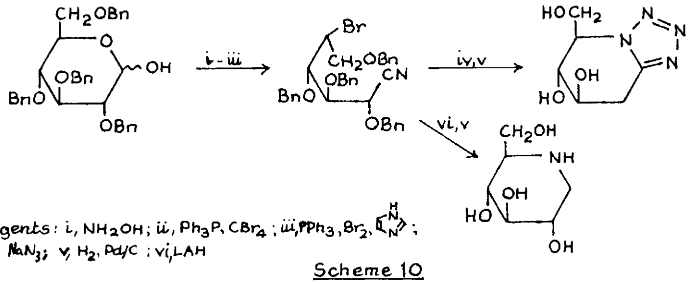
Reagents: i, Zn, NaBH$_3$CN, BnNH$_2$

Scheme 9

The synthesis of a glucose-derived tetrazole as a new β-glucosidase inhibitor as well as a synthesis of deoxynojirimycin have been reported (Scheme 10).[42]

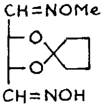
The reductive amination of 2,3,5-tri-*O*-benzyl-D-arabinofuranose with benzylamine followed by mesylation and catalytic hydrogenolysis afforded 1,4-dideoxy-1,4-imino-L-xylitol.[43]

Several examples of the preparation of spin-labelled sugar analogues are reported.[44] Thus for example, conversion of the known dioxime (38) (*J. Carb. Chem.*, 1990, *9*, 823) into the *meso-N*-hydroxypyrrolidine (39) with sodium cyanoborohydride can be achieved. The products undergo aerial oxidation to give nitroxide radicals. (The structures of some of the radicals were studied by ESR spectroscopy.) On the other hand, oxidation of (39) with mercuric oxide affords a nitrone from which β-*C*-glycosides can be obtained.



Reagents: i, NH_2OH; ii, Ph_3P, CBr_4; iii, PPh_3, Br_2, ; iv, NaN_3; v, H_2, Pd/C; vi, LAH

Scheme 10



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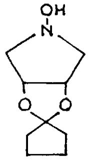


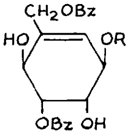
(39)

The synthesis of amino-alditol derivatives of naturally occurring hydrolysable tannins is mentioned in Chapter 7 and the preparation of some C-6 and C-7 analogues of *N*-acetyl-6-amino-2,6-dideoxyneuraminic acid as well as the isolation and synthesis of the fungal metabolite nectrisine are covered in Chapter 9. The synthesis of 4-*O*-(β-D-galactopyranosyl) derivatives of deoxynojirimycin can be found in Chapter 3 and castanospermine derivatives are covered in Chapter 24.

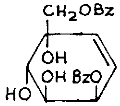
2 Cyclitols

A review has appeared on the carbasugars (see Chapter 1).

Three new cyclitols named piperenol A (40) and its acetate (41) and piperenol B (42) have been isolated from *Piper cubels* and *Piper clarkii*.[45]

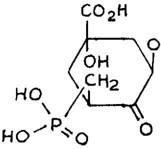


(40) R = H
(41) R = Ac

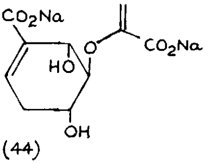


(42)

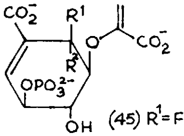
The isolation and characterization of several new isomers of (-) quinic acid, obtained by boiling quinic acid in a mixture of acetic and sulfuric acids in order to obtain reference materials for identifying components of roasted coffee, has been achieved.[46] Quinic acid has also been used in a short synthesis of compound (43), a phosphonate analogue of a reactive intermediate formed during 3-dehydroquinate synthase (DHQ synthase)-catalysed conversion of 3-deoxy-D-*arabino*-heptulosonic acid-7-phosphate (DHAP) to 3-dehydroquinate (DHQ), as an irreversible inhibitor of DHQ synthase.[47]



(43)



(44)

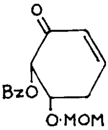


(45) R^1=F, R^2=H
(46) R^1=H, R^2=F

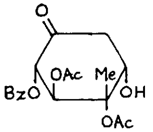
The synthesis of compound (44) as a potential transition-state analogue inhibitor of isochorismate synthase (IS) has been reported.[48] Compounds (45) and (46) have been synthesized from the known 6-fluoroshikimic acids (*J. Chem. Soc., Chem. Commun.*, 1989, 1386) by treatment first with shikimate kinase then 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase and shown to be competitive inhibitors of chorismate synthase.[49]

The synthesis of methyl 1,5-di-*O*-acetyl-3,4-bis-*O*-(bicyclophosphoroanylato) quinate and a conformational analysis by NMR have been performed.[50]

The preparation of some novel inosenoses e.g. (47) by way of the Ferrier reaction on 6-deoxy-hex-5-enopyranosides involving catalytic quantities of mercury II salts in a neutral solvent has been reported.[51] It was shown that mercury(II) trifluoroacetate had the highest activity.



(47)



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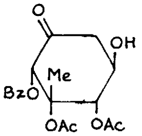

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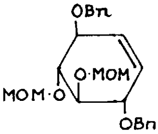
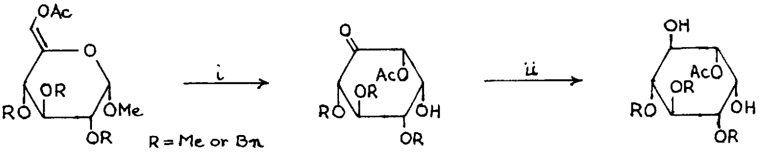


(50)

The Ferrier reaction has also been used to prepare some novel methyl-branched tetrahydroxycyclohexanone derivatives such as (48) and (49).[52] Further applications of the same reaction has led to the preparation of 2,3,6-tri-*O*-benzyl-D-*myo*-inositol from D-glucose, *via* the intermediate C_2-symmetric cyclohexene (50)[53] and to a biomimetic synthesis of D-*myo*-inositol derivatives as illustrated in Scheme 11.[54]

A high yielding synthesis of *chiro*- and *myo*-inositols from methyl-α-D-glucopyranoside which are useful for the preparation of glycosyl phosphatidyl inositol derivatives has been reported.[55]

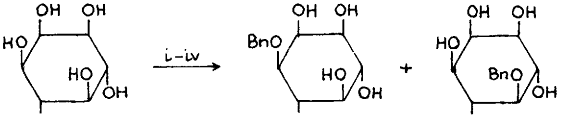


Reagents: i, $Hg(O_2CCF_3)_2$, Me_2CO; ii, $NaBH(OAc)_3$

Scheme 11

Three reports have appeared concerned with the liquid crystalline behaviour of some inositol ethers. Thus starting from *myo*-inositol and using standard procedures, various partially protected derivatives of general formula C_nH_{2n+1} (n=4-8) to fully protected derivatives where n=6 were prepared.[56] Various ether derivatives with C_4 to C_8 chains of *myo*- and *scyllo*-inositols were prepared in a similar way.[57] Ester derivatives of *myo*- and *scyllo*-inositols as well as some ether derivatives of cyclopentanes are disclosed.[58]

Myo-inositol can be per-borylated with triethylborane then regioselectively benzylated by way of an *O*-stannylated intermediate (Scheme 12).[59] Selectivities were also studied with allyl bromide and benzoyl chloride together with various proportions of the reagent.



Reagents: i, Et_3B; ii, $MeCO CH=\overset{OSnBu^n_3}{C}Me$; iii, BnBr, Bu_4NBr; iv, MeOH

Scheme 12

The preparations of racemic 1,3,4,6-tetra-*O*-allyl and 1,3,4,5-tetra-*O*-allyl *myo*-inositol from *myo*-inositol, excess dibutyltin oxide and allyl bromide have been reported.[60] The latter compound was resolved *via* its (-)camphanate ester. The 1,3,4-tri-*O*-allyl *myo*-inositol was also made by using three equivalents of dibutyltin oxide.

Full details on the synthesis of *pseudo*-β-D-mannopyranose and *pseudo*-β-D-fructopyranose from quinic acid have appeared[61] (see Vol. 24, p.200). Also reported is the synthesis of *pseudo*-α-D-glucopyranose from quinic acid in which none of the original chiral centres are retained.[62]

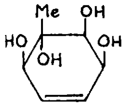
The preparation of 2-deoxy-2-fluoro-*myo*-inositol and 1-deoxy-1-fluoro-*scyllo*-inositol together with 2-deoxy-2-fluoro-*myo*-[2-^{3}H]inositol and 1-deoxy-1-fluoro-*scyllo*-

[1-^{3}H]inositol has been reported from 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol as potential inhibitors of the phosphoinositide cycle.[63]

Several papers on the transformation of benzene and substituted benzenes to *cis*-diols using *Pseudomonas putida* have appeared. A summary on the preparation of cyclitols and natural products such as (+)-pinitol, (+)-conduritol F as well as D-(-)-*myo*-inositol-1- and 1,4,5-tri-phosphate from benzene have been reported.[64] Standard chemical transformations from benzene *cis*-diol involving resolution of an alcohol intermediate by way of (+)-sec phenylmethyl ethers led to a preparation of (+)-conduritol F and its enantiomer[65], whereas resolution of an alcohol intermediate using lipase-catalysed acetylation afforded (+)- and (-)-conduritol C.[66]

Pseudomonas putida oxidation of halogenobenzenes has led to the preparations of (+)-conduritol E and (-)-conduritol F,[67,68] (-)-conduritol C,[69] (+)-conduritol C,[70] dihydroconduramine and conduramine A-1 tetraacetate[71] and conduramine A-1.[68]

Similar microbial oxidation of toluene and subsequent transformations led to the formation of *C*-methylconduritol F (51) and finally to the *C*-methylycyclitol, (-)-laminitol (52).[72]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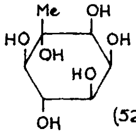

(52)

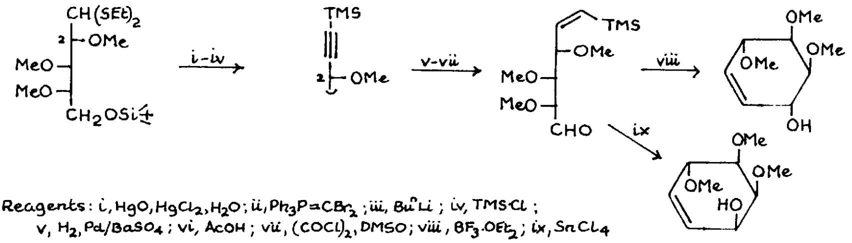
The preparations of (-)-1L-2,4-diamino-2,3,4-trideoxy-*allo*-inositol and (-)-1L-2,4-diamino-2,4-dideoxy-*chiro*-inositol by the hetero Diels-Alder reaction of *O*-isopropylidene protected *cis*-cyclohexa-3,5-diene-1,2-diol with 2,3:5,6-di-*O*-isopropylidene-1-nitroso-α-D-mannofuranosyl chloride have been reported.[73] (See Vol. 24, p.204, Ref. 79 and 83 and p.136, Ref.86 for similar work.)

The selective cleavage of a methyl ether in the presence of cyclohexylidene acetals with aluminium trichloride/tetra-*n*-butylammonium iodide led to the synthesis of (-)-conduritol F from L-quebrachitol.[74] (See Vol. 24, p.202 for the use of aluminium trichloride-sodium iodide cleavage of methyl ethers.) Also described is the first reported synthesis of (+)-conduritol B from an intermediate readily available from quebrachitol (see Vol. 24, p.205, Ref. 90).

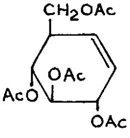
A strategy for the synthesis of conduritols and related cyclitols by way of a stereodivergent vinylsilane-aldehyde cyclization has been reported (Scheme 13).[75] The stereochemistry of the cyclization was rationalized in terms of boron trifluoroetherate coordination control and tin(IV) chloride chelation control.

The preparation of 1-D-1,2-anhydro-*myo*-inositol (conduritol B epoxide) as a potential glycosidase inhibitor has been reported.[76]

The preparation of the branched-chain cyclitol (53) by the addition of the carbanion derived from Meldrum's acid to conduritol B peracetate mediated by palladium(0) has been reported.[77] The compound was required for glycosidase inhibition studies.


Reagents: i, HgO, $HgCl_2$, H_2O; ii, $Ph_3P=CBr_2$; iii, Bu^nLi; iv, TMSCl; v, H_2, $Pd/BaSO_4$; vi, AcOH; vii, $(COCl)_2$, DMSO; viii, $BF_3.OEt_2$; ix, $SnCl_4$

Scheme 13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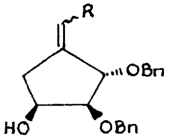
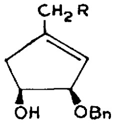

(54)

R = H, Me, TMS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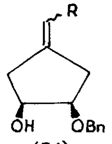
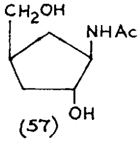

(56)

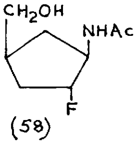
The reaction of 1,2,6-trideoxy-3,4-di-*O*-benzyl-6-iodo-L-*arabino*-hex-1-ynitol with tri-*n*-butyltin hydride afforded the cyclopentene derivatives (54)-(56).[78]

A highly stereoselective synthesis of racemic amino-bromo-cyclitols from the Diels-Alder adduct derived by reaction of furan with cyanovinyl acetate (Vol. 23, p.183) has been reported.[79]

The preparation of the cyclopentane derivatives (57) and (58) from *N*-(4-methoxybenzyl)2-azabicyclo[2.2.1]hept-5-en-3-one have been described.[80]

The synthesis of the amine triol (59) has been described and used to demonstrate that its a biosynthetic precursor of aristeromycin in *Streptomyces citricolor*.[81]


(57)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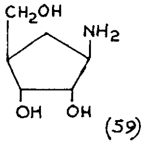
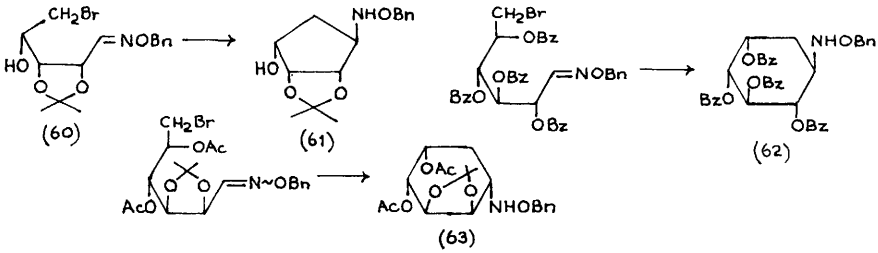

(59)

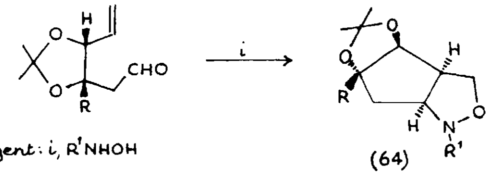
The 5-membered amino cyclitol (61) could be prepared by radical induced cyclization of bromoxime (60).[82] In a similar way the 6-membered cyclitols (62) and (63) were prepared.[83]

The preparation of some *N*-amino acid derivatives of 2-deoxystreptamine and neamine[84] and the preparation of cyclopentane-based isoxazolidines (64) by a nitrone-alkene cycloaddition have been reported.[85]

The nitrone, oxime and nitrile oxide cycloadditions to D-*ido*-hept-6-enose and its D-*gulo*-isomer have been used in the preparation of aminocylitols (65) and (66) as

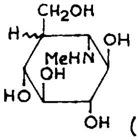


(60) (61) (62) (63)

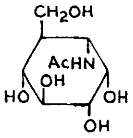


Reagent: i, R^{1}NHOH

(64)



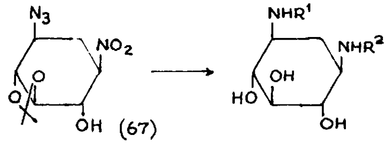
(65)



(66)

potential glycosidase inhibitors.[86]

Two constituent components of the amino cyclitol antibiotics hygromycin B and destomycin A, *ie.* (+)-(68) and (-)-(69), known as hyosamine have been synthesized from the common precursor (67), which is readily accessible from D-mannose.[87]

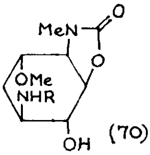


(67)

(68) R^1= Me, R^2=H

(69) R^1= H, R^2= Me

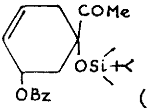
The use of 2,2,2-trifluoro-1,1-diphenylethane (TDE) sulfenyl group for the protection of amines has been demonstrated in the preparation of compound (70). The protecting group can be removed with sodium in liquid ammonia or with hydrochloric acid.[88]



(70) R = $Ph_2\overset{CF_3}{C}$-S-+

D-Quinic acid has been converted into the cyclitol derivative (71) a precursor in a synthesis of daunomycinone.[89]

The preparation of an active site-directed inhibitor (72) of a β-D-galactosidase (E. Coli) which is potentially capable of reacting at two different places in the active site of the enzyme by virtue of a reactive vinyl oxirane and diazirino functional groups has been reported.[90]



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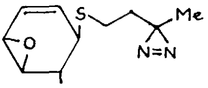
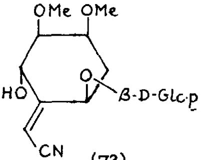


(72)

A number of *O*-tosyl and *O*-mesyl derivatives of L-quebrachitol have been prepared and displaced with azide followed by hydrogenolysis and acetylation to give a range of *O*-methylinosamine and *O*-methylinosadiamine derivatives.[91]

The first total synthesis of simmondsin (73) a naturally occurring cyanoglucoside has been achieved from L-quebrachitol and D-glucose.[92] The key steps involve the deoxygenation of epoxide (74) with lithium aluminium hydride, cyanomethylation of the ketone (75) by Horner-Emmons alkenylation (with separation of Z and E isomers) and glycosidation of alcohol (76) with 2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl trichloroacetimidate.



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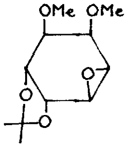

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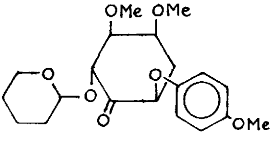

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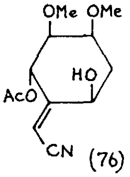
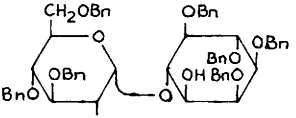


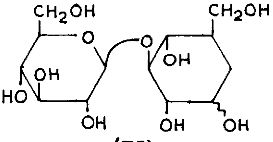
(76)

The synthesis of the partially protected 2-azido-2-deoxy-D-glucosyl-D-*myo*-inositol (77) as a precursor of a potential insulin mimetic and membrane protein anchoring site has been described.[93]

The synthesis of *pseudo*-disaccharides such as laminarabinose (78) by coupling the known (*Carbohydr. Res.*, 1985, *136*, 77) 5α-*carba*-1,2:4,6-di-*O*-isopropylidene laminarabinose-α or β-D,L-glucopyranose with 2,3,4,6-tetra-*O*-acetyl-α-D-



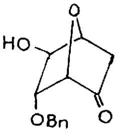
(77)



(78)

glucopyranosyl bromide followed by de-isopropylidenation and analysis as its peracetate has been reported.[94]

The use of Vogel's "naked sugar" approach to the synthesis of *myo*-inositol derivative (80) from bicyclic ketone (79) and the use of the latter in the preparation of glycoside (81) has been reported.[95]



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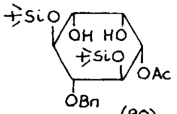
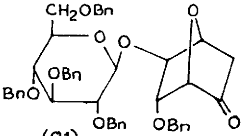


(80)



(81)

The preparation of 1-D-1-*O*-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-*myo*-inositol along with the 1L-1-*O*-, 2-*O*-, 1D,L-4-*O*- and 5-*O*- derivatives was carried out in order to confirm the structure of a compound isolated from human pregnancy urine.[96] However, none of the products had ^1H NMR spectra corresponding to those of the isolate.

The synthesis of cyclophellitol and analogues as well as Validamycins C, D and F is mentioned in Chapter 19, the coupling of some of the products derived from NBS treatment of Validoxylamine A and trehalostatin can also be found in Chapter 19, the preparation of carbocyclic nucleosides is mentioned in Chapter 20 and the synthesis of oligoglucosyl-inositols in Chapter 4, and the preparation of some highly functionalized cyclopentanes from carbohydrates is covered in Chapter 24.

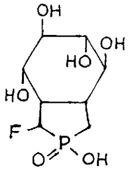
A review on the preparation and separation of inositol tetrakisphosphates and the establishment of enantiomeric configuration by use of L-iditol dehydrogenase has appeared.[97] The synthesis and biological evaluation of inositol derivatives as inhibitors of phospholipase C (PLC) has been reviewed.[98] A review on the chemistry, preparation and enzymatic reactions of inositol phosphates[99] and a review on the biochemistry, stereochemistry and nomenclature of inositol phosphates [100] has also been reported. A part review on phosphonate analogues of *myo*-inositol triphosphate has appeared.[101]

Several symposia have been held on the synthesis of inositol polyphosphates as follows: those derived from quinic acid;[102] novel routes to inositol phosphates using *Pseudomonas putida* oxidation of arenes;[103] new *myo*-inositol derivatives containing phosphate, sulfate and sulfonamido groups;[104] synthesis and calcium releasing activity of some polyphosphates;[105] synthesis of *myo*-inositol 1,4,5-triphosphate (Ins (1,4,5)P$_3$) and *myo*-inositol 1,3,4,5-tetrakisphosphate *via* silyl ethers;[106] preparation of 1,4,5-, 2,4,5-, 1,3,4-, 1,3,4,5-, 1,3,4,6- and 2-deoxy 1,4,5-D-*myo*-inositol phosphates;[107] optically active *myo*-inositol derivatives as intermediates for the preparation of inositol phosphates.[108]

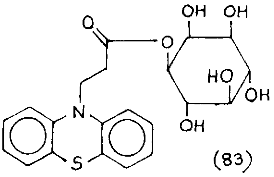
A paper dealing with the mechanistic aspects of inositol monophosphatase, concluding that it differs from other phosphatases in its ability to bind simultaneously both phosphoryl group acceptor molecules, inositol and water to form a ternary complex, has appeared.[109]

The resolution of D,L-2-deoxy-2,2-difluoro-*myo*-inositol (1,4,5)-triphosphate with S(-)-camphanic acid chloride has been described.[110] The D-enantiomer is a good analogue of Ins(1,4,5)P$_3$ and a substrate for Ins(1,4,5)P$_3$-5-phosphatase and 3-kinase. The L-enantiomer is an inhibitor of Ins(1,4,5)P$_3$-5-phosphatase.

The fluorophosphonate analogue (82) of *myo*-inositol 1,2-cyclic phosphate has been synthesized in order to study the biological role of the latter.[111]



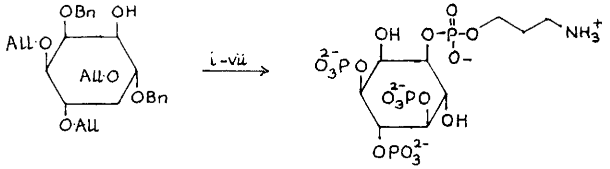
(82)



(83)

The synthesis of *myo*-inositol derivative (83) by esterification of racemic 2,3,4,5,6-pentabenzyl *myo*-inositol as a potential inhibitor of PLC has been reported.[112]

The synthesis of a phosphodiester derivative of D,L-*myo*-inositol 1,3,4,5-tetraphosphate has been described (Scheme 14).[113] The ester was subsequently linked *via* the amine to an affinity resin and a photoaffinity label in order to probe the IP$_4$ receptor.

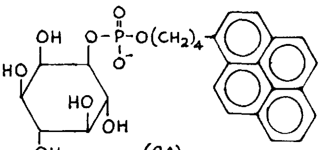


Reagents: i, Pr$^i_2$NP(H)O(CH$_2$)$_3$NHCbz ; ii, MCPBA ; iii, (Ph$_3$P)$_3$RhCl; iv, HCl ; v,(BnO)$_2$PNPr$^i_2$; vi, MCPBA , vii, H$_2$, Pd/C

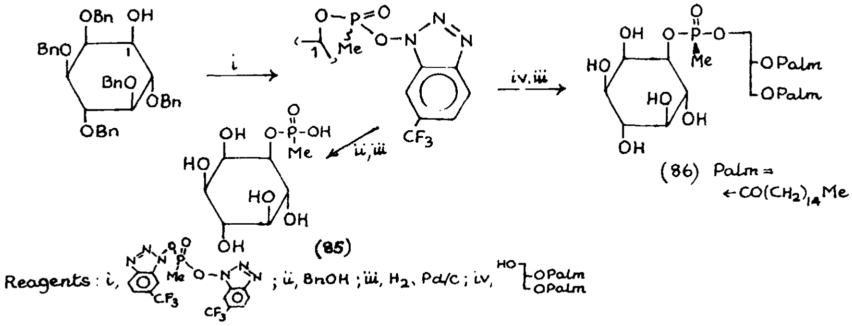
Scheme 14

Also reported by the same authors is a chiral synthesis of the P-1-tethered IP$_4$ compound shown in Scheme 14 in which the cyclitol ring is prepared by a Ferrier reaction of an enol acetate derivative derived from D-glucose in a similar way to that described in Scheme 11 of this chapter.[114] Further, the preparation of tethered phytic acid derivatives to probe the IP_6 and IP_5 receptors has been reported[115] together with the preparation of tethered derivatives of $Ins(1,4,5)P_3$.[116]

The preparation of a photoaffinity probe possessing biotinyl and azidobenzoyl moieties of Ins(1,4,5)P3 has been described which has similar biological function and potency to IP_3 with respect to inhibition of $[^3H]IP_3$-5-phosphatase as well as the ability to photolyse at the IP_3 recognizing domain of the protein.[117] The synthesis of the *myo*-inositol derivative (84) as a fluorescent substrate for assaying phosphatidylinositol-specific PLC has been reported.[118]


(84)

The syntheses of a methylphosphonate analogue (86) of phosphatidylinositol together with its diastereomers as well as the methylphosphonate analogue (85) of *myo*-inositol-1-phosphate using the chiral *myo*-inositol derivative shown in Scheme 15 has been reported.[119]

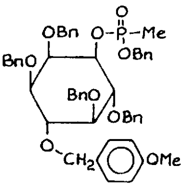


Scheme 15

Also reported is the synthesis of the phosphonate analogue (89) in which the key step involves the treatment of methylphosphonate (87) with n-butyl lithium then triflate (88).[120]

Also reported by some of the same group is the preparation of the racemic 5-phosphonate analogues (90) and (91) of *myo*-inositol 1,4,5-triphosphate[121] and phosphonate derivatives (92) and (93).[122]

The synthesis of disaccharides related to glucosyl phosphatidyl inositol anchors



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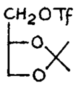

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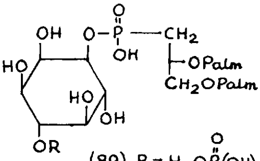
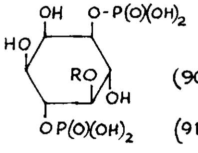
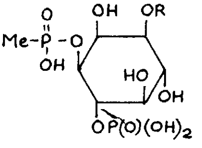


(89) R = H, $O\overset{O}{\overset{\|}{P}}(OH)_2$



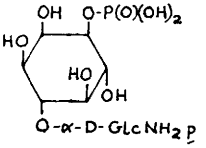
(90) R = $-\overset{O}{\overset{\|}{\underset{OH}{P}}}-Me$

(91) R = $-\overset{O}{\overset{\|}{\underset{OH}{P}}}-CHF_2$

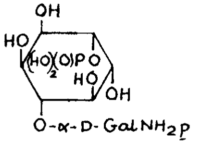


(92) R = H

(93) R = $P(O)(OH)_2$



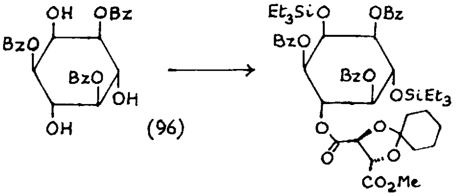
(94)



(95)

of membrane proteins (94) and (95) have been described.[123]

The synthesis of chiral *myo*-inositol 1,3,4,5-tetrakis phosphate in which the key step involved an enantioselective tartaroylation followed by *O*-silylation of the racemic 1,3,5-tribenzoate (96) to afford compound (97) has been reported.[124]



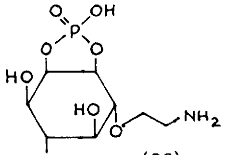
(96) (97)

The preparation of L-*chiro*-inositol 2,3,5-triphosphate from L-quebrachitol has been reported.[125] The synthesis uses the commercially available phosphitylating agent diethylchlorophosphine for the first time in inositol chemistry.

The synthesis of *myo*-inositol 1,4,5-triphosphate has been achieved from *myo*-inositol derivatives by formation of D-mannose orthoester derivatives.[126]

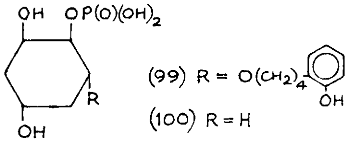
The preparation of the racemic cyclic phosphate (98) as a model for the putative insulin second messenger has been achieved.[127]

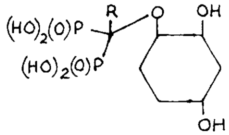
A short synthesis of D-*myo*-inositol-1-phosphate from *myo*-inositol involving resolution by way of D-camphanate acetal formation where the required diastereomer precipitates out of the reaction mixture has been reported.[128] In a similar way the same group has achieved a synthesis of D-*myo*-inositol-1,4,5-triphosphate and 1,4-triphosphate.[129]


(98)

A new route to D- and L-*myo*-inositol 2,4,5-triphosphates from D- and L-*chiro*-inositol derivatives by inversion of an axial OH group has been achieved.[130] (See Vol. 23, Ref. 69, p.186 for earlier work.) Also reported is a synthesis of D-*chiro*-inositol 1,3,4-triphosphate.

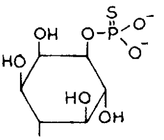
6α-Substituted-2β-4α-dihydroxy-1β-phosphoryloxycyclohexanes, e.g. (99) have been synthesized and shown to be more potent than the lead compound (100) at inhibiting inositol monophosphatase[131] (see Vol. 24, p.205, Ref 92).

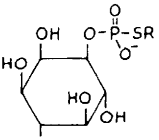

(99) R = $O(CH_2)_4$
(100) R = H


R = H, Me
(101)

The methylene bisphosphonic acid derivatives (101) were also prepared and found to be potent inhibitors of *myo*-inositol monophosphatase.[132]

The enantiomerically pure inositol 1-phosphorothioate (102) has been prepared from racemic 2,3,4,5,6-pentakis-*O*-benzyl-*myo*-inositol using resolution *via* camphanate esters.[133] Direct preparation of (102) from 6-*O*-phosphorothiono-D-glucose using inositol synthase was not successful. The same authors have reported similar work elsewhere.[134]

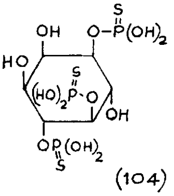

(102)

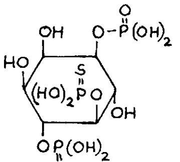

(103) R = $C_{16}H_{33}$

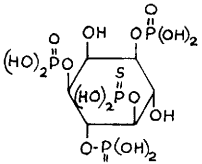
The preparation of the thiophosphate derivative (103) as a substrate for PI-PLC has been reported.[135]

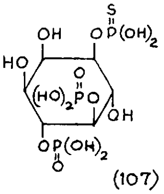
The preparation of racemic *myo*-inositol phosphorothioates (104)-(107) has been described.[136] Compounds (104), (105) and (107) were substrates for Ins(1,4,5)P_3-3-kinase whereas (106) was a competitive inhibitor.

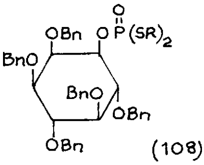
The synthesis of racemic *myo*-inositol phosphorodithioate esters (108) as well as some phosphorothioate and phosphorodithioate analogues of dinucleotides has been reported.[137]


(104)


(105)


(106)


(107)


(108) R = Bn or Ph.

The preparations of the 1,2-dinitrate, 1-nitrate, 2-nitrate and 2,5-dinitrate *myo*-inositol derivatives have been described.[138] The preparation of radiolabelled inositol-1-phosphate by way of sequential enzyme reactions on radiolabelled glucose has been reported.[139]

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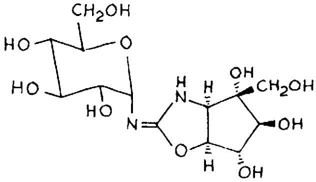
19

Antibiotics

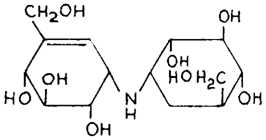
1 Amino-Glycoside Antibiotics

A new trehalose inhibitor, the pseudo-disaccharide trehazolin (1), has been obtained from Micromonospora sp. SANK 62390.[1]

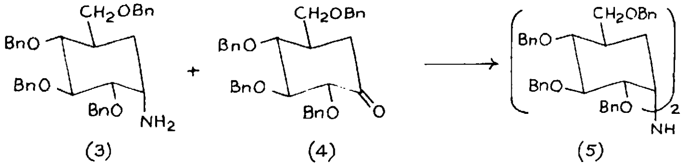
The total synthesis of (+)-validamycins C,D, and F from validoxylamine A precursors has been described.[2] All eight possible mono-β-D-glucosides of validoxylamine A (2) have been prepared, using a combination of enzymic and chemical procedures.[3] The reaction of validoxylamine A or its per-O-benzylated derivative with NBS under different conditions led to mixtures of amino- and keto-cyclitol derivatives, the two products (3) and (4) then being used to prepare the dimeric amino-cyclitol (5) which is a potent trehalose inhibitor (Scheme 1).[4]



(1)



(2)

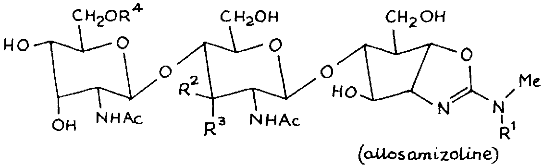


Scheme 1

New representatives of the allosamidin class of yeast chitinase inhibitors (6) have been reported, isolated from the mycelium of S. sp. 684.[5] A synthesis of allosamidin is mentioned in Chapter 3. Other papers describe the synthesis of the allosamidin component (-)-allosamizoline from D-glucosamine.[6,7]

A review of synthetic approaches to antibiotics mentions those towards lincosamine from carbohydrate and non-carbohydrate precursors.[8]

Modifications to kanamycin antibiotics include the preparation of 3'-deoxy-3'-fluorokanamycin A and its 3,4'-dideoxy-3'-fluoro



(6) R^1 = H or Me
R^2, R^3 = H, OH
R^4 = Me or H

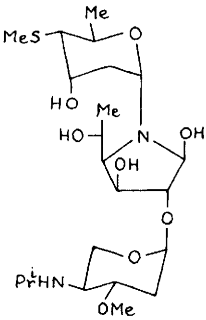
analogue,[9] a series of 6"-substituted kanamycin B derivatives prepared from its 6"-triisopropylbenzenesulphonyl ester which can be selectively prepared in good yield,[10] and derivatives prepared from these 6"-modified compounds by further modification at C-1 to include an hydroxylmethyl group.[11] Complete ^1H and ^{13}C n.m.r. assignments have been made for kanamycin A and B.[12] Butirosin derivatives with 5"-amidino- and 5"-guanidino- substituents have been prepared, the latter being more biologically active than the 5"-hydroxy parents.[13]

Nitroguaiacol derivatives of streptomycin have been synthesized by modification of the branched-carbon function in the streptose unit, the products being photoreactive compounds useful in studying the mode of action of the antibiotic.[14]

A simple and selective method for detecting new aminoglycoside antibiotics from actinomycete strains has been described.[15]

A synthesis of the core trisaccharide (7) of esperamycin has been described, using glycal precursors for each of the subunits.[16]

Derivatives of 2-deoxystreptamine and neamine are mentioned in Chapter 18.



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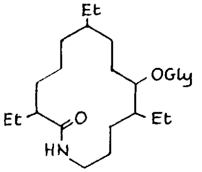
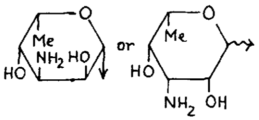
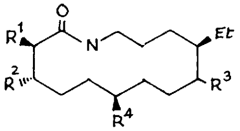
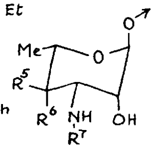


(8) Gly =





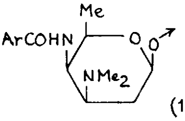
(9) R^1 = Me, CH(OH)Me, or Et
R^4 = Me or Et
R^2 or R^3 =
R^5, R^6 = H, OH
R^7 = H or $CONH(CH_2)_2Ph$



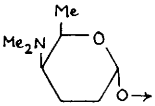
2 Macrolide Antibiotics

A new class of antifungal agents, the macrolactams A and B (8), have been isolated from Actinomadura vulgaris, and contain either mycosamine or the isomeric talo-aminosugar (unknown anomeric configuration).[17] These are closely related to the fluvimicins, antibiotics active against influenza virus, and isolated from a number of unidentified actinomycete strains, which are amino-glycosides of tridecane lactams whose structures are summarized by (9).[18] A following paper characterizes fluvimicin A_1 as the α-L-talopyranosyl isomer (R^1=Me, R^2=sugar, R^3=H, R^4=Me,R^5=H),[18a]

Viranamycins A and B are new 18-membered macrolide antibiotics which contain monosaccharide substituents; viranamycin B contains 4-O-carbamoyl-2,6-dideoxy-β-arabino-hexopyranoside.[19] Another new macrolide antibiotic macrolide antibiotic contains the novel diaminohexopyranose (10).[20] New spiroketal 24-membered macrolide antibiotics, dunaimycins, contain the glycosidically-linked tetradeoxy-aminosugar (11).[21]



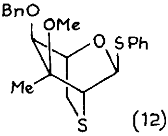
(10)



(11)

Avermectins and milbemycins have been reviewed.[22,23] A total synthesis of avermectin $B1_a$ has been carried out from non-carbohydrate precursors, using a 2-hydroxypropanal derivative to synthesize the oleandrose unit.[24] Avermectin analogues having spacer units between the glycone and aglycone are mentioned in Chapter 3.

A total synthesis of erythromycin A involved use of the thioglycoside of the anhydro-thio sugar (12) which allowed easy glycosylation of the 3-hydroxy group on the macrolide ring; desulphurization then gave the required cladinose glycoside.[25]



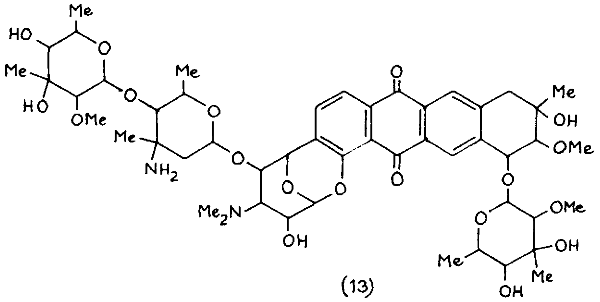
(12)

A series of N-alkyl derivatives of amphotericin B have been prepared by involving the amino group of the amino-sugar in Michael addition reactions to N-sustituted maleimides, some of which showed antifungal activity.[26] Similarly effective fungicides have been prepared by N-silylation of the amino-sugar in nystatin.[27]

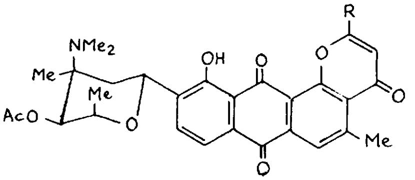
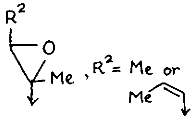
^{13}C N.m.r. spectroscopic data for elaiophylin and 21 of its derivatives have been reported.[28]

3 Anthracyclines and Related Polycyclic Antibiotics

A new anthracycline antibiotic, respinomycin A1 (13), has been isolated from a Streptomyces strain; spectroscopic evidence for the structure given did not indicate the sugar stereochemistry.[29]

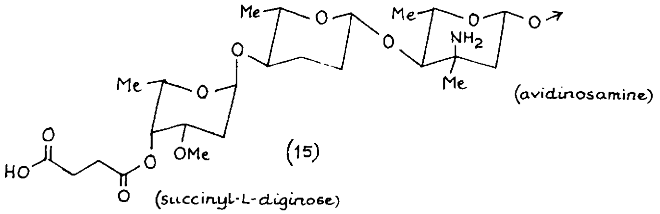

(13)

Another Streptomyces strain produced the antibiotics BE-12406A and BE-12406B, relatives of gilvocarcins and containing glycosidically-linked α-L-rhamnopyranose.[30] New antitumour antibiotics saptomycins D and E (14), obtained from S. sp. HP 530, contain 4-O-acetyl-N,N-dimethylvancosamine linked as a C-glycoside (the close relative pluramycin has angolosamine as well as vancosamine with the same aglycone).[31]


(14) R =


New isotetracenone antibiotics, atramycin A and B, obtained from S. atratus B 790, contain glycosidically-linked α-L-rhamnopyranose.[32] Minor components of the benanomicin complex obtained from Actinomadura strains have been identified, some of which lack the xylose residue present in the main components.[33]

Structural studies on platelet aggregation inhibitor avidinorubicin indicate that it contains rhodosamine and the trisaccharide moiety (15) containing two units of a new aminosugar, avidinosamine, in place of decilonitrose present in decilorubicin.[34] Model studies directed towards the synthesis of decilorubicin and using organometallic reagents have employed the 2,3-anhydro-mannoside (16) to prepare the amino-os-5-ulose derivative (17) and hence C-5 adducts (18)(Scheme 2).[35]



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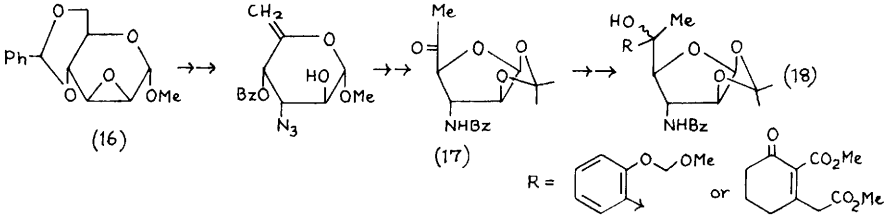
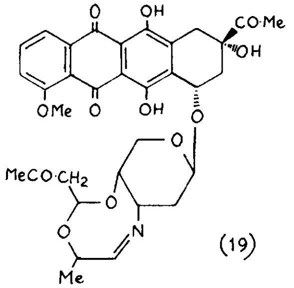


Scheme 2

Synthetic work reported has included the preparation of the anti-leukemic barminomycin II (19)[36] and of ciclamycin 0,[37] and the synthesis of D-ring pyridine and pyrazine analogues of 11-deoxydaunomycin.[38] Standard methodologies have also been employed to make



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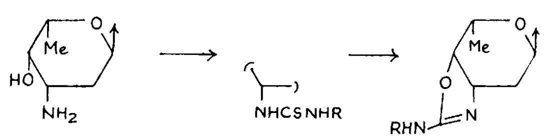


Scheme 3

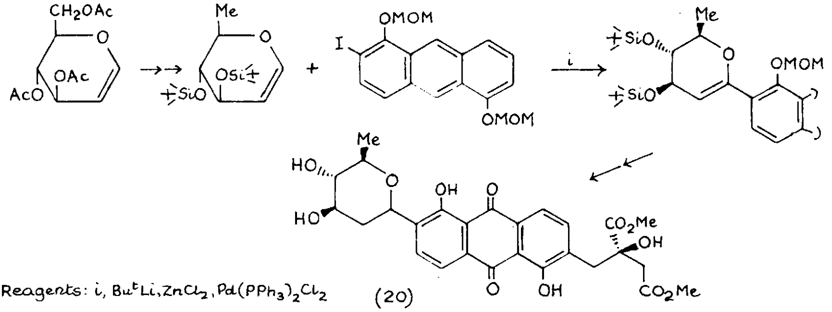
isorhodomycins,[39] 11-methoxyanthracyclines,[40] 4-demethoxydaunomycin,[41] 14,14-difluoro-4-demethoxydaunorubicin,[42] 2,6-dideoxyhexopyranosides of daunomycinone, rhodomycinone, and tetracenomycinone,[43] and anthracyclines containing L-eremosamine.[44] The synthesis of anthracyclines related to daunomycin has been reviewed.[45]

Thiourea derivatives of daunorubicin have been made by reaction of the aminosugar with ethyl or phenyl-isothiocyanate; on S-methylation, these derivatives reacted further with amines, the thiouronium salt undergoing intramolecular cyclization with the 4'-hydroxy group to give oxazolino analogues (Scheme 3).[46] A series of N-acyl derivatives of doxorubicin have been prepared as potential antitumour agents.[47]

Unnatural (-)-medermycin has been prepared using L-rhamnose to make the required enantiomeric aminosugar (angolosamine);[48]

remarkably the unnatural form is almost as biologically active as the (+)-form, the synthesis of which was reported in 1990.[48a]

(+)-Daunomycinone has been prepared by asymmetric synthesis using a benznaphthaquinone derivative in Diels-Alder reaction with a dienyl-β-D-glucopyranoside, the required adduct being the major diastereoisomer obtained.[49] The C-glycoside vineomycinone B_2 (20) has been synthesized from tri-O-acetyl-D-glucal and an anthracene derivative, the C-glycoside being formed in the step shown in Scheme 4.[50]

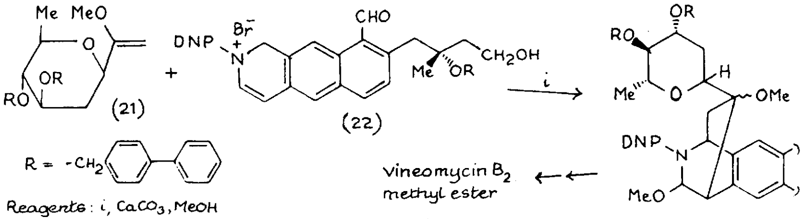


Reagents: i, $Bu^tLi, ZnCl_2, Pd(PPh_3)_2Cl_2$

(20)

Scheme 4

A synthesis of vineomycin B_2 methyl ester also utilizes D-glucal, but uses the enol ether derivative (21) in Diels-Alder cycloaddition with the azaanthracene (22) to form the required ring skeleton (Scheme 5).[51]



Reagents: i, $CaCO_3$, MeOH

Scheme 5

Another total synthesis of vineomycinone B_2 based on the use of a glycosyl fluoride is mentioned in Chapter 3.

Model reactions have been carried out for the coupling of disaccharides to the phenolic groups of the mithramycin aglycone.[52]

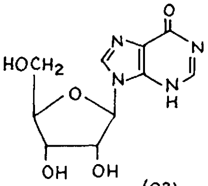
The structures of variamycin A and B have been confirmed by use of n.m.r.[53] and m.s.[54] data.

The synthesis of daunosamine has been reviewed.[55] A synthesis of rhodinose is mentioned in Chapter 12.

4 Nucleoside Antibiotics

The synthesis of nucleoside derivatives as potential drugs for AIDS therapy has been reviewed.[56,57]

Five naturally occurring nucleosides have been identified as herbicides: 5'-deoxyguanosine, coaristeromycin (23), coformycin (24), 5'-deoxytoyocamycin (25), and 9-β-D-arabinofuranosyladenine.[58]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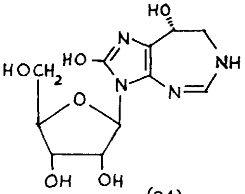
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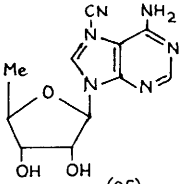
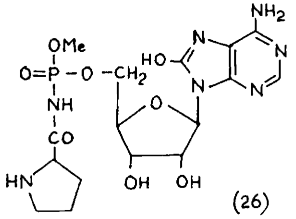

(25)

Phosmidosine, a new antifungal nucleotide, obtained from S. sp. RK-16, is a phosphamide of 8-hydroxyadenosine (26).[59]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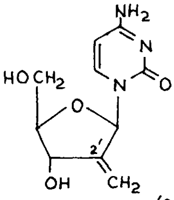
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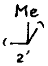
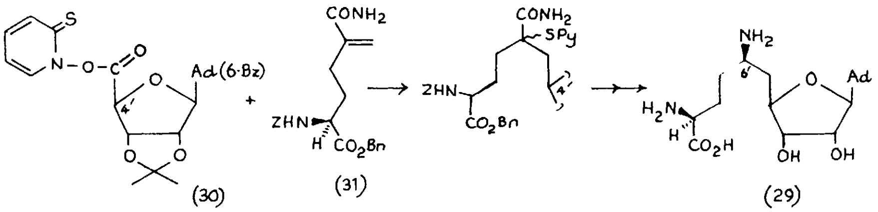

(28)

2'-Deoxy-2'-methylidenecytosine (27), prepared from the corresponding 2'-ketosugar by Wittig reaction, shows potent antileukemic activity.[60] Radical deoxygenation of the tertiary alcohol also obtained from this keto-nucleoside led to the branched D-arabinofuranosylcytidine (28) which also showed antileukemic activity.[61]

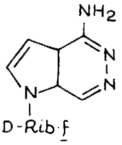
A synthesis of sinefungin (29) and its 6'-epimer has been reported, which uses the adenosine-based thiopyridinyl ester (30). This underwent photchemical reaction with the alkene (31) to form the skeleton required for the products (Scheme 6).[62]



Scheme 6

A series of sinefungin analogues have been prepared by chain extension reactions on a known 5-cyano-phosphonate derivative of ribose.[63] A biosynthetic study on sinefungin using doubly-labelled substrates has shown that adenosine is a precursor, the ribose residue being incorporated intact.[64]

The diazinyl analogue (32) of tubercidin has been prepared following reaction of hydrazine with the pyrrole intermediate (33) which was obtained conventionally from ribose.[65] Improved syntheses of formycin and pyrazofurin have been described, and the intermediate nitro-pyrazole (34) was also used to make amino-sulphonyl analogues (35).[66]



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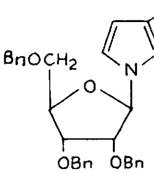

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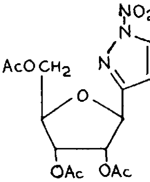

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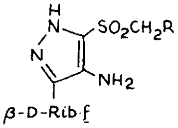
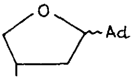


(35) R=H,CONH$_2$

The adenosine analogues (36) have been synthesized and shown to have anti-HIV activity.[67] Tunicaminyl-uracil (37) has been prepared using the ingenious and novel intramolecular, radical-addition condensation procedure shown in Scheme 7.[68]



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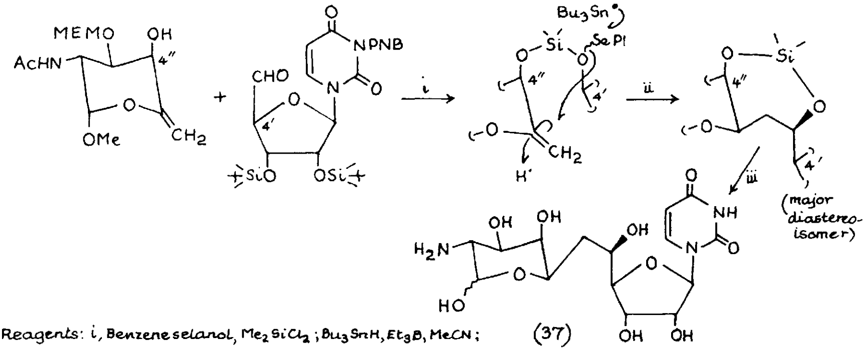
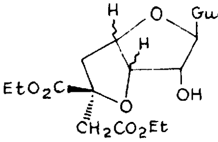


Reagents: i, Benzeneselanol, Me$_2$SiCl$_2$; Bu$_3$SnH, Et$_3$B, MeCN; iii, Ceric ammonium nitrate, 3N HCl

Scheme 7

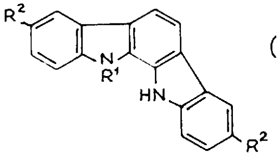
A total synthesis of nikkomycin B from a uracil nucleoside precursor has been reported.[69] The stereoisomers (37a) of 4',5'-

dihydrogriseolic acid have been synthesized.[69a]



(37a)

Fifteen new N-glycosides of indolo[2,3-a]carbazoles (tjipanazoles) have been obtained from the blue-green alga Tolypothrix tjipanasensis whose structures are summarized in (38); some are antifungal agents.[70]



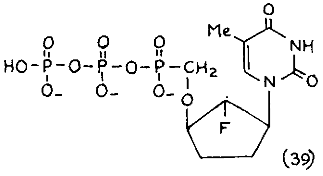
(38) $R^1 = \beta$-D-Xyl, Glc, 6-deoxy-Gul, α-L-Rham, $R^2 = H, Cl$

The thiohepturonic acid nucleoside moiety of albomycin δ_1 has been synthesized from a thioxylofuranosyl precursor by standard reactions.[71] Chapter 20 includes a reference to the synthesis of a deoxy-thiofuranosyl nucleoside with antiviral activity.

(+)-Tartaric acid has been used in an efficient synthesis of (-)-aristeromycin,[72] and another synthesis utilizes enzymic resolution of a cyclopentene triol precursor.[72a] Other references to the synthesis of aristeromycin are made in Chapters 18 and 20.

The nucleoside triphosphate mimic (39) has been synthesized from racemic cyclopent-2-en-1-ol and shown to be a potent inhibitor of HIV-coded reverse transcriptase; related cyclopentyl nucleotides were also prepared.[73]

A 14-step synthesis of neplanocin from L-ribulose in 15% overall yield has been described.[74] Another paper reports a 5-step conversion of D-ribono-1,4-lactone to the neplanocin precursor (40).[75]



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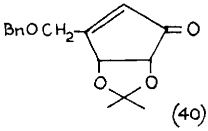

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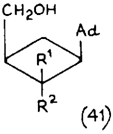


(41) $R^1=H, R^2=OH$

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

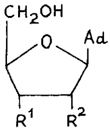
$R^1=R^2=H$

(42) $R^1=H, R^2=CH_2OH$

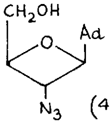
Labelled 8-^{14}C carbovir has been synthesized by cyclizing a diaminopyrimidine precursor with labelled triethoxymethane.[76]

The oxetanocin analogues (41) have been prepared from oxetanocin

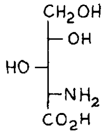
A (42) by forming the corresponding methylene compound followed by double-bond cleavage.[77] An enantioselective conversion of dimenthyl fumarate to *trans*-1,2-bis(benzoyloxymethyl)cyclobutanone, previously used for synthesizing oxetanocin analogues, has been reported.[78] 3-Deoxy-3-*C*-hydroxymethyl-D-glucose has been used to prepare 2,3-dideoxy-2- and -3-*C*-hydroxymethyl-*erythro*-pentose derivatives (43) and (44) which can be regarded as ring-enlarged oxetanocin analogues; (43) showed anti-HIV activity, (44) did not.[79] Another paper describes the synthesis of the azido-oxetanocin analogue (45) which showed antiviral activity; the *C*-2 epimer of (45) was also made together with 3-deoxy-3-fluoro analogues of oxetanocin, but these were biologically inactive.[80] A symposium report on the synthesis of oxetanocin has been published.[81]



(43) $R^1 = CH_2OH$, $R^2 = H$
(44) $R^1 = H$, $R^2 = CH_2OH$



(45)



(46)

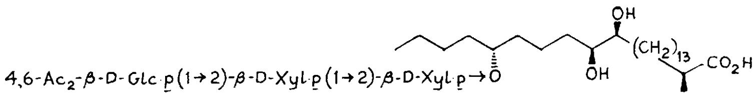
The polyoxin constituent polyoxamic acid (46) has been synthesized in a multistep procedure from L-arabinose.[82]

A prumycin analogue is referred to in Chapter 9, and dinucleoside phosphates containing AZT and cordycepin constituents are mentioned in Chapter 20.

3-*N*-β-D-Glucopyranosylcytidine has been identified as an intermediate in the biosynthesis of blasticidin S.[83]

5 Miscellaneous Antibiotics

Glykenins, a family of related antibiotic substances isolated from a *Basidiomycetes* strain, are oligosaccharide derivatives of hydroxy fatty acids, *e.g.*, compound (47).[84,85]

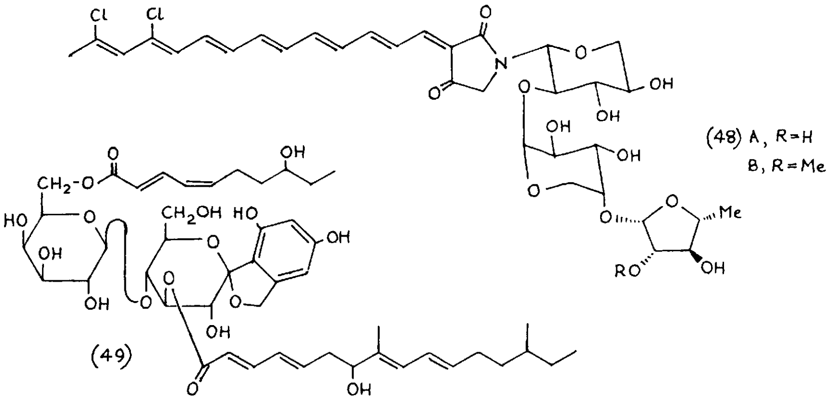


(47)

Aurantosides A and B (48) are cytotoxic tetramic acid glycosides isolated from a marine sponge.[86]

A new β-1,3-glucan synthesis inhibitor, L-687,781, obtained from *Dictyochaeta simplex*, has been assigned the structure (49), and is thus a relative of the papulacandins.[87]

New diglycoside polyether antibiotics, CP-91,243 and CP-91,244,



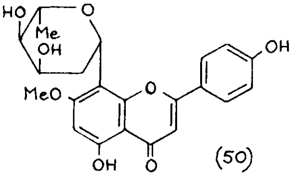
(48) A, R=H
B, R=Me

(49)

obtained from mutant strains of Actinomadura roseorufa, contain 2,3,6-trideoxy-D-threo-hexopyranose or its 4-O-methyl ether glycosidically linked to the polycyclic polyether core.[88]

Piscicidal constituents of flowers of Edgeworthia chrysantha have been shown to be sitosterol 3-O-(6-O-linoleoyl- and 6-O-linolenoyl-β-D-glucosides). They were also synthesized by standard methods.[89]

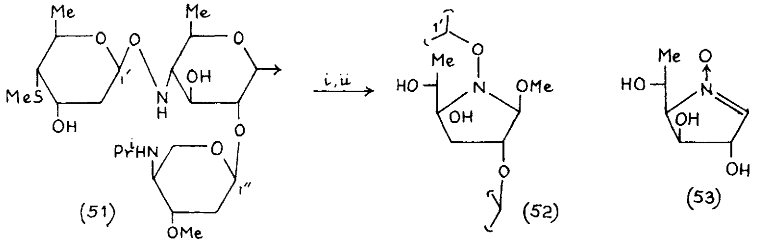
The digitoxosyl flavone C-glycoside aciculatin (50), isolated from the Philippine plant Chrysopogon aciculatis, exhibits cytotoxic and potential antitumour properties.[90]



(50)

New glycopeptide antibiotics, MM 55266 and MM 55268, produced by a strain of Amycolatopsis, contain three sugar units attached separately to a peptide core; units of glucose and mannose are thought to be β-linked, whereas a 2-amino-2-deoxyglucuronic acid residue is α-linked (from J values).[91] Helvecardins A and B are novel glycopeptide antibiotics obtained from Pseudonocardia compacta subsp. helvetica; they possess the same peptide aglycone as β-avoparcin, and the same neutral and aminosugars (ristosamine, glucose,mannose) and the B component lacks mannose.[92] An n.m.r. study of the glycopeptide eremomycin and its derivatives has been reported.[93]

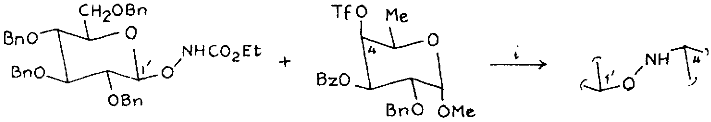
The oligosaccharide unit (51) of esperamicin A has been converted to the rearranged unit (52)(Scheme 8), leading to the nitrone (53), which could also be synthesized from D-fucose; this indicated a D-gluco configuration for this aminosugar.[94]



Reagents: i, $NaBH_4$, EtOH ; ii, MeOH, AcOH

Scheme 8

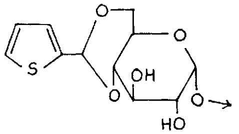
The construction of the N-O glycosidic linkage present in calicheamicin has been studied; the condensation outlined in Scheme 9 showed promise.[95] Conformational studies on calicheamicin are mentioned in Chapter 21.



Reagent: i, NaH

Scheme 9

The chemistry and biology of teniposide, which contains the thiophen acetal (54) of glucose, has been reviewed.[96] Arsenic-containing ribosides are mentioned in Chapters 17 and 22.

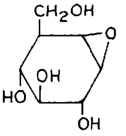


(54)

The total synthesis of the chitinase inhibitor allosamidin which utilized the sulphonamido-glycosylation of glycals has been reported.[97] The total synthesis of hygromycin A has also been reported.[98]

The synthesis of the antineoplastic glycoside phyllanthoside which used conventional methods to form the required disaccharide has been described;[99] the same group has used similar methods to make the phyllanthostatins 1-3.[100]

The β-glucosidase inhibitor cyclophellitol (55) has been synthesized from L-quebrachitol[101] and from L-glucose;[102] the latter report also described the formation of 1,6-epi-cyclophellitol (56)(an α-glucosidase inhibitor) from D-galactose; the hexose sugars were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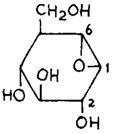
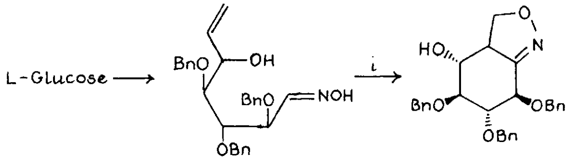

(56)

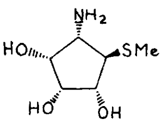


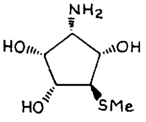
Reagent: i, NaOCl

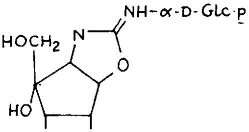
Scheme 10

cyclized to cyclohexane analogues by the nitrile-oxide reaction shown in Scheme 10.[102,103] Another brief communication by this group reports the synthesis of the α-manno isomer of cyclophellitol (C-2 epimer of (56)), as expected an α-mannosidase inhibitor, and of the aziridine analogue of (55), a very active β-glucosidase inhibitor.[104]

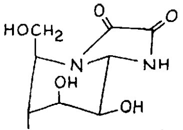
Several syntheses of mannostatin A (57) have been reported, both enantioselective[105] and racemic.[106,107] The 1,3-isomer (58) was also made.[107] (The last reference reports the tetraacetyl derivatives.) Trehalostatin (59) has been isolated from a fermentation broth of Amycolatopsis trehalostatica.[108]

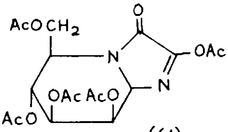

(+)(57)


(±)(58)


(59)

Kifunensine (60), obtained from the actinomycetes Kitasatosporia kifunense, which is an immunomodulator and α-mannosidase inhibitor, yields the expected diisopropylidene derivative, and on acetylation, the pentaacetyl compound (61).[109] Kifunensine has been synthesized

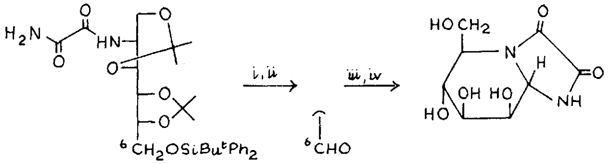

(60)


(61)

from D-mannosamine via the N-oxamide derivative of the corresponding 2-amino-2-deoxy-D-mannitol and hence 5-amino-5-deoxy-D-mannose as outlined in Scheme 11.[110] In a similar way 8-epikifunensine, the gluco analogue of (60), has been synthesized from glucose via a 5-amino-5-deoxy-D-glucose intermediate.[111]

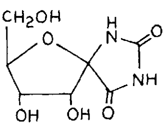
A series of papers on the synthesis of the herbicide hydantocidin (62) and its analogues describe its synthesis from diethyl

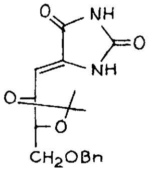
D-tartrate via D-threose and the hydantoin compound (63),[112] the synthesis of the four D- and four L-stereoisomers (64) of (61) by analogous routes from D- and L-tartrate precursors,[113] a 13-step procedure for a large scale synthesis of hydantocidin from D-fructose in 16% overall yield,[114] and standard cis or trans hydroxylation of the alkenes (65) to give the possible stereoisomers (66) of hydantocidin.[115] The structure and conformation of hydantocidin has been investigated by combined m.s. and ^{1}H n.m.r. analysis.[116]



Reagents: i, Bu$_4$NF; ii, CrO$_3$(Py)$_2$; iii, NH$_3$, MeOH; iv, 75% TFA(aq)

Scheme 11


(62)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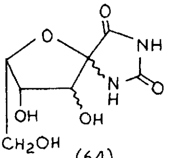
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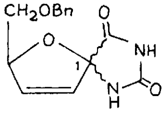
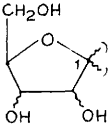
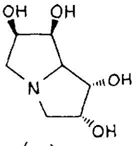

(65)


(66)

A preparation of the α-mannosidase inhibitor (67) from the heptonolactone (68) has been described.[117]

References to nojirimycin and related aminocyclitol compounds can be found in Chapter 18.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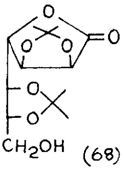
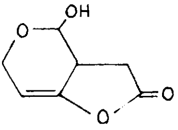
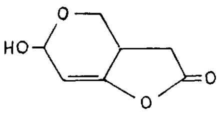

(68)


(69)


(70)

Syntheses of the antibacterial carbohydrate analogue patulin (69) from L-arabinose and of neo-patulin (70) from D-xylose have been described; the syntheses utilize branched-chain sugars derived by Wittig reactions on pentosulose intermediates.[118]

The synthesis and antitumour activity of glycoylamino-indoloquinolines is mentioned in Chapter 10. Glycosyloxyphenyl derivatives of mitomycin A have been prepared, but they offered no advantages over the unglycosylated materials.[119]

Aminosugar derivatives involved in stable cupric complexes have been found to exhibit some cytotoxic activity.[120]

Spin-labelled derivatives of N-nitroso-ureido sugars have been prepared from 2-amino-2-deoxy sugars and their anti-cancer activity has been evaluated.[121]

A preliminary communication describes the structure of a new papulacandin type antibiotic, L-687,781, a β-1,3-D-glucan synthesis inhibitor, obtained from Dictyochaeta simplex.[122]

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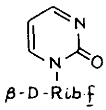
20
Nucleosides

1 Synthesis

Standard condensation methods have been employed in the synthesis of β-D-ribofuranosyl derivatives of 2(1H)-pyrimidinone ('zebularine', 1) and some fluorinated analogues,[1] 6-hydroxylamino-purines and -1-deazapurines (together with 2'-deoxy-analogues),[2] and 8-mercaptopurines.[3] Quinazolines can be ribosylated regioselectively at *N*-1 by silyl methods,[4] as can lumazines, where the formation of the 2,2'-anhydronucleoside and subsequent acid hydrolysis gave 1-β-D-arabinofuranosyl-lumazines of type (2).[5] The imidazo[4,5-*d*][1,3]-diazepine nucleoside (3) was the major regioisomer formed in Vorbruggen-type coupling procedures.[6]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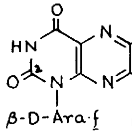
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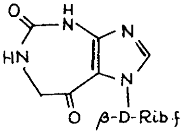
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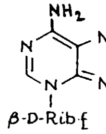
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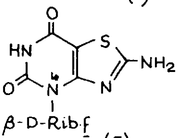
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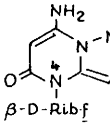
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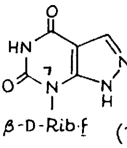
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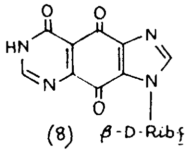
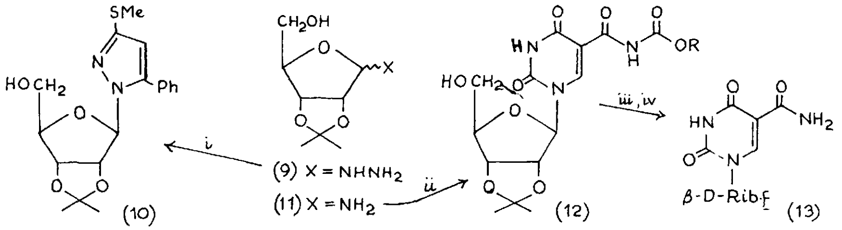

(8)

3-β-D-Ribofuranosyladenine (3-isoadenosine, 4) is formed by reaction of tri-*O*-benzoylribofuranosyl bromide with adenine and subsequent deprotection.[7] There has been a further report on a thiazolo[4,5-*d*] pyrimidine analogue of guanine, that includes some 5'-esters and deoxy-derivatives (see Vol. 24, p. 225).[8] Ribosylation of a silylated 2-aminothiazolo [4,5-*d*]pyrimidine gave the 4-glycosylated system (5), and similar standard condensations were used to make the pyrazolo[1,5-*a*]pyrimidine nucleoside (6), the 7-ribosylated pyrazolo[3,4-*d*]pyrimidine (7) and its β-D-arabino-furanosyl analogue,[9] and the imidazo[4,5-*g*]quinazoline quinone nucleoside (8). This last can be regarded as a stretched inosine, and the quinone unit was introduced after ribosylation by Fremy-salt oxidation of an amino-substituted benzenoid ring.[10] It has been shown that a micellar surfactant can catalyse the glycosylation of silylated pyrimidines and their 6-aza-analogues by 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in acetonitrile.[11] A paper on base-analogues of tubercidin is mentioned in Chapter 19.

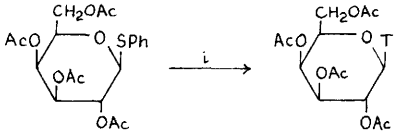
The D-ribofuranosyl hydrazine (9) can be used to produce pyrazole nucleosides such as (10) (Scheme 1) with β-selectivity, and similar 2'-deoxy-compounds were also made.[12] Ribofuranosylamine (11) (Scheme 1) can be used as a precursor of 5-substituted uridines of type (12), which can be converted to 5-carboxamidouridine (13).[13] 1-β-D-Ribofuranosyl-6-nitro-indole has been made by the indole-indoline method.[14]



Reagents: i, PhCOCH=C(SMe)$_2$, Zeolite A-3, EtOH; ii, EtOCH=C(CONHCO$_2$R)$_2$, Et$_3$N; iii, NaOH, Et$_3$N, H$_2$O; iv, TFA, H$_2$O

Scheme 1

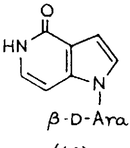
The use of thioglycosides, activated by NIS, has been developed for nucleoside synthesis, as illustrated by Scheme 2.[15]



Reagents: i, NIS, TfOH, bis(TMS)thymine, 83%

Scheme 2

Arabinofuranosyl pyrrolo[3,2-*c*]pyridines (3,7-dideazapurines) such as (14) have been prepared with β-selectivity using Seela's phase-transfer glycosylation methods,[16] and an improved synthesis of 9-β-D-arabinofuranosyladenine (ara A), suitable on a large scale, has been described in which (15), produced by alkylation of the oxazolidine, is a key intermediate.[17] The N^2, β-isomer (16) was the major product formed by BF$_3$-catalysed glycosidation of the base using the substituted D-xylofuranosyl-1-acetate. Related D-glucofuranose cases were analogous.[18] Protected α-L-arabinofuranosyl nucleosides of type (17) have been made by standard glycosylation of silylated bases. These could be fully deprotected by methanolic ammonia, or alternatively selective deacetylation by hydrazinolysis, followed by free-radical deoxygenation, gave 2'-deoxy-α-L-*erythro*-pentofuranosyl nucleosides.[19] Some β-D-glucopyranosyl-iodopyrazoles have been prepared conventionally.[20]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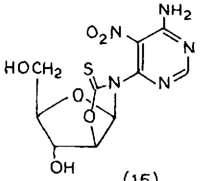
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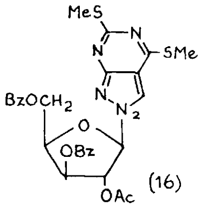
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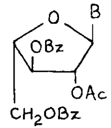
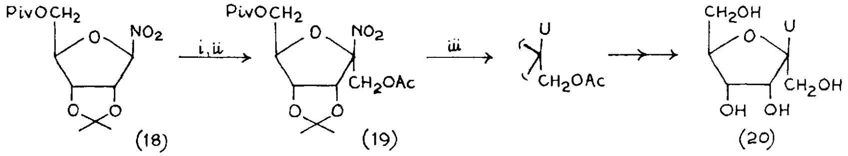

(17)

A route to ketose-derived nucleosides relies upon the 1-deoxy-1-nitro-ribofuranose derivative (18) as an important intermediate. Henry reaction of this was the key to the synthesis of 'psicouridine' (20) outlined in Scheme 3, anomer (19) being the major kinetic product initially formed. Alternatively, Michael reactions of (18) with, for example, acrylonitrile, permitted the introduction of 3-carbon chains at the anomeric position.[21]

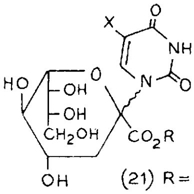

Reagents: i, CH_2O, K_2CO_3 ; ii, Ac_2O, Py ; iii, bis-TMS-uracil, $FeCl_3$

Scheme 3

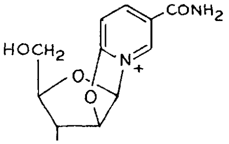
N-Glycosides (21) of 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) have been prepared. Use of a glycosyl acetate as donor towards silylated bases gave mixtures of α- and β-anomers, whilst the peracetylated β-glycosyl chloride and sodium salts of the pyrimidines gave just the α-nucleosides, albeit in modest yields.[22]

2 Anhydro- and Cyclo-nucleosides

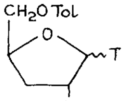
Some conformationally-restricted analogues of nicotinamide nucleosides such as (22) have been prepared by cyclization of pyridone ribonucleosides with a 2'-*O*-mesyl group. On base treatment the former gave rise to β-D-arabinofuranosyl-2-pyridones.[23] The mixed anomers (23) have been made by conventional condensation; the β-anomer formed the 2,2'-anhydronucleoside on base treatment, whereas the α-anomer gave the 2',5'-anhydrosystem (24).[24] 2,2'-Anhydro-3'-deoxy-5-ethyluridine has been prepared and shown to be an inhibitor of uridine phosphorylase.[25] The 2,2'-anhydronucleoside (25) was isolated in low yield from the reaction of the β-D-*gluco*-nucleoside with DAST; further treatment with DAST gave the product of fluorination with inversion at C-3', which was the major product of the original DAST reaction.[26]



(21) R = Me, Bn
X = H, F, Me



(22)



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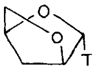
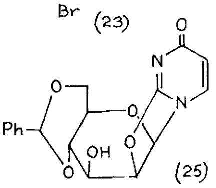
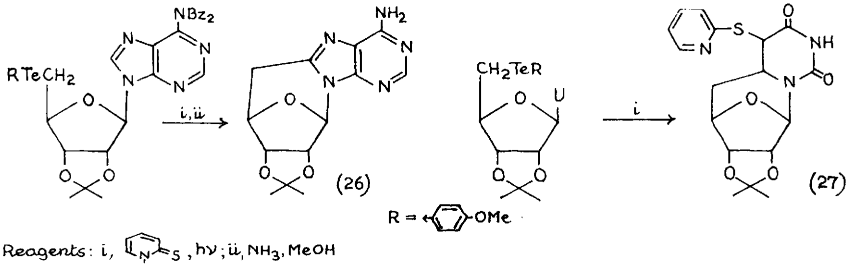


(24)

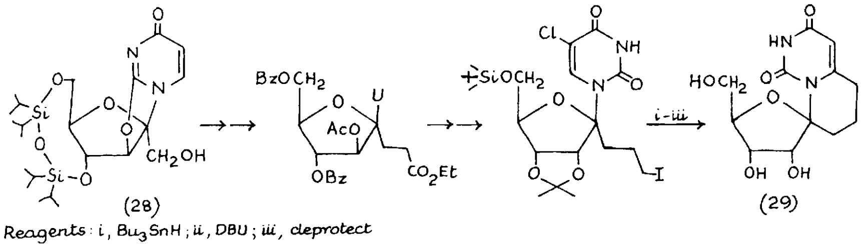


(25)

The Gif group have used methyl radicals formed by photolysis of *N*-acetoxy-2-thiopyridone to generate 5'-radicals in nucleoside systems. The formation of the 5',8-cyclopurine nucleoside (26) by this method is shown in Scheme 4, as is a similar reaction in the pyrimidine series. In this case (27) could be reductively desulfurized with Raney nickel. The tellurides used as radical precursors were formed by displacement of 5'-*O*-mesylates.[27] Free-radical cyclization was also employed in a synthesis of 6,1'-propanouridine (29) from the known anhydronucleoside (28) as indicated in outline in Scheme 5.[28]



Scheme 4



Scheme 5

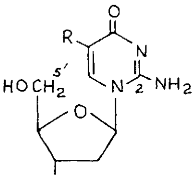
A number of papers involving the use of anhydronucleoside intermediates in synthesis are discussed in subsequent sections.

3 Deoxynucleosides

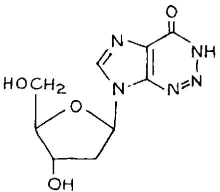
A way has been developed for the synthesis of 2'-deoxynucleosides labelled with deuterium at C-1' which involves the reduction of a protected 2-deoxy-D-ribono-γ-lactone with deuteriated DIBAL to introduce the label, prior to standard condensation. Base-catalysed exchange on the deoxyribonolactone can give label also at C-2'.[29]

Base-sugar condensations have been used to prepare 2'-deoxyribosides of pyrazin-2-ones,[30,31] 3,4,6-trisubstituted pyrazolo[3,4-*d*]pyrimidines,[32] and indazoles, where about equal amounts of 1- and 2-glycosylated products were obtained, although with β-selectivity.[33] Reaction of 2-deoxy 3,5-di-*O*-toluoyl-α-D-*erythro*-pentofuranosyl chloride with 2-amino-6-chloropurine under Seela's phase-transfer conditions gives the β-N^7-glycosylated product as the major isomer.[34]

Ammonolysis of 2,5'-anhydronucleosides was used to prepare 2-aminopyrimidinones of type (30, R=alkyl),[35] whilst 2-aza-2'-deoxyinosine (31) has been prepared by free-radical deoxygenation, with a view to its incorporation into oligonucleotides.[36] Glycosylation by the sodium-salt method gave a 2:1 excess of (32) over the N^3-regioisomer,[37] and a similar regioselectivity was observed in the preparation of aminoester (33), which could also be produced, with the same regioselectivity, by enzymic transglycosylation from deoxyuridine using encapsulated cells of *E.coli*.[38] Nucleoside phosphorylases have been used to prepare 2'-deoxyribosylzeatin[39] and [2-^{11}C]-thymidine[40] from the appropriate base and 2-deoxyribose-1-phosphate. An enzymic route to 2'-deoxyadenosine involves hydrolysis of DNA to a mixture of deoxynucleosides followed by transdeoxyribosylation of exogenous adenine.[41]



(30)



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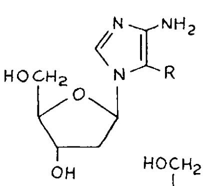
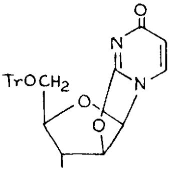
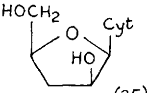


(32) R=CN

(33) R=CO2Et



(34)

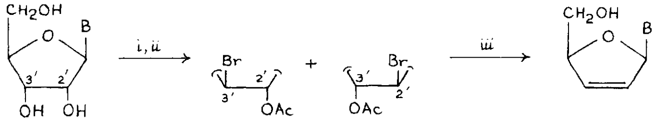


(35)

The anhydronucleoside (34) has been used as a precursor for various 3'-deoxynucleosides, such as (35), by free-radical deoxygenation and hydrolysis of the anhydrosystem. The 2'-epimer of (35) was also made by a route involving selective silylation at 0-2' followed by deoxygenation.[42] A similar regioselective silylation of adenosine to the 2',5'-di-*O*-TBDMS derivative was also used in an improved route to 3'-deoxyadenosine (cordycepin),[43] and its analogue with 2-iodo-6-chloropurine as base. This latter paper also describes the formation of the 2'-deoxynucleoside via the 3',5'-*O*-TIPS derivative.[44]

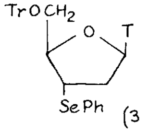
5'-Deoxy-2',3'-*O*-isopropylideneinosine can be made by reduction of the 5'-deoxy-5'-iodocompound, and was used as a precursor for various *N*6-substituted 5'-deoxyadenosines.[45]

The synthesis of 2',3'-dideoxynucleosides and their 2'-enes (d4 systems) continues to attract considerable attention, both as regards advances in methodology and the synthesis of new analogues of this type. The reductive elimination sequence indicated in Scheme 6, involving the mediator viologen, has been advocated, particularly in cases where the final alkene is acid-sensitive.[46] In the reductive formation of nucleoside 2',3'-enes from vicinal bisxanthates, Barton and coworkers have introduced the use of diphenylsilane-AIBN[47] and triethylsilane-dibenzoylperoxide,[48] these silane-based methods avoiding the potential toxicity problems associated with organotin reagents. A full account has been given of the use of an α-phenylthio group at C-2 of a sugar unit to direct coupling with a base to the β-face, after which oxidation-elimination gives d4 systems (see Vol. 24, p. 229),[49] and a further paper has appeared in which selenium fulfils the same purpose (see Vol. 24, p. 229).[50] Phenylselenyl substituents at C-3' have also been used to generate 2',3'-enes; opening of the 2,3'-anhydrothymidine derivative with phenylselenyl anion gave (36), which gave the d4 system on oxidative elimination. The PhSe group could also be introduced in the 'up' orientation by displacement of a mesyloxy group.[51] Iodocompound (37) has been made from the 2-deoxy-D-*erythro*-pentose derivative by inversion at C-3. Coupling with base units proceeded in a stereorandom manner after which base-catalysed elimination gave 2',3'-didehydrodideoxy systems, including the 5-methoxymethyluracil compound.[52] The epoxyalcohol (38) can be made by Sharpless asymmetric epoxidation; treatment of this with



Reagents: i, $(MeO)_3CMe$, H^+; ii, AcBr; iii, $Na_2S_2O_4$, viologen, H_2O, K_2CO_3, CH_2Cl_2

Scheme 6



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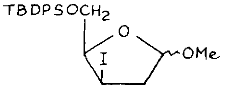
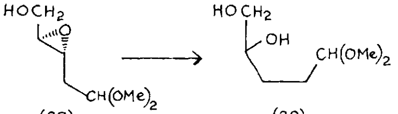


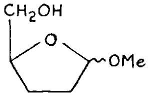
(37)



(38) (39)

DIBAL gave the diol (39) regioselectively, which could be converted to ddC and its α-anomer.[53] Synthon (40) can also be prepared from L-glutamic acid, and a modified method for doing this has been described, together with the use of (40) in making 5-alkoxymethyluracil derivatives.[54] Similar chemistry starting with D-glutamic acid has led to the enantiomer (41) of ddC, which shared some anti-HIV activity, and the same group also described some enantiomeric d4 compounds such as (42) by use of L-*ribo* intermediates.[55]

The dideoxydidehydro derivative (43) of 6-azauridine has been prepared using a Corey-Winter reaction to introduce the double bond, as has the d4 analogue of 5-chlorouridine,[56] and some previously published data on (43) from other workers (Vol. 24, p. 230) have been amended.[57] The dideoxyderivative of 3-isoadenosine (4) was made by stepwise deoxygenation, and this derivative was shown to isomerize to the N^7-analogue (ddA) in aqueous solution, and to be slowly deaminated by mammalian adenosine deaminase to 2',3'-dideoxyisoinosine.[7]



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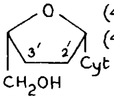
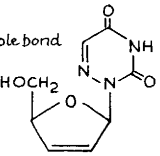
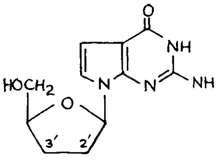


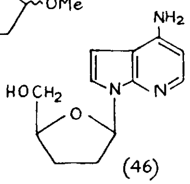
(41)
(42) 2',3'-double bond



(43)



(44)
(45) 2',3'-double bond



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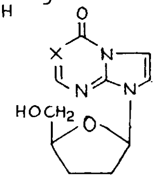
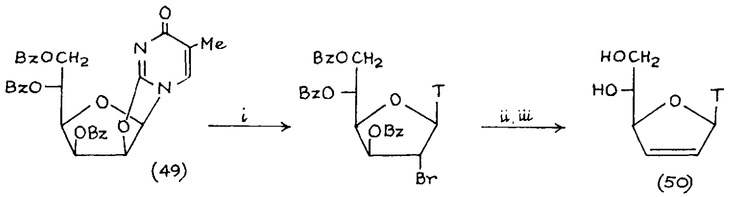


(47) X = N
(48) X = CH

The dideoxyderivative (44) of 7-deazaguanosine, and the corresponding adenosine analogue (pyrrolo[2,3-*d*]pyrimidines) have been prepared by sugar-base condensation,[58] and the unsaturated analogue (45) was prepared by elimination from a 2'-deoxy-system.[59] The triphosphates of (44) and (45) were found to be inhibitors of HIV-reverse transcriptase, indicating that N^7 is not essential for activity.[58] Similar analogues of 3-deazaadenosine (imidazo[4,5-*c*]pyridines), were made from the ribonucleoside (see also Vol. 24, p. 228),[60] and of 1,7-dideazaadenosine from the 2'-deoxynucleoside.[61] 5-Aza-7-deaza isosteres of ddI (47)[62,63] and ddG,[62] and the 5-aza-1,7-dideaza-analogue (48) of ddI (an imidazo[2,3-*b*]pyrimidine) has also been reported, as has the 8-aza analogue of ddA.[63]

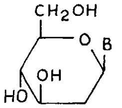
The anhydronucleoside (49) has been used as a precursor of the chain-extended hexose analogue (50) of d4T as indicated in Scheme 7.[64] The saturated compound was also prepared, and other workers have also made this by an alternative route.[65] Base-sugar condensation gave rise to the 2-deoxy-D-*arabino*-hexopyranosyl nucleosides (51, B=T, U, Cyt), which could be converted to alkenes (52) via bis(dithiocarbonates), and hence to the reduced materials.[66]



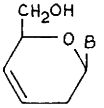
Reagents: i, HBr, DMF; ii, Cu/Zn; iii, OMe^-

Scheme 7

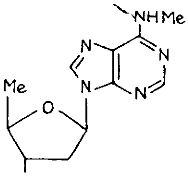
The *N*-deoxyribosyltransferase of *Lactobacillus leichmanii* has been used to make the 2',5'-dideoxynucleoside (53) by transfer of the sugar unit from 5'-deoxythymidine.[67]



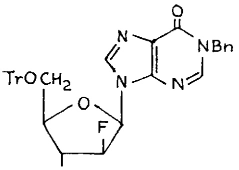
(51)



(52)



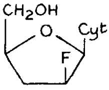
(53)



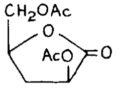
(54)

4 Halogenonucleosides

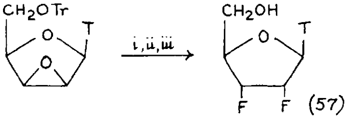
During a synthesis of 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-hypoxanthine, the intermediate (54) was obtained in modest yield by displacement of triflate with inversion using TASF, this reaction representing the first successful introduction of a 2'-β-fluorosubstituent in a preformed purine nucleoside.[68] The anti-HIV activity associated with (2,3-dideoxy-2-fluoro-β-D-*threo*pentofuranosyl)cytosine (55) has led to further work on its synthesis. Workers at Hoffmann-La Roche have reported a route in which deoxygenation at C-3 of the sugar is carried out, without the use of organotin compounds, before coupling to the base; in this approach the lactone (56), produced by elimination-reduction from tri-*O*-acetyl-D-arabinonolactone was a key intermediate, fluorine being introduced by a double inversion procedure.[69] The NIH group have also described an improved route to (55) and the adenine analogue by free-radical deoxygenation at C-3 before coupling.[70] An n.m.r. method has been noted for easy distinction between α- and β-anomers of 2'-deoxy- and 2',3'-dideoxy-2'-fluoroarabinofuranosyl nucleosides such as (55), on the basis of the size of the two-bond coupling between C-1' and fluorine.[71] The Sloan-Kettering team has described a range of fluorinated pyrimidine nucleosides including the *ribo*-difluoroderivative (57) which was made from a D-*lyxo*-epoxide (Scheme 8), the D-*arabino*-difluoride (58), prepared from FMAU via a 2,3'-anhydronucleoside, the fluoroalkene (59), the fluorinated AZT (60) and the compound with azide and fluorine interchanged, and the α-fluorinated -2',3'-dideoxycompound (61) (for earlier work on some of these structural types see Vol. 24, p. 230-1).[72]



(55)

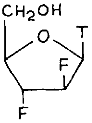


(56)

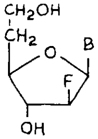


Reagents : i, KHF_2, $EtOCH_2CH_2OH$, 140°; ii, DAST; iii, $H_3\overset{+}{O}$

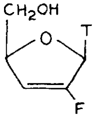
Scheme 8



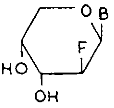
(58)



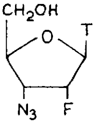
(62)



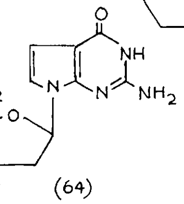
(59)



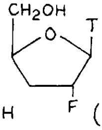
(63)



(60)



(64)

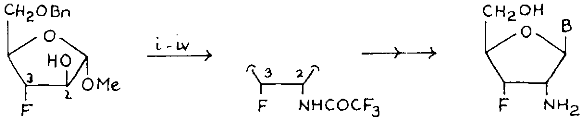


(61)

Pyrimidine homonucleosides of type (62) have been prepared by condensation methods,[73] as have the arabinopyranosyl compounds (63) and their α-anomers; periodate-borohydride cleavage of the 3'-4'-bond on these latter types produced the appropriate seconucleosides.[74]

An improved synthesis of the anti-HIV agent 3'-deoxy-3'-fluorothymidine has as the key step the opening of a 2,3'-anhydrosystem with Et_2AlF and HF in dimethoxyethane, where yields were much improved over those obtained using other fluoride sources.[75] The fluorinated pyrrolopyrimidine (64) was made by double inversion from the 2-deoxynucleoside; the triphosphate of (64) turned out to be a good inhibitor of HIV reverse transcriptase.[59]

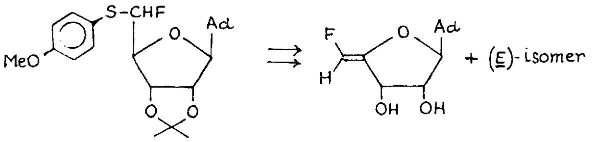
In a synthesis of 2'-amino-2',3'-dideoxy-3'-fluoronucleosides, the D-*ribo*-compounds (66) were prepared as outlined in Scheme 9. Some of the D-*lyxo*-isomer of (65) was also produced during the oxidation-reductive amination, and was used to make α-D-lyxofuranosyl analogues of (66).



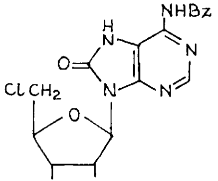
Reagents: i, DMSO, Ac_2O; ii, NH_2OMe; iii, LAH; iv, CF_3COSEt

Scheme 9

The fluoroalkene (68), and its (*E*)-isomer, have been proposed as mechanism-based inhibitors of *S*-adenosylhomocysteine hydrolase. They were prepared by oxidation and elimination from the α-fluorosulfide (67), itself made from the 5'-sulfoxide using DAST (see Vol. 22, p.212 and also Section 6). A number of similar fluoroalkenes, with other sugar modifications, were similarly prepared.[77]



(67) (68)

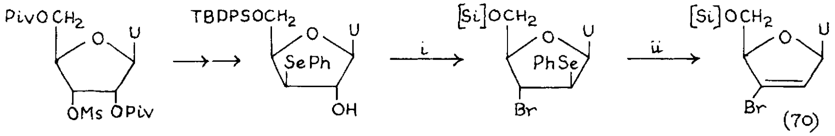


(69)

When ribonucleosides were treated with thionyl chloride in pyridine-acetonitrile, the 5'-chloro-5'-deoxy-2',3'-*O*-sulfinylnucleoside derivatives were formed. The cyclic sulfite could be removed by NH_3 in methanol to give 5'-chloro-5'-deoxynucleosides.[78]

The 5'-chloro-5'-deoxynucleoside (69) is the product of treatment of *N*^{6}-benzoyl-2,3-*O*-isopropylideneadenosine with cupric chloride, with the 5'-*O*,8-cyclonucleoside as an intermediate.[79]

The 3'-bromo-2',3'-dideoxydidehydrouridine derivative (70) has been prepared as indicated briefly in Scheme 10. The thionyl bromide reaction also gave some of the 2'-bromo-2'.3'-dideoxy-3'-phenylselenyl product with D-*xylo*-configuration, which on elimination gave the 2'-bromoalkene.[80]



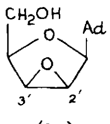
Reagents: i, $SOBr_2$, imidazole, CCl_4; ii, MCPBA

Scheme 10

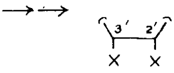
5 Nucleosides with Nitrogen-substituted Sugars

1-(2-Azido-2-deoxy-β-D-arabinofuranosyl)-cytosine (cytarazid) and -thymine have been prepared in an improved way involving Mitsunobu reaction at C-2' of a 3', 5'-*O*-TIPDS derivative,[81] and 2'-azido-3'-deoxythymidine has been made from epoxide intermediates.[82]

The diazidodideoxyadenosine (72), and hence the corresponding diamine (73), have been made from epoxide (71) by ring opening at C-3', followed by displacement of a triflate. In this work, the direct formation of the D-*lyxo*-epoxide (71) from ara-A by treatment with Ph_3P and DEAD is noteworthy.[83] The use of Bu_3SnH/AIBN has been advocated for the conversion of (72) into (73),[84] and other reductions of azidonucleosides,[84,85] with 'transient *O*-silylation' being used if necessary to ensure solubility in the reduction medium (dioxan).[85]

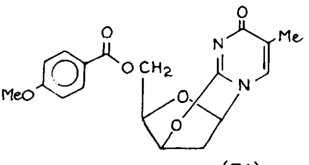


(71)



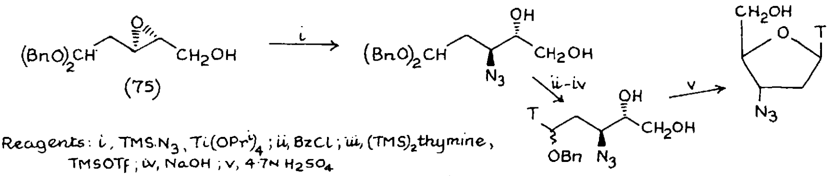
(72) $X = N_3$

(73) $X = NH_2$



(74)

Further approaches to AZT have been reported. The anhydronucleoside (74) was obtained directly from thymidine by two sequential Mitsunobu reactions, and, after treatment with LiN_3 and deacylation, gave AZT in 73% overall yield.[86] The same group has also used D-xylose to prepare AZT, by condensation of 1,2-di-*O*-acetyl-3,5-di-*O*-benzyl-D-xylofuranose with silylated thymine, and deoxygenation at C-2 to give a known intermediate for AZT.[87] In an approach from acyclic precursors, the Sharpless epoxidation product (75) was manipulated as indicated in Scheme 11; the stereospecificity in the cyclization, which gave only the β-anomer, was rationalized in terms of the gauche effect.[88] Another group has independently developed very similar chemistry, which was also used to make L-AZT from the enantiomeric epoxide.[89] NBS-induced coupling of silylated thymine to a thioglycoside (see also Section 1) has been used to make AZT, but mostly the α-anomer was obtained.[90] Pedersen's group has used the Michael addition of azide to the enal (76), derived from D-glucal (Vol. 23, p.137), as the key to a synthesis of AZT; since neither the conjugate addition nor the subsequent glycosidation were stereospecific, both 1'- and 3'-epimers were also produced.[91] Similarly, the enantiomer of the 5-*O*-benzoyl analogue of (76), accessible by ring-opening of L-arabinal (Vol. 23, p.216) was used to make L-AZT and its epimers.[92]

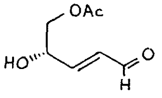


Reagents: i, TMS.N_3, $Ti(OPr^i)_4$; ii, BzCl; iii, $(TMS)_2$thymine, TMSOTf; iv, NaOH; v, 4·7N H_2SO_4

Scheme 11

With regard to analogues of AZT, 3'-azido-2',3'-dideoxyribonucleosides of some 5-substituted uracils[93] and of 5-halo-2-pyrimidinones[94] have been prepared by fairly conventional methods. The Vorbruggen-type coupling of the D-xylose derivative (77) and purine (78) was employed in a stereospecific synthesis of azidodideoxyderivatives of guanosine and of 2-

amino-6-methoxypurine riboside; the presence of the mesyloxy group from an early stage and the subsequent photochemical deoxygenation at C-2' are noteworthy.[95] Two groups have reported the use of intermediates of type (17, B=T) to make the 4'-epimer of AZT after deoxygenation at C-2' and inversion at C-3'.[96,97] A second team has reported the synthesis of the AZT homologue (79) (see Vol. 24, p. 232), together with related compounds epimeric at C-3',[98] and the chemistry of Scheme 7 could be modified to give (80).[64] Pedersen's approach involving Michael addition has been applied to the C_6-enal (81), and similar silylated species, derived from D-glucal, to produce the 3'-epimer of (80) and the 1',3'-bis-epimer; the Michael addition was stereoselective in this case, but base-sugar condensation was not.[65,99]



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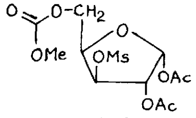
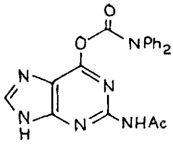


(77)



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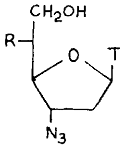
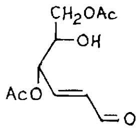
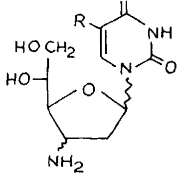


(79) R = H

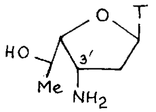
(80) R = OH



(81)



(82)



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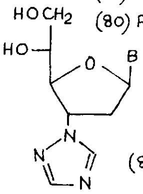

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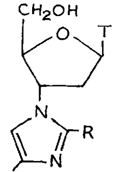
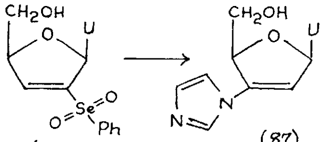
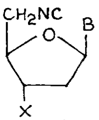


(85) R=H, Me



(86)

(87)



(88)

A number of *N*-acyl- and thioureido-derivatives of 3'-amino-3'-deoxythymidine have been prepared.[100] Michael addition of phthalimide to enal (81) was used in the synthesis of the 3'-amino-2',3'-dideoxyhexofuranose nucleosides (82) (all four isomers, R=H, Me, halogen),[101] and a similar enal prepared by mercuric-ion catalysed hydrolysis of L-rhamnal was used in the same way to make the L-acosaminyl nucleoside (83) and its β-anomer, and the L-ristosaminyl systems (epimers at C-3').[102] Michael addition of 1,2,4-triazole to (81) led, after base-sugar condensation, to the triazolyl-substituted nucleosides (84, B=T, U), together with the analogous hexopyranose systems.[103] The imidazolyl nucleosides (85) can be made by reaction of 3'-amino-3'-deoxythymidine with 1,4-dinitroimidazoles,[104] whilst the unsaturated imidazole nucleoside (87) was made by treating the phenylselenone (86) (see Section 6) with imidazole.[105]

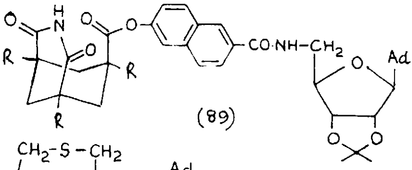
5'-Deoxy-5'-isocyanonucleosides of type (88, B=T, U; X=OH, N_3) have been prepared by dehydration of the 5'-formamido-compounds.[106] Although detailed discussion is beyond the scope of this report, the preparation of compounds of type (89) in which 5'-amino-5'-deoxyadenosine is linked via a spacer to a derivative of Kemp's triacid is noteworthy. Rebek's fascinating work on self-replicating systems has shown that these compounds catalyse their own formation from the adenosine derivative and an active ester of the left-hand side.[107,108]

6 Thio- and Seleno-nucleosides

The displacement of a 2'-mesylate by 9-(4-methoxyphenyl)xanthene-9-thiol (see Vol. 24, p. 233-234) was the key step in the first synthesis of 2'-thioadenosine, and 2'-thio-ara-A was also prepared by the same protocol.[109]

There has been a resurgence of interest in 4'-thionucleosides (sugar-in-ring analogues), with the preparation of 2'-deoxypyrimidine nucleosides of type (90) by base-sugar condensation, the thio sugar unit being prepared either by Bobek's procedure (Vol.10, p. 84)[110] or by novel methods (see also Chapter 11).[111,112] The BVDU analogue had promising antiviral activity.[112]

An improved route has been described for the synthesis of 5'-*S*-aryl (or alkyl)-5'-thionucleosides,[78] and it has been shown that the *S*-aryl compounds can be oxidized directly to 5'-fluoro-5'-thionucleoside derivatives using XeF_2, in addition to the two-stage process involving oxidation to the sulfoxide and then treatment with DAST to induce a Pummerer-type process (see Vol. 22, p.212). Further oxidation of the α-fluorosulfides gives sulfones such as (91).[113] Another reference to the use of such intermediates was discussed earlier,[77] and there has been a further report on the preparation of 5'-(fluoromethylthio)adenosine and 5'-fluoro-5'-methylthioadenosine from the methylsulfinyl derivative and DAST (see Vol. 23, p.216)[114]. 5'-(Di- and trifluoromethylthio)adenosine have been prepared by alkylation with the appropriate chlorofluoromethane,[115] as have fluorinated *S*-ethyl compounds of type (92),[115,116] and the *S*-(3-fluoropropyl)analogue.[116] The cyclic



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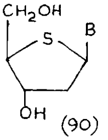
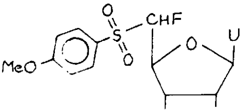
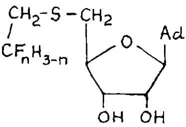


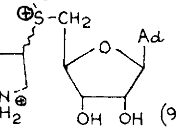
(90)



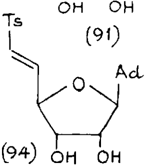
(91)



(92) n=1–3



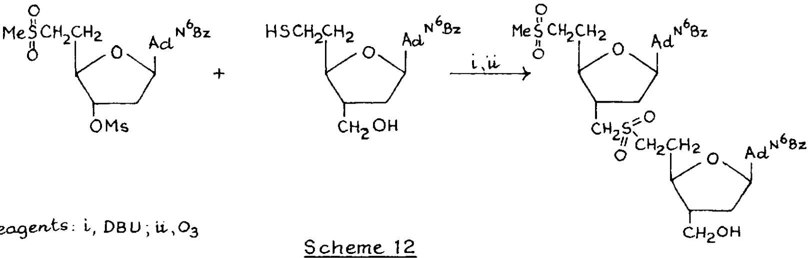
(93)



(94)

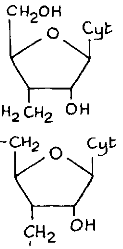
analogue (93) of decarboxylated *S*-adenosylmethionine was made for evaluation as an inhibitor of polyamine biosynthesis,[117] and the extended sulfone, and hence its saturated analogue, was made by a Wittig approach from the 5'-aldehyde.[118]

A number of groups have described elegant approaches to dinucleotide analogues in which the phosphodiester is replaced by a sulfur-containing isosteric chain. The key step in an approach to a sulfone analogue is illustrated in Scheme 12, both building blocks being accessible from diisopropylidene glucose,[119] whilst the related structure (95) has been made by displacement of a C-3-branched mesylate by the sulfur of a 5'-thiocytosine unit.[120] Wadsworth-Emmons chemistry was used to link together the two halves of the sulfonate (96), capable of extension in an iterative fashion, and in this work, the sulfonate analogue (97) of AMP was also made.[121] Others have made the *O*,*S*-acetal-linked unit (98), and incorporated it into deoxyoligonucleotides.[122]

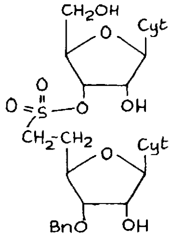


Reagents: i, DBU; ii, O_3

Scheme 12



(95)



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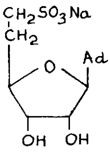

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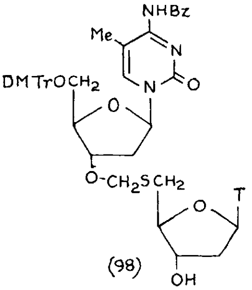
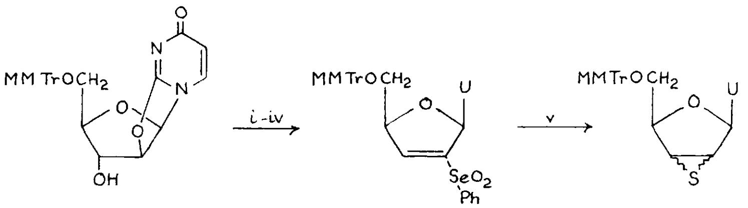


(98)

An unsaturated phenylselenone [the 5'-monomethoxytrityl derivative of(86)] has been made by the reaction sequence of Scheme 13, which also illustrates one of its reactions;[105] others are mentioned in Sections 5 and 7, and there are interesting comparisons with the chemistry of the isomeric 3'-phenylselenone discussed in Volume 23. Some synthetic applications of phenylselenyl derivatives of nucleosides are mentioned in Sections 4, 7, 8 and 11.

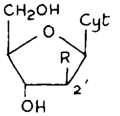


Reagents: i, $(PhSe)_2$, LAH; ii, MsCl, Py; iii, $KOBu^t$; iv, MCPBA; v, H_2S

Scheme 13

7 Nucleosides with Branched-chain Sugars

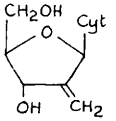
The cytidine derivatives (99) have been prepared from the 2'-tertiary alcohol with O-3' and -5' protected as the TIPDS derivative, by free radical deoxygenation of the methyl oxalyl esters. The tertiary alcohol was produced by organometallic addition to a 2'-ketonucleoside.[123] This approach could be extended to the *C*-alkynyl derivative (100),[124] and a similar deoxygenation of a C-2'-cyanohydrin (mixed epimers) gave the 2'-*C*-cyano-2'-deoxycompound (101), of D-*arabino*-configuration.[125] There has been an extended account of the synthesis of the antineoplastic agent 2'-deoxy-2'-methylene-cytidine (102), and various 5-substituted analogues, by Wittig syntheses (see Vol. 22, p.213),[126,127] and a similar approach has been applied to making (103, B=U, Cyt).[127,128] During this work, it was observed that the Wittig reaction on a 3'-ketonucleoside was slow under salt-free conditions, and n.m.r. evidence for the intermediate oxaphosphetane (104) was observed.[128] The Wittig approach has been extended to the synthesis of the adenine analogues of (102) and (103) and of (105) and the corresponding 3'-methylene compound, some of these products being inhibitors of *S*-adenosylhomocysteine hydrolase and ribonucleotide diphosphate reductase.[129] The fluoroalkene (107), also designed as an inhibitor of ribonucleotide diphosphate reductase, has been made by the interesting sequence of Scheme 14. Although (106) was the major first product, some of the isomeric alkenyl sulfone was also produced, and in the same way gave the (Z)-isomer of (107).[130]



(99) R = Me, Et

(100) R = -C≡CH

(101) R = -C≡N



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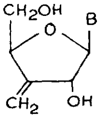
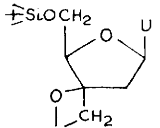
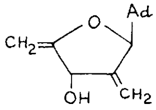


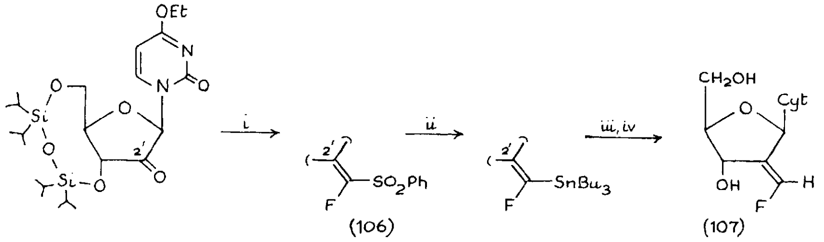
(103)



(104)

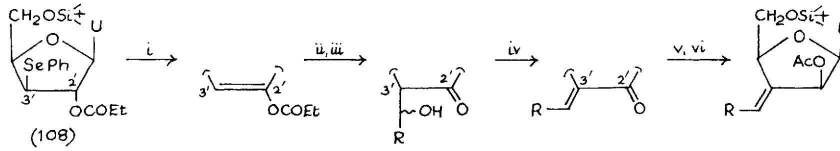


(105)



Reagents: i, LiN(TMS)$_2$, PhSO$_2$CH$_2$F, ClP(O)(OEt)$_2$; ii, Bu$_3$SnH, AIBN; iii, CsF; iv, NH$_3$,MeOH

Scheme 14

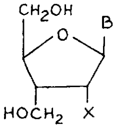


Reagents: i, MCPBA; ii, MeLi; iii, RCHO; iv, MsCl or SiO$_2$; v, NaBH$_4$,CeCl$_3$; vi, Ac$_2$O

Scheme 15

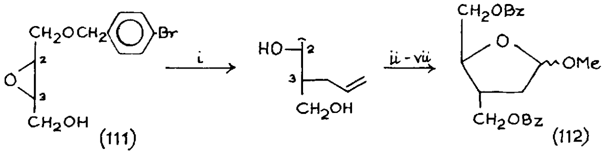
An approach to C-3' branched systems, involving the first use of aldol reactions in the area of ketonucleosides, is illustrated in Scheme 15; the phenylselenyl intermediate (108) was made as outlined earlier (Scheme 10), and similar work was done in the adenine series.[131]

There have been further reports on the synthesis of 3'-deoxy-3'-*C*-hydroxymethylnucleosides (109), which have been made by condensation methods, and deoxygenated at C-2' to give types (110).[132] Alternatively, the 2'-deoxy series, including the important anti-HIV agent (110, B=Cyt), can be made from the sugar unit (112), accessible (Scheme 16) from the asymmetric epoxidation product (111).[133] A paper on similar adenosine analogues, which can be related to oxetanocin, is mentioned in Chapter 19.



(109) X = OH

(110) X = H

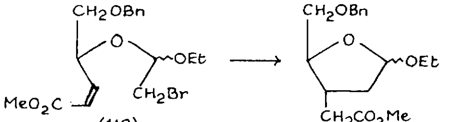


Reagents: i, $CH_2{=}CHCH_2MgBr$; ii, BzCl; iii, OsO$_4$; iv, NaIO$_4$; v, HCl,MeOH; vi, Na,NH$_3$(l); vii, BzCl

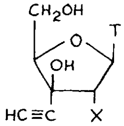
Scheme 16

In a synthesis of 3'-*C*-carbomethoxymethyl-3'-deoxythymidine, and related nucleosides, the cyclization of bromide (113), induced by Bu$_3$SnH-AIBN, was the key step.[134] Thymine nucleosides (114, X=OH, H) have been made by α-selective attack of ethynylmagnesium bromide on 3'-keto-derivatives.[135] A variety of *C*-3' branched uracil nucleosides (115) have been prepared by a sequence involving conjugate additions of cuprates to an enal derived from D-xylal (Vol. 23, p. 216),[136] whilst (116) has been made by a sequence in which the chain-branch was introduced by an α-specific free radical reaction between a 3-deoxy-3-iodosugar unit and acrolein (see Chapter 14), followed by non-specific base-sugar condensation.[137]

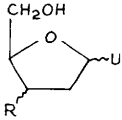
Intramolecular free-radical cyclizations have been used to fuse a second ring onto the sugar of a nucleoside template. Treatment of thiocarbonyl imidazolides (117) with Bu_3SnH-AIBN gave lactones (118), and use of a 3'-*O*-thiocarbonyl -2'-*O*-cinnamoyl derivative gave a product with the lactone fused in the opposite sense.[138] The same reagents converted the phenylselenide (119) into the cyclic ether (120), and the same strategy was used to annulate the ether ring both in the opposite sense (from a 3'-deoxy-3'-phenylselenide), and to the β-face. Use of propargyl ethers gave *exo*-methylene products.[139] The same group have used a similar approach to construct a link from a C-3' radical to an allyl ether or acryloyl ester at O-6', as in the formation of (121).[140]



(113)



(114)



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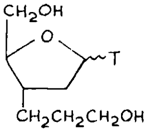

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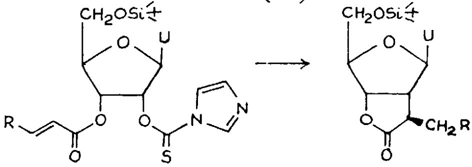
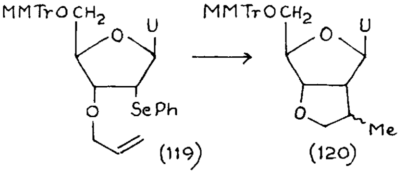


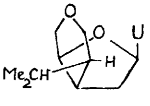
(117) R = H, Me, Ph

(118)



(119)

(120)



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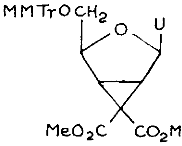

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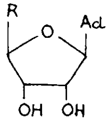
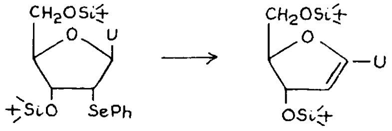


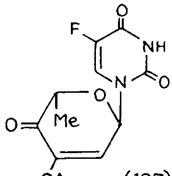
(123) R = -CH=CH2

(124) R = -C≡CH



(125)

(126)



(127)

Either palladium-catalysed cross-coupling or halogen-lithium exchange and reaction with electrophiles can be used to convert bromoalkene (70) into

C-3' branched species.[80] Reaction of the 5'-ether of alkenyl selenone (86) with dimethyl malonate anion gave the cyclopropane (122); a similar reaction, but with D-*lyxo*-specificity, occurred with nitromethane.[105]

8 Nucleosides of Unsaturated Sugars and Keto-sugars

Papers dealing with 2'.3'-didehydro-2',3'-dideoxy derivatives were discussed with their saturated analogues in Section 3.

The alkene (123) has been prepared by a Wittig reaction,[118] and the alkyne (124), an irreversible inhibitor of *S*-adenosylhomocysteine hydrolase, was made by a Wadsworth-Emmons reaction between dimethyl diazomethylphosphonate and *N*⁶-benzoyl-2',3'-*O*-isopropylideneadenosine -5'-aldehyde.[141]

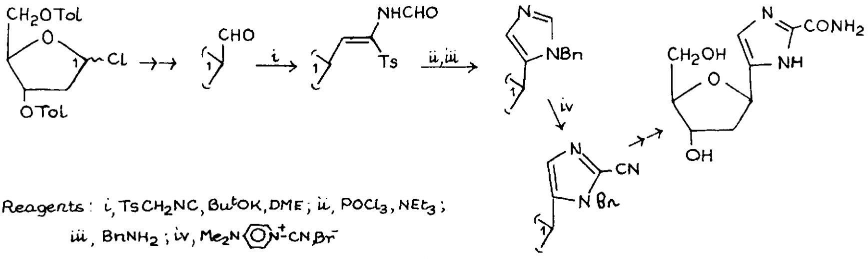
Phenylselenyl nucleoside derivatives have been used as precursors of alkenyl systems, as in the case of the conversion of (125), made from the 2,2'-anhydronucleoside, into (126) on treatment with MCPBA. The same approach was also used to prepare 2'-, 3'- and 4'-enes, although with variable regiocontrol in the eliminations.[142]

An account of a conference lecture has described work by the Leiden group on unsaturated pyranose nucleosides (see also Section 4),[143] and the enone (127) has been prepared from an L-rhamnopyranosyl nucleoside.[144]

9 *C*-Nucleosides

In an account of a plenary lecture, Buchanan has reviewed the synthesis and biosynthesis of *C*-nucleosides, with particular emphasis on work from his own group,[145] whilst a review article from Vogel's group discusses their use of 'naked sugars' for the synthesis of, *inter alia*, *C*-nucleosides.[146]

Pseudouridine has been isolated from patients with renal insufficiency as an inhibitor of glucose utilization.[147]



Reagents: i, $TsCH_2NC$, Bu^tOK, DME; ii, $POCl_3$, NEt_3; iii, $BnNH_2$; iv, $Me_2N\text{-}C_5H_4N^+\text{-}CN\ Br^-$

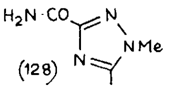
Scheme 17

An imidazole *C*-nucleoside isosteric with 2'-deoxy-ribavirin has been prepared by the interesting reactions outlined in Scheme 17,[148] and mono-*N*-

methyl derivatives of *C*-ribavirin, such as (128), have been prepared by cyclizations onto the methylimidate of 2,5-anhydro-D-allonic acid.[149] A new route to 4-deoxypyrazofurin (129) involves a dipolar cycloaddition between tri-*O*-benzyl-β-D-ribofuranosyldiazomethane and methyl propargylate as the key step,[150] whilst 3-(α-D-lyxofuranosyl)pyrazoles (130) have been made by acid-catalysed cyclization of D-*galacto*-pentitols.[151] The L-arabinopyranosyl analogue (131) of tiazofurin, and the D-xylopyranosyl compound, have been made from the glycosyl cyanides, along with 1',2'-enes,[152] on which various allylic substitutions could be performed to give products such as (132).[153]

There have been further reports on pyridine *C*-nucleosides. 4-Carbamoyl-2-β-D-ribofuranosylpyridine[154] and 3-carbamoyl-5-β-D-xylofuranosylpyridine[155] have been prepared by Alderweireldt's approach (see Vol. 21, p. 211), and some 2'-deoxy-1',2'-didehydro-pyridine *C*-nucleosides have been prepared by base-catalyzed elimination.[154] Addition of lithiopyridines to 2,3-*O*-isopropylidene-5-*O*-TBDMS-D-ribonolactone gives adducts such as (133), which can be reduced to β-pyridyl *C*-nucleosides with Et_3SiH.[157] Coupling of the anomeric free radical, produced by photolysis of an *N*-acylthiohydroxamate, with pyridinium and quinolinium salts gave 2-pyridyl *C*-nucleosides and 2-quinolinyl systems such as (135), where β-selectivity was found.[158]

Reaction of a previously-reported intermediate (Vol. 22, p. 216) with hydrazine has led to a synthesis of the pyridazine (136),[159] and the same group have reported that treatment of (137) with *o*-phenylenediamine, followed by DDQ, gives the homo-*C*-nucleoside (138).[160]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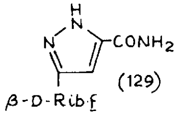
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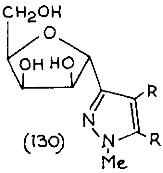
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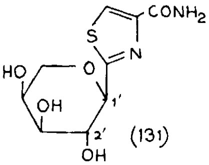
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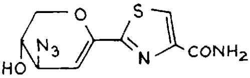
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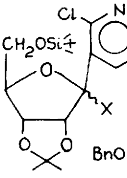
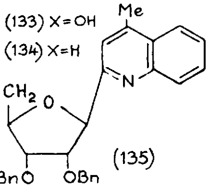

(133) X = OH
(134) X = H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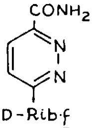
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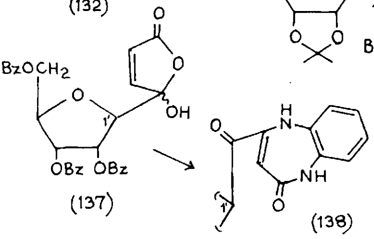
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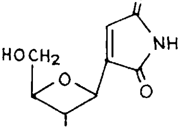
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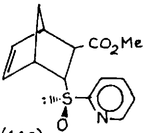
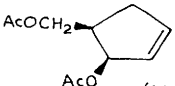

(140)

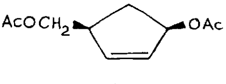
The oxetanosyl *C*-nucleoside (139), related to showdomycin, has been prepared from known intermediates (Vol. 22, p.150),[161] and, in a synthesis of carbocyclic showdomycin, diastereofacially-selective addition of cyclopentadiene to a chiral α,β-unsaturated sulfoxide gave the key intermediate (140).[162]

10 Carbocyclic Nucleoside Analogues

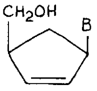
Organopalladium chemistry has featured in a number of reports on 2',3'-dideoxydidehydro carbocyclic nucleosides. The two *cis*-isomers (141) and (142) were the major products from a modified Prins reaction between cyclopentadiene and paraformaldehyde. Coupling of this mixture with adenine under Pd(0) catalysis gave racemic 2',3'-dideoxydidehydroaristeromycin (143).[163] Other workers have developed a similar procedure, where lipase-catalysed esterification could be used to effect a resolution of compounds of type (142), and this work led to the synthesis of the enantiomer of the important antiviral agent carbovir (144).[164] Another similar synthesis of (-)-carbovir (144), using two sequential reactions via π-allyl palladium intermediates, is outlined in Scheme 18, the starting monoacetate also being derived by enzymic resolution.[165] The Glaxo group have reported other routes to (-)-carbovir (144), either from natural (-)-aristeromycin (carbocyclic adenosine), involving the conversion of an adenine base to guanine,[164] or by regiospecific opening of the epoxide in the known chiral compound (145) by a guanine synthon.[167]



(141)

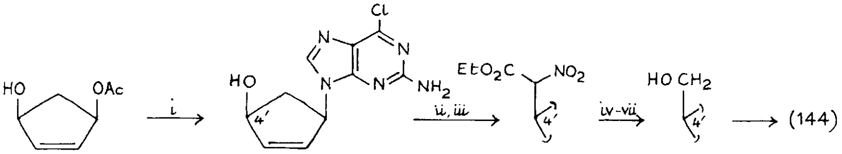


(142)



(143) B = Ad

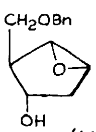
(144) B = Gua



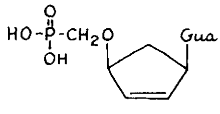
Reagents: i, 2-Amino-6-chloropurine, $Pd(PPh_3)_4$; ii, $(MeO_2C)_2O$; iii, $O_2NCH_2CO_2Et$, $Pd(PPh_3)_4$; iv, NaCl, DMSO; v, Bu^tOK; vi, O_3; vii, $NaBH_4$

Scheme 18

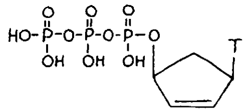
The same group have used organopalladium chemistry to prepare the racemic phosphonate (146), isosteric with carbovir monophosphate, and the corresponding diphosphoryl-phosphonate (a triphosphate isostere). The thymine analogue was also made,[168] as was the triphosphate (147), which was a good inhibitor of HIV-reverse transcriptase.[169] The 5'-nor-analogue (148) of carbocyclic guanosine has also been reported.[170]



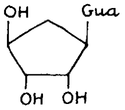
(145)



(146)

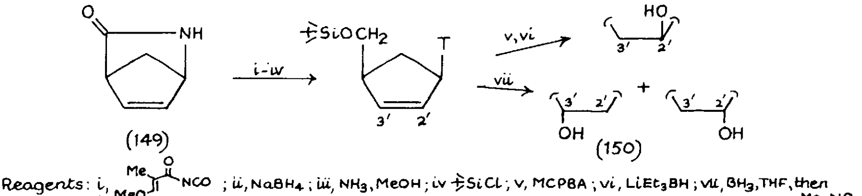


(147)



(148)

Full details have been given of the synthesis of carbocyclic nucleosides from the azabicyclo compound (149), readily available from cyclopentadiene (see Vol. 23, p.221),[171] and these studies have been extended as outlined in Scheme 19 to provide some deoxy systems; carbocyclic thymidine (150) was only the minor regioisomer produced by the hydroboration, and was better obtained by deoxygenation of the 3',5'-*O*-TIPDS derivative of carbocyclic ribothymidine.[172]

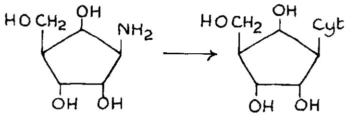


Reagents: i, ; ii, NaBH4 ; iii, NH3, MeOH ; iv ⋺SiCl ; v, MCPBA ; vi, LiEt3BH ; vii, BH3,THF, then Me3NO.

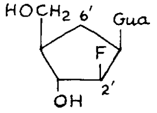
Scheme 19

The racemic carbocyclic cytidine analogue (152) has been made in a one-pot procedure by sequential treatment of (151) with cyanogen bromide (to form the 2-amino-oxazoline) followed by propargyl nitrile and ammonia.[173]

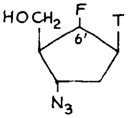
Glaxo workers have again reported on fluorinated carbocyclic nucleosides (see Vol. 24, p. 240-241 and earlier volumes). They have described in more detail the synthesis of the strongly antiherpetic guanosine analogue (153), and also given routes to the 2'-α-fluoroanalogue and the analogues of 2'-deoxyguanosine with fluorine in either orientation at C-6'.[174] A full account has been given of the route to fluorinated carbocyclic AZT analogues (154 and its 6'-α-epimer) (Vol. 23, p.222) from strained tricyclic ketones, and this work has been adapted so as to make the difluoride (155).[175] The CHF analogue (156) of ddT (Vol. 24, p. 241) has been described more fully; its triphosphate was only a poor inhibitor of HIV reverse transcriptase,[176] whilst interestingly the phosphonate analogue (157) has been found to be strongly inhibitory.[168] The chiral monoacetate (158), formed by lipase-catalysed desymmetrization of the diacetate has been converted in a multistep process to the CHF analogue (159) of adenosine, and a similar enzymic hydrolysis gave an intermediate that could be used to make the enantiomer of (159).[177]



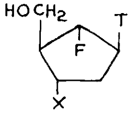
(151) (152)



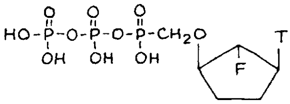
(153)



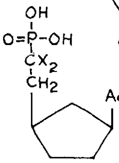
(154)

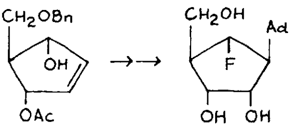


(155) X = F
(156) X = H

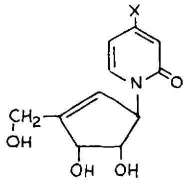


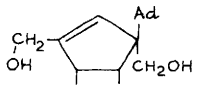
(157)





(158) (159)





(161)

(160) X = OH,NH$_2$
(162) X = H,F

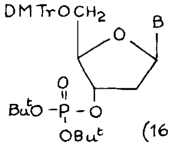
The pyridone analogues (160) of neplanocin have been prepared from a previous intermediate (Vol. 23, p.196),[178] as has 'psicoplanocin A' (161), a carbocyclic nucleoside combining the structural features of neplanocin A and psicofuranine.[179]

Some phosphonates of carbocyclic dideoxynucleosides, such as (162), have been prepared.[180] Some carbocyclic nucleoside analogues have been made by using a modified Mitsunobu reaction to link the base and the carbocycle,[181] and there has been a second report of carbocyclic clitocine (see Vol. 24, p. 241), along with a guanosine-type analogue.[182]

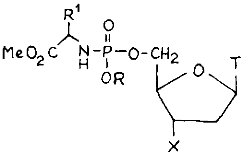
11 Nucleoside Phosphates and Phosphonates

Treatment of compounds (163) with TMSCl-Et$_3$N leads to the non-acidic cleavage of the *t*-butyl esters, thus opening up the possibility of the use of this protecting group in the oligonucleotide area.[183]

Various 5'-*O*-dialkylphosphate derivatives of 2'-deoxynucleosides modified at C-3', including AZT, have been prepared but did not have antiviral activity,[184] whereas some phosphoramidates of AZT of type (164), designed as membrane-soluble prodrugs of AZT-monophosphate, did possess significant activity against HIV.[185] Similar diesters and phosphoramidates have also been prepared from ara-C,[186] as have derivatives (165) of FdT.[187] Lipophilic phosphotriesters of ara-C (166) and of 5-fluorouridine have been made as anticancer prodrugs, the aliphatic chain being introduced to facilitate passive transport, and the mannosyl unit to permit intracellular hydrolysis.[188] The phosphate (167), and the corresponding 3'-phosphodiester, have been prepared conventionally using the phosphite method; these esters bind Cu^{II}, and the corresponding complexes were shown to hydrolyse RNA at neutral pH.[189] The 5'-phosphate of 6-*O*-methyldeoxyguanosine has been prepared in standard fashion.[190]

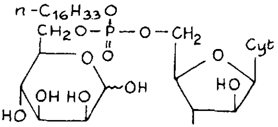


(163)

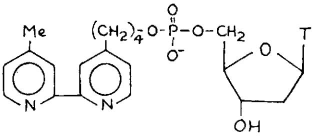


(164) X = N_3

(165) X = F



(166)



(167)

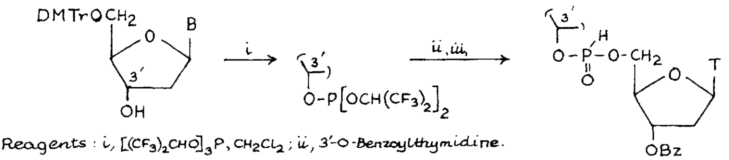
Treatment of nucleoside 5'-phosphates with sodium cyclotriphosphate gives 2',5'- and 3',5'-diphosphates and 2',3'-cyclic-5'-diphosphates, with the product distribution dependent on pH, reaction temperature and reaction time.[191] 3',5'-Diphosphates of labile deoxynucleosides can be prepared by the action of phosphoryl tetrakis-triazole, followed by hydrolysis.[192]

In the area of cyclic phosphates, a series of phosphoramidates of cyclic AMP have been prepared by reaction of cAMP Bu_4N^+ salt with PCl_5 and alkylamines; some from long chain aliphatic amines were cytotoxic to various tumour cell lines.[193] There has been a further report on trigonal bipyramidal structures as models for the hydrolysis of nucleoside 3',5'-cyclic phosphates (see Vol. 24, p. 244),[194] and Kaniyama's group have described the regioselective cleavage of cytidine 2',3'-cyclic phosphate to the 3'-phosphate using a water-soluble calix[4]arene as a synthetic mimic for ribonuclease,[195] and the hydrolysis of 2',3'-cyclic phosphates by cyclodextrins under conditions of varying pressure.[196]

Adenosine 2'- and 3'-monophosphate monomethyl and monoisopropyl esters undergo isomerization and hydrolytic cleavage to the 2',3'-cyclic phosphate and the alcohol at comparable rates under acidic conditions, whilst at neutral pH, a pH-independent phosphate migration prevails.[197] However the hydrolysis of the 2-chlorophenyl ester of uridine-3'-phosphate to 2-chlorophenol and uridine monophosphates is rapid compared with the phosphate migration under acidic conditions.[198] These studies have been extended to the interconversion and hydrolysis of 2',5'- and 3',5'-dinucleoside phosphates, where for adenosine systems, acid-catalysed depurination competed with phosphate migration and hydrolysis at pH<3.[199]

As regards methodology for oligonucleotide synthesis, earlier work (Vol. 22, p. 219) on the non-oxidative chlorination of alkyl nucleoside 3'-

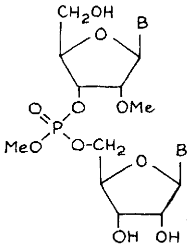
hydrogenphosphonites to give phosphorochloridites has been extended and described in more detail,[200] and a new way of making di(deoxynucleoside) hydrogenphosphonates, using tris(1,1,1,3,3,3-hexafluoro-2-propyl)phosphite, is outlined in Scheme 20; this method was applied to oligodeoxynucleotide synthesis, in conjunction with a new capping agent.[201,202] Letsinger's group have developed a method for the preparation of oligodeoxynucleotides by the phosphite procedure without the need for base protection, where a step was used to remove any products of the reaction of adenine or cytosine units.[203]



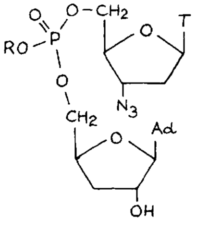
Reagents : i, $[(CF_3)_2CHO]_3P$, CH_2Cl_2 ; ii, 3'-O-Benzoylthymidine.

Scheme 20

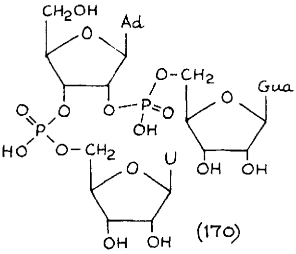
Improved preparations of phosphoramidites of various modified 2'-deoxynucleosides have been described,[204] and several oligodeoxynucleotides containing L-2'-deoxycytidine and -uridine have been made.[205] A range of dinucleoside phosphotriesters, additionally methylated at O-2', of type (168), have been prepared via phosphoramidite intermediates, and their conformations studied.[206] Various oligoribonucleotides with specific 2'-*O*-methylation have been synthesized using the 2'-*O*-[1-(2-fluorophenyl)-4-methoxypiperidin-4-yl] protecting group.[207] Structures of type (169), combining the features of AZT and of cordycepin, and with a lipophilic alkyl group for penetration of the blood-brain barrier, have been made,[208] as have various 'branched' oligoribonucleotides such as (170),[209] and analogues of 2'-5' A with modifications at the 2'- sugar unit.[210]



(168)

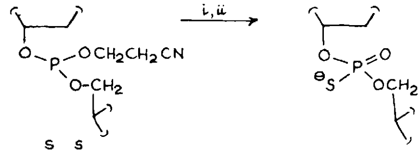


(169) R = C_6H_{13}, $C_{16}H_{33}$



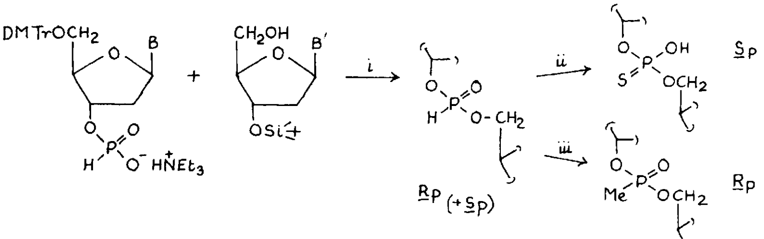
(170)

In the area of modified internucleosidic links, phosphorothioate oligonucleotides have been prepared by automated synthesis using the chemistry of Scheme 21,[211] and Caruthers' group have described two routes to di(deoxynucleoside)phosphorodithioates.[212] Separable diastereomers of



Reagents: i, $Et_2NC(=S)-S-C(=S)NEt_2$; ii, NH_3 aq

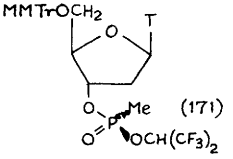
Scheme 21



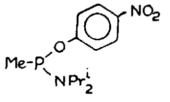
Reagents: i, PvCl; ii, S_8, Py, CS_2; iii, BuLi, MeI

Scheme 22

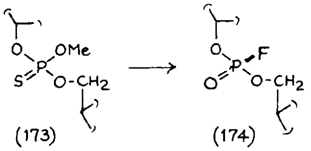
dinucleotide H-phosphonates can be made as shown in Scheme 22, and converted stereoselectively into phosphorothioates and methylphosphonates.[213] Reaction of 5'-*O*-monomethoxytrityl-thymidine with $MePOCl_2$, followed by $(CF_3)_2CHOH$, gave (171) and its separable epimer; reaction of (171) with 3'-*O*-acetyl-thymidine gave the dinucleoside methylphosphonate with inversion at phosphorus.[214] The reagent (172) was used to prepare dinucleoside methylphosphonates and methylphosphonothioates, providing the first case of a P^{III} coupling reagent containing the *p*-nitrophenoxy group.[215] Dinucleotide phosphorofluoridates (174) can be made stereoselectively, with presumed inversion, from methyl dinucleoside phosphorothioates (173),[216] and the absolute configuration at phosphorus in dithymidyl phosphoromorpholidates and phosphoromorpholidothioates has been assigned.[217]



(171)



(172)



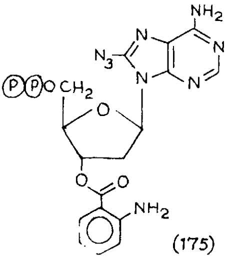
(173) (174)

A review has appeared on nucleotide sugars,[218] GDP-β-L-fucose has been prepared stereoselectively,[219] and UDP-glucuronic acid has been prepared enzymically on a gram scale.[220]

The diphosphate (175), and the corresponding triphosphate, have been prepared as fluorescent and photoactivatable analogues for probing nucleotide binding sites.[221] An efficient one-pot procedure has been described to convert unprotected ribonucleosides into their 5'-triphosphates, involving reaction with $POCl_3$ in trimethyl phosphate, followed by treatment of the resultant phosphorodichloridate with tributylammonium phosphate in DMF; a mechanism involving cyclic triphosphates was proposed.[222] ADP and acetyl phosphate undergo Fe(III)-catalysed conversion to ATP in aqueous solution,[223] and the 5'-triphosphate of 5-amino-1-(2'-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide has been prepared and subjected to enzymic polymerization.[224] Condensation between the phosphorylimidazole of N^7-methyl GMP and nucleoside diphosphates, in the presence of Mn(II) ions at pH7, has led to the synthesis of the cap portion of mRNA (i.e. 7mGpppB).[225]

Various triphosphate analogues have been reported. Eckstein's group has prepared the 1,3-dithiotriphosphate of AZT, the first example of this modification, and also the 1,1-dithioderivative of TTP.[226] The same workers have also made the 2 epimers of 1,2-dithio-GDP, and converted them to the four diastereomers of 1,2-dithio-GTP.[227] The α,β-methylene, fluoromethylene and difluoromethylene analogues of dATP and TTP have been synthesized,[228] as has the β,γ-difluoromethylene analogue of AZT triphosphate, the phosphonate proving to be some 30 times less inhibitory towards HIV reverse transcriptase than the triphosphate.[229]

The 5'-hydrogenphosphonates of AZT and its analogues with the other DNA bases have been prepared and shown to have anti-HIV activity.[230]



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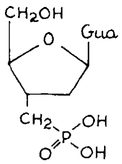

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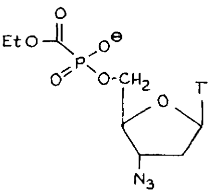

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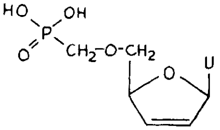
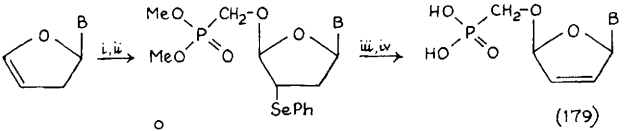


(178)

There have been a number of reports on phosphonate analogues of nucleoside monophosphates, including a further paper on 2',3'-dideoxy-3'-phosphonomethyl analogues (see Vol. 18, p.203) which reports the guanosine compound (176) for the first time.[231] Phosphonoformate esters of anti-HIV nucleosides, such as (177), have been prepared,[232] as has the 5'-*O*-phosphonomethyl compound (178), by alkylation of the unsaturated nucleoside, protection of the uracil NH being necessary.[233] The isosteric phosphonates of type (179) have also been made, as outlined in Scheme 23, with the unsaturated thymidine member being a potent antiretroviral agent.[234,235] The phosphonomethyl derivative (180) of 3'-deoxy-3'-

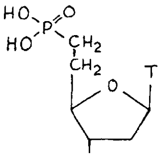
fluorothymidine has been synthesized by a Wittig approach,[236] whilst an Arbusov reaction was used to form the phosphonate during the synthesis of some 3',5'-dideoxy-5'-*C*-phosphonomethyl nucleosides.[237]



(179)

Reagents: i, PhSeCl; ii, $(\mathrm{MeO})_2\overset{\mathrm{O}}{\overset{\|}{\mathrm{P}}}\mathrm{CH_2OH}$, $AgClO_4$; iii, $NaIO_4$; iv, TMS·Br

Scheme 23



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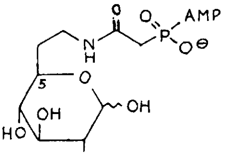

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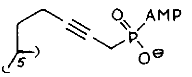

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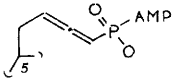


(183)

A series of interesting phosphonates (181)-(183) were designed as potential multisubstrate analogues for hexokinase, but were not, however, strongly inhibitory. They were made by chain extension at C-6 of a glucofuranose intermediate, and coupling to AMP using carbonyldiimidazole. This paper also reports the synthesis of the β,γ-methylene-γ-methylthio analogue of ATP.[238] Some phosphonate analogues of carbocyclic nucleosides were mentioned in Section 10.

12 Ethers, esters and acetals of nucleosides

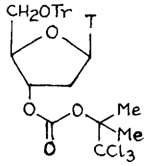
Reese's group has described the use of various substituted 9-phenylxanthen-9-yl ethers as potential protecting groups; when placed on O-5' of thymidine, the lability of the group towards acid, relative to the parent 9-phenylxanthen-9-yl (pixyl) group, could be tailored by the choice of substituents.[239] A series of 5'-*O*-DMTr- protected nucleosides were converted to their 2'-*O*-TBDMS ethers, which were used in making oligoribonucleotides.[240] 5'-*O*-(Trialkoxy)silyl derivatives of nucleosides have been made; the triisopropoxy derivatives were highly acid-labile but stable to base, whilst the tri-*t*-butoxysilyl ethers were remarkably acid-stable, and, since their cleavage was no faster using HF than using HCl, it was concluded that nucleophilic attack was not occurring at silicon.[241]

When the four RNA nucleosides were converted to their lipophilic tris(triisopropylsilyl) ethers, it was found that these derivatives could facilitate the transport of other nucleosides, including important antivirals, through liquid membrane systems, using complementary base pairing.[242]

N-Acyl-5'-*O*-(substituted)trityl nucleosides can be benzoylated or *p*-methoxybenzoylated selectively at O-2'. The rate of aroyl migration from O-2' to O-3' is slower for the anisoyl derivatives, and depends on the exact nature of the 5'-*O*-protection.[243] The removal of the 2,2,2-trichloro-1,1-dimethylethoxycarbonyl (trichloro-*t*-BOC) group from (184) can be done efficiently using $Sn(SPh)_3^-$ and tetrabutylammonium cobalt(II) phthalocyanine tetrasulfonate.[244]

In a route to aminoacyl tRNA's, the dinucleotide pCpA could be coupled efficiently to an *N*-protected aminoacid cyanomethyl ester using Et_3N in DMF to give a mixture of 2'- and 3'-*O*-aminoacyl derivatives [(185) and the 2'-isomer]. The products could be ligated to tRNA and, if the protecting group is the photolabile nitroveratryloxycarbonyl (NVOC) group, deprotected photochemically.[245] Mitsunobu reactions have been used to make 5'-*O*-aminoacyl-2'-deoxynucleosides; use of excess of reagents can lead to a further aminoacylation with inversion at C-3'.[246]

Enzymic acetylation of thymidine and deoxyuridine using vinyl acetate and an engineered mutant of subtilisin gives the 5'-*O*-acetyl derivatives specifically,[247] whilst the lipase from *Candida cylindraceae* catalyses the selective hydrolysis of the 3'-*O*-acetyl group of 3',5'-di-*O*-acetylthymidine. Use of porcine pancreatic lipase, on the other hand, selectively hydrolyses the 5'-*O*-acetyl group.[248] Selective enzymic acetylation at O-5' has also been reported for zeatin 2'-deoxyriboside.[249]



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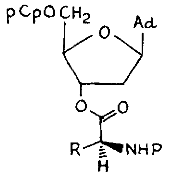

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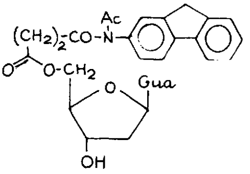

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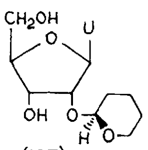

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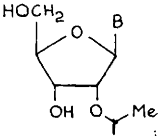

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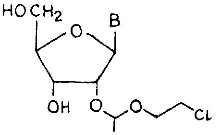
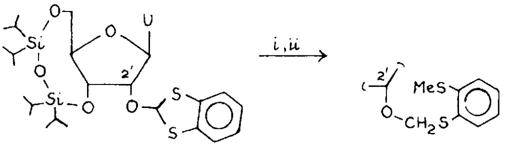


(189)

The 5'-*O*-acryloyl derivative of 5-fluorouridine has been prepared with a view to obtaining polymers, N^3-protection being necessary prior to acylation,[250] and various specific *O*-benzoyl derivatives of adenosine, xylo-A and ara-A have been reported for evaluation as inhibitors or substrates of adenosine deaminase.[251] AZT has been linked by an ester group to the specific octapeptide binding region of CD4, the T-cell surface glycoprotein to which the HIV-1 envelope glycoprotein gp120 binds. Related dipeptide analogues of various 2',3'-dideoxynucleosides were also made.[252]

In studies related to the intercalation of fluorene into DNA, the ester (186) underwent transfer of its acetylaminofluorene unit to C-8 of the guanine residue on standing in aqueous acetone, implying a stacking relationship between the two aromatic systems.[253]

The more laevorotatory diastereomers of 2'-*O*-THP-uridine (187) and -*N*^{4}-benzoylcytidine have been shown by X-ray to have (*S*)-chirality (see 187). These isomers underwent selective reaction at O-5' with FmocCl, whilst the (*R*)-epimers reacted selectively at O-3'. This could be rationalized in terms of hydrogen bonding from the 3'-OH to the oxygen of the THP ring, which is much more favourable in the (*R*)-isomers.[254] The 1-(isopropoxy)ethyl group, has been used to protect O-2' in oligonucleotide synthesis (eg. 188); it is somewhat more labile than the THP group.[255] The 1-(2-chloroethoxy)ethyl (Cee) group, as in (189), has also been used; this is more stable to acid than is the THP group, and survives conditions for removing a 5'-*O*-DMTr unit.[256,257] The [[(2-methylthio)phenyl]thio]methyl (MPTM) group has also been employed for protection of O-2' in making oligoribonucleotides, and can be introduced as in Scheme 24.[258]



Reagents: i, Bu$_3$SnH, AIBN ; ii, MeI

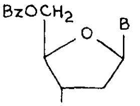
Scheme 24

Use of modified Swern-type conditions can give good yields of *O*-methylthiomethyl (MTM) derivatives (190), which can be used to make various other derivatives such as the 3'-*O*-halomethyl compounds and, thence by Arbusov reactions, 3'-*O*-phosphonomethyl nucleosides.[259] A similar 3'-*O*-MTM derivative was used to make the methylene analogue (191) of a dinucleoside phosphate, and a 5'-*O*-MTM ester of thymidine was used to link glucose and serine to O-5' of thymidine via methylene acetals.[260]

The spin-labelled spiroketal (192) derived from uridine has been prepared, and its e.s.r. properties studied.[261]

13 Miscellaneous Nucleoside Analogues

There have been a number of further reports (see Vol. 23, p.227) on nucleoside analogues with modifications in the furanose ring, with some cases of good bioactivity. Workers of Hoffmann-LaRoche have made the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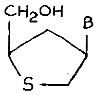
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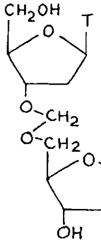
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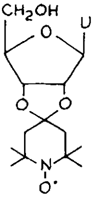
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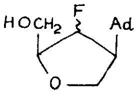
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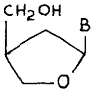
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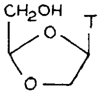
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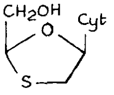
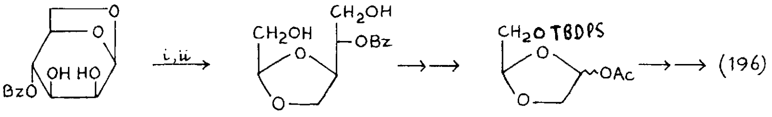

(197)

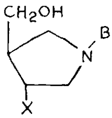
fluorinated derivatives (193, both epimers) of 'iso-ddA', by modifications of the route to the parent system (Vol. 23, p.227),[262] and the racemates (194, B=U, Cyt, Gua) have been reported, but did not show antiviral activity.[263] Tetrahydrothiophene analogues of type (195) have been made from D-glucose, but were inactive,[264] and there have been further syntheses of the anti-HIV agents dioxolan-T (196) and BCH-189 (197) in racemic form.[265] A chiral route to (196) has also been described, and is outlined in Scheme 25.[266] The same group has also developed a chiral route to BCH-189 (197), along similar lines, from 1,6-anhydro-6-thio-D-mannose.[267] A number of groups have independently developed routes to pyrrolidine analogues of type (198)[268-270] and (199),[271] which have disappointing activity.



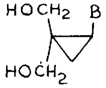
Reagents: i, $NaIO_4$; ii, $NaBH_4$

Scheme 25

Two groups have also reported the preparation of racemic cyclopropyl systems of type (200), of which the guanine species can be regarded as a conformationally-restricted analogue of the antiviral acyclonucleoside penciclovir.


(198) X = H

(199) X = N_3, F, OH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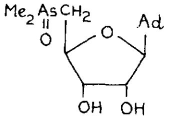
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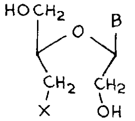
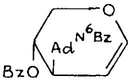

(202) B = U, T

X = N_3, F, H


(203)

Ultrasonic techniques have been applied in an improved synthesis of 5'-deoxy-5'-cyano-2',3'-*O*-isopropylidene adenosine.[274]

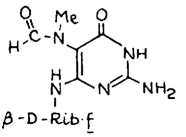
A previous report (Vol. 24, p. 247) on the synthesis of nucleosides linked to porphyrins has been extended to the preparation of water-soluble systems in which up to three uridine units are linked to a porphyrin core, made water-soluble by also having quaternary pyridinium groups.[275]

A novel arsenic-containing nucleoside, 5'-deoxy-5'-dimethylarsinyladenosine (201) has been isolated from a species of giant clam.[276]

Various 2',3'-seconucleosides of type (202), related to known antivirals, have been made,[277,278] and 3',4'-seco-2'-deoxyadenosine has been prepared by cleavage of 2'-deoxyribopyranosyladenine. This paper also describes the formation of the adenyl-substituted glycal (203) by allylic rearrangement, and hence various adenyl-deoxyalditols.[279] Papers on acyclonucleosides are not discussed in this Report.

14 Reactions

The kinetics of hydrolysis of 2',3'-dideoxyguanosine have been studied.[280] The relative rates of depurination of various 8-amino substituted purine nucleosides under acidic conditions have been determined, and to further understand the kinetic susceptibility of these compounds towards hydrolysis, the protonation at N-1 has been studied by ^{15}N- and ^{1}H nmr spectroscopy, and changes in sugar ring conformation were noted on protonation. Semi-empirical M.O. calculations were carried out to understand the factors that contribute to the preferential sites of protonation.[281] A symposium on synthetic and hydrolytic aspects of 7-methyladenosine has been published,[282] and it has been reported that the hydrolysis of 7-methylguanosine at physiological pH opens the imidazole ring to give (204); hydrolysis of the glycosidic link is much slower, in contrast to earlier reports.[283] An extensive mechanistic study has been carried out on the acid hydrolysis of ribofuranosides and deoxyribofuranosides of benzotriazoles and 8-azapurines, in which compounds glycosylated on N-1, N-2, and N-3 were studied. The hydrolyses were mechanistically similar to those of purine nucleosides, although in most cases reaction via the substrate dication was exceptionally slow. The reasons for the lability of N^3-alkylated purines was discussed in the light of results with N^1- and N^3-glycosylated 4-methylbenzimidazoles.[284] The tautomerism, protonation, electronic properties and hydrolytic stability of various tricyclic nucleosides derived from guanosine, such as (205), have been studied.[285] Some papers relating to hydrolyses of nucleoside phosphates were mentioned in Section 11.



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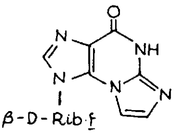
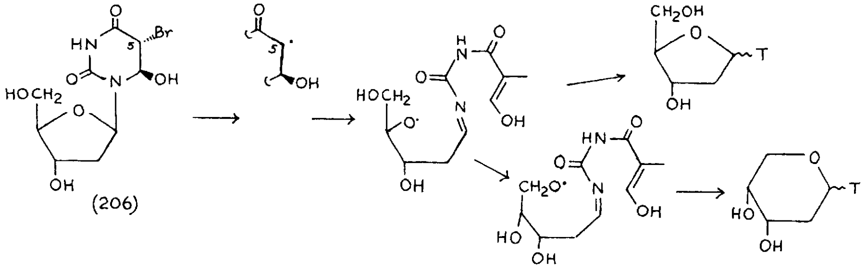


(205)

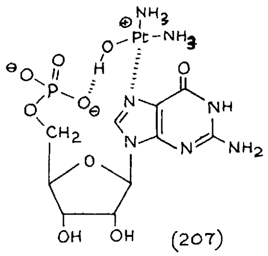
In a study related to oxidatively-damaged thymidine units in DNA, the bromohydrin (206), on exposure to light, heat or radical initiators, underwent the chemistry in Scheme (26), where the formation of β-furanose product represents a process of self-repair.[286]



(206)

Scheme 26

The complex formed between cisplatin and GMP (Vol. 21, p.218-9) was found to be surprisingly labile when compared to the complex with guanosine itself. It was proposed that the 5'-phosphate activates the OH$^-$ ligand towards substitution, as required for its anticancer action, through hydrogen bonding (see 207).[287] Reaction of Cp_2MoCl_2 with dAMP gives the complex (208).[288] The interaction between zinc octaethylporphin, with two β-naphthyl units at opposite meso-positions, and bis-*O*-(tri-isopropylsilyl) deoxyadenosine gives a 1:2 complex, with one adenosine unit held as an apical ligand, and the other held on the opposite face of the porphyrin by hydrogen bonding.[289]



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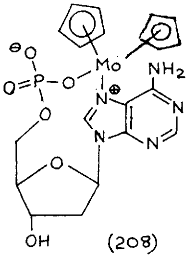

(208)

Earlier work (Vol. 21, p. 218-9) related to the mechanism for DNA cleavage by bleomycin has been reinvestigated by other workers, and the earlier conclusions have been reassessed.[290] In a study of the interaction of the diastereomeric 7,8-diol 9,10-epoxides derived metabolically from benzo[*a*]pyrene and DNA constituents, AMP gave a major product from reaction of O-2' with the epoxide, as well as products from reaction of the amino group.[291]

Electrochemical characteristics of derivatives of cytosine and arabinofuranosylcytosine,[292] and of uridine and its arabinofuranosyl analogue,[293] have been examined.

15 Spectroscopic Properties and Conformational Studies

The conformational dynamics of 3'-deoxy-3'-fluorothymidine and AZT have been investigated by high-field ^{1}H-nmr and MM2 calculations, with the conclusion that, in solution, AZT has about a 1:1 balance between the North and South geometries.[294] Similar conformational studies have also been reported for 3'-amino-3'-deoxythymidine (reduced AZT),[295] 1-deoxy-β-D-psicofuranosylthymine,[296] 8,2'-*O*-cyclo-arabinofuranosyladenine,[297] and for wyosine and its isomers.[298] Some related papers are discussed in Chapter 21.

The interaction of dGMP with alkaline earth metal ions has been investigated in aqueous solution at neutral pH by FT i.r., ^{1}H-n.m.r. and X-ray powder diffraction, and evidence is presented for conformational transitions of the sugar and base orientation.[299]

The assumptions underlying empirically-based force-field development have been evaluated, and have been applied to generate force energy conformational maps for adenosine and deoxyadenosine.[300]

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21

N.M.R. Spectroscopy and Conformational Features

1 General Aspects

The investigation of stereochemical aspects of carbohydrates (configurational assignments, conformations in the solid state and in solution, orientations of substituents, and geometries of interactions with other species) by n.m.r. spectroscopy has been reviewed in a symposium report,[1] and two further reports deal with the application of the POMMIE method for two-dimensional n.m.r. spectral editing to various glycosides,[2] and with the structure determination of peracetylated mono- and oligo-saccharides from their acetyl ^{13}C carbonyl resonances.[3] Optimal settings for the 2D heterocorrelated experiments developed for the assignment of these carbonyl carbon atoms and of the corresponding methyl protons in carbohydrate acetyl groups have been presented (see Vol.24, Chapter 21, ref.10).[4]

A data base containing ^{13}C-n.m.r. parameters of monosaccharides and their glycosides, which allows computerized structure analysis of an unknown compound from its ^{13}C-n.m.r. spectrum has been established,[5] and a library of optimized geometries and conformations based on molecular mechanics calculations (MM2 CARB) has been compiled for a number of common monosaccharides.[6] Use of the double-DANTE sequence in 1D Hartmann-Hahn- and n.O.e.-spectroscopy has been recommended for overcoming some typical problems encountered in the n.m.r. analysis of carbohydrates.[7]

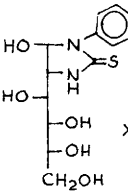
The kinetics of hydrogen exchange and the dynamics of water reorientation in aqueous glucose solutions have been studied over a wide range of concentrations by proton and deuterium relaxation measurements.[8] Trends in geometry, conformational energy, and proton affinity associated with the anomeric and related effects have been reproduced by semiempirical and *ab initio* calculations applied to methanediol.[9] Conditions have been reported under which all ^{1}H-n.m.r. signals of α- and β-D-glucopyranose 1-phosphate and α- and β-D-fructofuranose 6-phosphate are separated.[10]

2 Acyclic Systems

The ^{1}H- and ^{13}C-n.m.r. spectra of the imidazolidine-2-thiones (**1**) have been recorded.[11]

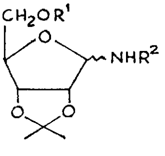
The experimentally observed vicinal ^{1}H-^{1}H coupling constants of 25 alditol- and deoxyalditol peracetates have been successfully reproduced by molecular mechanics computations of rotamer populations in combination with a suitably extended Karplus equation.[12] The conformations of arabinitol, ribitol, xylitol, glucitol, and mannitol in pyridine d_5 and in D_2O have been deduced from their $^3J_{H,H}$ values, measured on a 620 MHz instrument. The experimental study was supplemented by molecular dynamics simulations performed on the two hexitols, with the aim of obtaining additional information on torsional angles and flexibility.[13] The ratios of epimeric nitroalditols formed by application of the Henry reaction to glyceraldehyde and to all aldo-tetroses, -pentoses, and -hexoses have been determined by use of standardized ^{13}C-n.m.r. techniques. The finding of moderate selectivity favouring C-2, C-4-*threo*-configurated products was attributed to operation of the *gauche* effect.[14] In addition, the solution conformations of these nitroalditols in D_2O were investigated by ^{1}H-n.m.r. spectroscopy at 500 MHz.[15]

A ^{13}C-n.m.r. study on the gelation of *N*-octyl-D-gluconamide in aqueous solution has been published.[16]



X = H, Me, or Cl

(1)

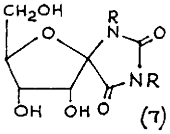


(2) $R^1 = R^2 = H$
(3) $R^1 = R^2 = Ac$
(4) $R^1 = H, R^2 = COCF_3$
(5) $R^1 = H, R^2 = COC(NOH)CO_2Et$
(6) $R^1 = Ac, R^2 = COC(NOH)CO_2Et$

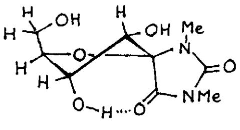
3 Furanose Systems

The ^{1}H-n.m.r. parameters of the four D-penturonic acids and of 2-deoxy-D-*erythro*-penturonic acid in D_2O have been recorded, and aqueous solutions of their 1-^{13}C-substituted analogues have been studied by ^{13}C-n.m.r. spectroscopy over a range of pH values, with particular emphasis on the ring-opening reactions of the furanose rings. The rate constants for ring-opening were determined at pH 1.5 for the protonated and at pH 4.5 for the ionized forms.[17,18]

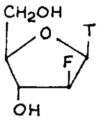
The favoured conformations of α- and β-D-fructofuranose have been examined by molecular mechanics. Values of low energy were found primarily near $^4T_3$- and secondarily near $_4T^3$-ring shapes, with transition paths between the two forms through $^O E$- and $_O E$-conformers for the α- and β-anomer, respectively.[19]



(7) R = H
(8) R = Me



(9)

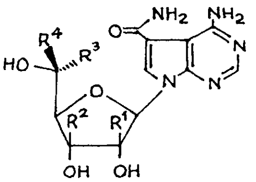


(10)

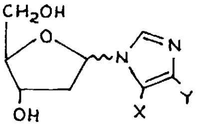
^{1}H- And ^{13}C-n.m.r. spectroscopy were used to establish the anomeric configurations and the conformations of the *exo*-cyclic substituents of the *N*-acyl-1,2-*O*-isopropylidene-D-ribofuranosylamine derivatives (**2**)-(**6**),[20] and the structure of the novel herbicide hydantocidin (**7**) has been analysed by n.m.r. and m.s. methods; n.O.e. measurements on the dimethylated derivative (**8**) in DMSO-d_6 and in CD_3OD indicated a fixed conformation (**9**).[21]

The STO-3G-optimized structures of nine different, staggered gas-phase conformers of ascorbic acid, one of which was very close to the crystal structure as determined by x-ray analysis, have been published.[22] Additional studies on the conformation of ascorbic acid are covered in Chapter 16.

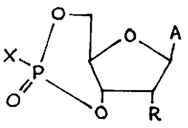
A review with 32 refs. on the role of molecular conformation in the passive membrane permeability of AZT, focusing mainly on molecular mechanics studies and including an overview on the conformational equilibrium of AZT, has appeared.[23] A variable temperature ^{1}H-n.m.r. spectroscopical investigation of the preferred conformations of the sugar rings of thymidine- and 2′-deoxyuridine-derivatives indicated a relationship between structural rigidity and antiviral activity. Thus, the active compounds AZT, FMAU (**10**), and 3′-deoxy-3′-fluorothymidine, are largely inflexible, with predominant S (*i.e.*, ${}^2T_3$) character, in contrast to all the other, inactive analogues examined, which were flexible with significant contributions from both the ${}^2T_3$ and the ${}^3T_2$ forms.[24] Similar conformational analyses have been reported for the methyl substituted derivatives (**12**)-(**15**) of sangivamycin (**11**),[25] the isomeric deoxyribosides (**16**),[26] thymidyl (3′→5′)-thymidine and its 5′-thio- and 5′-deoxy-analogues,[27] a series of cyclic 3′,5′-phosphoramidates of nucleosides such as compounds (**17**),[28] and the bicyclo[3.1.0]nucleosides (**18**) and related structures.[29] Two further conformational studies on synthetic nucleosides are referred to in Chapter 20.



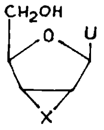
(11) $R^1 = R^2 = R^3 = R^4 = H$
(12) $R^1 = Me$, $R^2 = R^3 = R^4 = H$
(13) $R^2 = Me$, $R^1 = R^3 = R^4 = H$
(14) $R^3 = Me$, $R^1 = R^2 = R^4 = H$
(15) $R^4 = Me$, $R^1 = R^2 = R^3 = H$



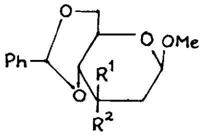
(16) $X = CO_2Et$, $Y = NH_2$
or $X = NH_2$, $Y = CO_2Et$



(17) $X = H$ or OH
$R = NMe_2$ or $NHBn$



(18) $X = CH_2, NH,$ or S



(19) $R^1 = H$, $R^2 = OH$
or $R^1 = OH$, $R^2 = H$

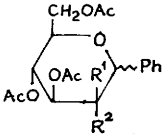
4 Pyranoses and Related Systems

^{13}C-N.m.r. parameters have been reported for 10 methyl 4,6-*O*-benzylidene-2- or -3-deoxy-D-hexopyranose derivatives, *e.g.*, compound **(19)**,[30] and for derivatives of α-D-mannopyranosyl chloride, α-L-rhamnopyranosyl chloride, 1,3-anhydro-β-D-mannopyranose, and 1,3-anhydro-β-L-rhamnopyranose.[31] The geminal carbon-proton coupling constants of α- and β-D-mannopyranose have been measured and compared with values found in mannan,[32] and the ^{1}H- and ^{13}C-n.m.r. spectra of monosulfated methyl α-D-mannopyranosides have been examined for the effects of sulfation on chemical shifts at particular positions in the molecules.[33]

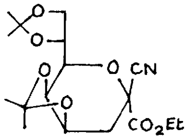
Structural studies by ^{1}H- and ^{13}C-n.m.r. spectroscopy and by CD measurements on acetylated α- and β-D-gluco- and -manno-pyranosyl arenes indicated that the rules used for determining the anomeric configurations of glycopyranosides are also valid for *C*-glycosides such as compounds **(20)** (see Vol.23, p.37 for synthesis).[34]

Both geminal and vicinal coupling constants were shown to be valuable criteria in the unambiguous anomeric assignment of *N*-acetylneuraminic acid, its methyl ester and its peracetylated methyl ester. Thus, the absolute values for both, ${}^2J_{C\text{-}2,H\text{-}3a}$ and ${}^3J_{C\text{-}1,H\text{-}3a}$ are considerably greater in α-anomers than in β-anomers (-8Hz and +6Hz for the α-, -4Hz and +1.3Hz for the β-anomer, respectively).[35,36] Data on long-range coupling constants in a series of aldohexose- and aldopentose-derivatives (including derivatives of deoxy-sugars and uronic acids) in their pyranose forms, obtained by means of delayed COSY experiments, have been compiled for use in the configurational assignment of sugar moieties of complex molecules with poorly resolved n.m.r. spectra.[37] Additivity constants for vicinal ^{1}H-^{1}H coupling constants in thiopyranose derivatives, determined from 81 experimental measurements, have been used successfully for the accurate prediction of further ${}^3J_{H,H}$ values in similar compounds.[38]

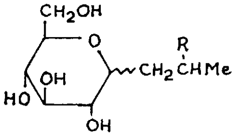
Theoretical calculations by the method of Wiberg and Boyd have been carried out to identify possible intermediate states in the conformational transitions of cyclohexane and tetrahydropyran. The results were compared with experimental data obtained from x-ray studies on unsaturated-, epoxy-, and *O*-isopropylidene-derivatives of pyranoses.[39]



(20) $R^1 = H, R^2 = OH$ or $R^1 = OH, R^2 = H$



(21)



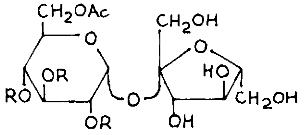
(22) R = H, ◀OH, or ···OH

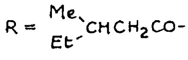
L-Iduronic acid, its methyl glycosides and its lactone have been subjected to conformational analysis by ^{1}H-n.m.r. spectroscopy. The solution of the free sugar in D_2O was found to contain at least five tautomers. The β-pyranose forms were present in the $^1C_4$ conformation, whereas in the α-anomer the ^2S_O conformation either predominated or contributed substantially.[40] The conformations of a series of *C*-glycosides of 4,5:7,8-di-*O*-isopropylidene-KDO, including the nitrile (**21**), have been investigated,[41] and the solution conformations of the *C*-glycosides (**22**) were found by n.m.r. spectroscopy to match those of the parent glycosides.[42] Conformational features of C-linked disaccharides are referred to in Chapter 3.

The activation energy and rate constants for the chair-chair interconversion of *cis*-inositol have been measured by comparison of simulated and experimental ^{1}H-n.m.r. spectra in D_2O between 278 and 323°K (E_a = 53.0 1.9kJmol^{-1}, K = 7s^{-1} at 278°K, 150s^{-1} at 323°K, ± 10%).[43]

5 Di- and Oligo-saccharides and Related Compounds

A simplification of the COSY ^{1}H-n.m.r. spectra of oligosaccharides by use of a 2-dimensional version of 3-dimensional HOHAHA COSY has been described.[44] A new and economical (in spectrometer time) technique for assigning oligosaccharide n.m.r. spectra, which employs selective excitation combined with a DANTE pulse train and chemical shift selective filtering (CSSF), was found suitable for problems of medium complexity, where each spin network contains at least one separate multiplet. It has been applied to hepta-*O*-acetyl-α-cellobiosyl azide as an example.[45]





(23)

A complete assignment of ^{1}H- and ^{13}C-chemical shifts of the sucrose tetraester (**23**) was made by comparison of spectra obtained from ^{1}H-detected heteronuclear quantum coherence and ^{1}H-detected heteronuclear 2D multiple-bond connectivity n.m.r. experiments,[46] and a variety of 2D n.m.r. techniques were tested by application to the structural analysis of raffinose peracetate.[47] The ^{1}H- and ^{13}C-n.m.r. spectra of 6-kestose and neokestose have been fully assigned,[48] and n.m.r. parameters have been used to identify 1-kestose and neokestose in crude plant extracts.[49] Further n.m.r. studies, combined with molecular mechanics calculations, indicated that the conformation of the central fructofuranose ring of kestose in solution differs from that previously observed in the crystal.[50] The full assignment of the ambient-temperature, high-fluid ^{1}H-n.m.r. spectrum for the reduced form (24) of a repeating tetrasaccharide unit of keratan sulfate has been achieved by 2D COSY and RELAYED-COSY experiments.[51]

β-D-Glc*p*NAc(6SO$_4$)-(1→3)-β-D-Gal*p*(6SO$_4$)-(1→4)-β-D-Glc*p*NAc(6SO$_4$)-(1→3)-D-Gal-itol

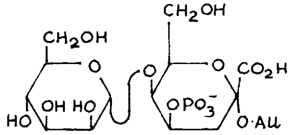
(24)

The ^{1}H- and ^{13}C-n.m.r. spectra of the *Shigella flexneri* type Y *O*-polysaccharide have been simulated, based on the recorded spectral parameters of the methyl glycosides **(25)**-**(27)** of its four constituent disaccharides. The fit between experimental and computed (CASPER program) chemical shifts has been closely examined.[52] The ^{1}H- and ^{13}C-n.m.r. spectra of a series of disaccharides containing α- or β-L-fucopyranose as the non-reducing moiety, *e.g.*, compounds **(28)**, have been used in a study on glycosylation shifts.[53]

(25) α-L-Rha*p*-(1→n)-α-L-Rha*p*-OMe n = 2 or 3
(26) α-L-Rha*p*-(1→3)-β-D-Glc*p*NAc-OMe
(27) β-D-Glc*p*NAc-(1→2)-α-L-Rha*p*-OMe
(28) α-or-β-L-Fuc*p*-(1→2)-α-or-β-D-Man*p*

A review with 243 references on the conformational analysis by molecular mechanics of complex carbohydrates, such as oligosaccharides, glycolipids, *N*- and *O*-type oligosaccharides of glycoproteins, and blood group antigens has been published,[54] and an angle-averaging procedure, developed for the conformational analysis of polymers, has been applied to disaccharides.[55]

The flexibility of the anhydropyranose ring of 1,6-anhydrolactose was found by ^{1}H-n.m.r. experiments and by theoretical computations to be restricted to φ -80 ±20° and ψ -120 ±40°, resulting in a 1:1 equilibrium between the $^{1}C_4$ and $B_{0,3}$ conformations in DMSO-d_6, with the $^{1}C_4$ form prevailing in D$_2$O.[56] The ^{1}H-n.m.r. spectra of methyl xylobioside in water and in methanol have been recorded at temperatures ranging from -15 to +85°C. The interglycosidic three-bond C-H coupling constants, but not the n.O.e. values, changed with temperature and/or solvent.[57] A conformational analysis by ^{1}H-n.m.r. spectroscopy of the calcium salt of the phosphorylated disaccharide **(29)** revealed the formation of a complex with Ca ions involving O-4 and O-6 of the mannose moiety and oxygen atoms of the phosphate group.[58]

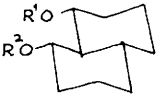


(29)

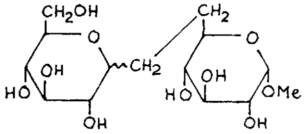
In an effort to derive information on the equilibrium about glycosidic bonds from ^{1}H-n.m.r. chemical shifts, the experimentally determined δ-values of α- and β-(1→2)-,(1→3)-, and (1→4)-linked glucobioses and methyl glucobiosides were related to HESA-calculated data.

Consideration of various through-bond and through-space effects yielded generalizations useful for predicting the conformations about the glycosidic linkages of other disaccharides and in particular about the sign of torsion angles ψ.[59]

The angular dependence of one-bond C-H coupling constants has been examined with model compounds related to (1→1)-, (1→2)-, (1→3)-, and (1→4)-linked disaccharides. Calculated, thermodynamically averaged values for $^{1}J_{C\text{-}1,H\text{-}1}$of methyl β-xylobioside, methyl β-maltoside, and methyl β-isomaltoside as well as for $J_{C\text{-}4',H\text{-}4'}$ of the last compound, using PSICO-computed conformer abundances, agreed well with experimental data.[60,61] In an investigation on the effect of the environment on the stability of isomaltose conformers, calculated $^{3}J_{C,H}$ values representing the average geometry about the glycosidic bond in four different solvents have been compared with measured coupling constants.[62]



(30) R^1= α-D-Glc-p, R^2= H
(31) R^1= H, R^2= α-D-Glc-p



(32) α-Linkage
(33) β-Linkage

Conformational studies by ^{1}H- and/or ^{13}C-n.m.r. spectroscopy in combination with theoretical calculations, focusing on the geometry of the interglycosidic linkage, have been carried out with the rigid isomaltose model (**30**) and its isomer (**31**).[63] Similar experiments have been reported for the *C*-disaccharide analogues (**32**) and (**33**) of methyl α-isomaltoside and methyl α-gentibioside, respectivly,[64] methyl β-lactoside, all its monodeoxy derivatives, its 3-*O*-methyl ether, and its *xylo*-analogue,[65] α-D-Man*p*-(1→2)-α-D-Man*p*-OMe,[66] the glycosaminoglycan degradation product (**34**),[67] the α-(1→4)-linked di- and tri-saccharides of D-galacturonic acid,[68] the peracetate of the cyclic trisaccharide (**35**),[69] and the four isomeric, α,α-, α,β-, β,α-, and β,β-linked, trisaccharides (**36**).

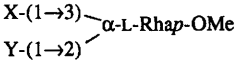
(**34**) β-D-Glc*p*A-(1→3)-D-Gal*p*NAc
(**35**) 6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1→6)-β-D-Glc*p*-(1
(**36**) D-Glc*p*-(1→2)-D-Glc*p*-(1→3)-α-DGlc*p*-OMe

In the last mentioned paper it was shown that the n.m.r. spectra for this type of trisaccharide can, in most cases, be calculated by application of the glycosylation effect to the respective disaccharide spectra.[70]

In a systematic investigation of branched trisaccharides, changes in the geometries of the glycosidic linkages of disaccharide glycosides (**37**) and (**38**) on introduction of a (1→2)- or (1→3)-branch, respectively, to give 2,3-disubstituted methyl α-L-rhamnopyranosides (**39**) have been measured (n.m.r. spectroscopy) and computed (molecular mechanics). In the main, insignificant restriction of rotation was observed, but in several cases conformational changes resulted in changed n.O.e. patterns and in deviation from additivity of glycosylation effects in the ^{13}C-n.m.r. spectra.[71]

(**37**) X-(1→3)-α-L-Rha*p*-OMe

(**38**) Y-(1→2)-α-L-Rha*p*-OMe

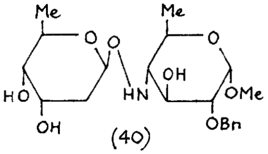


$$\begin{matrix}\text{X-(1}\to\text{3)} \searrow \\ \quad\quad\quad\quad\quad \alpha\text{-L-Rha}p\text{-OMe} \\ \text{Y-(1}\to\text{2)} \nearrow\end{matrix}$$

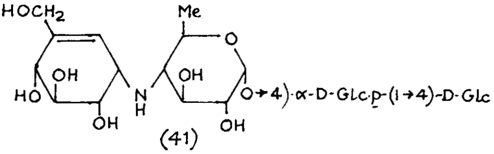
(**39**)

X,Y = α- or β-
D-Glc*p*-, D-Man*p*-,
L-Fuc*p*-, or L-Rha*p*

The conformational analysis by ^{1}H-n.m.r. spectroscopy of the disaccharide (**40**) and several monosaccharide analogues has been undertaken to gain information on the N-O interglycosidic linkage of calicheamycin oligosaccharides,[72] and similar studies on the glycosidase inhibitor acarbose (**41**) and its saturated *pseudo*-D-*gluco*- and *pseudo*-L-*ido*-analogues indicated that their preferred conformations are dependent on the ionization of the bridging nitrogen atom.[73]



(40)



(41)

A symposium paper on the 2D n.m.r. analysis of sialyl trisaccharides (**42**) has been published.[74] A new method for the measurement of long range C-H coupling constants has been applied to 6′-sialyllactose,[75] and in an extensive conformational investigation of sialyl oligosaccharides, such as compounds (**43**), the topographical differences between the lowest energy conformers of α-(2→3)- and α-(2→6)-linked derivatives have been highlighted.[76]

(**42**) α-NeuAc-(2→3)-β-D-Gal*p*-(1→4)-D-Glc

(**43**) α-NeuAc-(1→x)-β-D-Gal*p*-(1→y)-β-D-Glc*p*NAc

x = 3, y = 3 or x = 3, y = 4 or x = 6, y = 4

Molecular mechanics calculations on the conformational space of an α-(1→4)-glycosidic linkage in β-cyclodextrin have been presented.[77] The ^{1}H-n.m.r. spectra of natural and chemically modified cyclodextrins have been greatly altered by incorporation of chemical shift reagents into the internal cavity, resulting in transformation of the strongly coupled spectra into first order systems.[78] Performances of COSY and RELAY experiments in association with NOESY techniques allowed fast sequencing of substituted cyclic oligosaccharides; the procedure was applied to a cyclodextrin derivative for which self-inclusion of an aromatic moiety in the hydrophobic cavity induced large ring current effects, making the molecule amenable to 3-dimensional structure determination.[79]

Application of the selective INEPT method to a variety of natural product structures has been reviewed. Examples included flavonoid and terpenoid glycosides, where the technique proved useful in confirming the positions of saccharide substitution and intrasugar linkage.[80] Structural and/or conformational analysis by n.m.r. spectroscopy and/or computational methods have been reported for a number of complex carbohydrate-containing compounds: The new macrolide antibiotic roxithromycin,[81] ganglioside GD1a,[82] *O*-glycopeptides containing a β-D-xylopyranose group linked to a L-seryl residue (*N*-terminus of proteodermatan sulfate),[83] glycopeptides containing α-D-Gal*p*-NAc groups linked to L-threonin residues (*N*-terminus of interleukin-2),[84] a synthetic *N*-glycosylated cyclic heptapeptide,[85] and the *N*-terminus of the transmembrane sialoglycoprotein glycophorin A.[86]

A general molecular modelling methodology which employs molecular dynamics and energy-minimizing procedures with NOESY-derived constraints has been found particularly suitable for studies of unbranched complex carbohydrates. Its use was demonstrated on a fragment from the carbohydrate-protein linkage region of connective tissue proteoglycans.[87]

6 N.m.r. of Nuclei other than ^{1}H and ^{13}C

^{17}O-N.m.r. relaxation studies of α-(1→4)-linked glucans (glucose to maltoheptaose) in aqueous solutions over a wide range of concentrations have been reported. A discussion of the effect of chain length on correlation times is included.[88]

Selected acyclic and cyclic polyols, monosaccharides, disaccharides, higher oligosaccharides, and model compounds for lignin-carbohydrate complexes were reacted with 1,3,2-dioxaphosphanyl chloride, and the ^{31}P-n.m.r. spectra of the products were recorded in order to correlate the signals with structural details. Most of the carbohydrate derivatives exhibited well resolved resonances in the range 138-132 ppm, the number of lines corresponding to the number of hydroxyl groups present.[89]

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22

Other Physical Methods

1 I.r. Spectoscopy

Improved i.r. and Raman spectra were recorded at near liquid nitrogen temperatures of α-D-glucopyranose and its *C*-[1-^{2}H]-, *C*-[6,6-$^2H_2$]-, and per-*O*-deuterated analogues, for β-D-glucopyranose and its *C*-[6,6-$^2H_2$]- and per-*O*-deuterated analogues, and for the anomers of galactose and mannose. A modified valence force field calculation was developed to give a least squares agreement between observed and calculated frequencies for isotopic glucoses. The results provided insight into some older assignments of the group frequency type.[1] I.r. and Raman spectra of α,α-trehalose and its *C*-[2,3,4,6,6-$^2H_{10}$]-analogue (prepared using D_2O-Raney Ni) in the solid phase were recorded in the C-H and C-D stretching regions. Experimental values for frequency and intensity correlated closely with those calculated by normal co-ordinate analysis utilizing x-ray crystal structure data and taking into account the specific interactions of each C-H with nearby oxygen lone pairs. C-H stretching modes are sensitive to conformation. The relevance of the 2800-3000 cm^{-1} region in the deuterated sample for the study of the conformational properties of the interglycosidic linkage was discussed.[2] Bands corresponding to eight O-H stretching vibrations were identified in the polarized Raman and i.r. spectra of crystalline sucrose.[3]

Back-scattered Raman optical activity spectra were measured in the 700-1500 cm^{-1} region for a range of carbohydrates in aqueous solution. Features of the spectra were identified that appear to be characteristic of the stereochemistry of the sugars.[4] The i.r. spectra of methyl 2,3-di-, 2,3,6-tri- and 2,3,4,6-tetra-*O*-nitro-β-D-glucosides were examined in the 30-700 cm^{-1} range, and interpretation of the bands observed was given in terms of the conformation and location of the nitro-groups and of crystal lattice vibrations.[5]

2 Mass Spectrometry

Applications of fast atom bombardment (FAB)-m.s. and laser desorption-m.s. in the analysis of complex human milk oligosaccharides, phosphoinositol-linked glycans from surface glycoproteins, and high molecular weight glycosphingolipids (with up to 40 sugar residues) present in rabbit erythrocyte membranes, have been reviewed (45 refs.).[6]

Positive-ion FAB-m.s. appears to be very useful for determining the molecular weight and composition of underivatized di- and tri-saccharides. Information on the identity of the monosaccharide constituents can be obtained from metastable ion and collision activated dissociation (CAD) spectra of selected ions, but the type of linkage cannot always be determined unambiguously.[7] Principal component analysis has been applied to FAB metastable ion and CAD m.s. of mono- and oligo-saccharides.[8] The FAB-m.s. fragmentation of oligosaccharides has been studied in relation to the substituent at the reducing end.[9] The CAD spectra of the Na^+- adduct ions of several oligosaccharides have been compared with those of the protonated molecules.[10]

In a FAB-m.s. study of a range of derivatized sugars (incorporating methyl, benzyl, and *tert*-butyldiphenylsilyl ether and acetyl ester groups), $[M-H]^+$ was found to be the predominant ion rather than the usual $[M+H]^+$ ion, and a caution was given that this could cause confusion in the determination of molecular weight. The $[M+Na]^+$ ions were still present, although sometimes of low intensity.[11] The positive and negative ion FAB-m.s. and fragmentation of sulphated oligosaccharides derived from ovine lutropin have been described.[12] The position of the sulphate substituent in the four isomeric monosulphates of methyl α-D-mannopyranoside could be identified from the tandem FAB-m.s. analysis of the $[M+Na]^+$ and $[M-Na]^-$ ions.[13] The molecular weight and position of the sulphate ester on sulfatide (3-sulfogalactosylceramide) were determined without ambiguity by FAB-m.s.,[14] and the significant ions in the FAB-m.s. of 8-(mostly amino)-substituted 9-β-D-xylofuranosyladenines have been discussed.[15] *C*-Glycosidic flavonoids, isolated from *Passiflora incarnata* by reversed-phase h.p.l.c., were identified by positive and negative ion liquid secondary ion m.s. using a glycerol matrix and CAD to obtain daughter ion spectra.[16]

FAB ionization in combination with tandem m.s. has been used to differentiate the linkage position of five isomeric disaccharides in a study of the lithiated molecular ions,[17] and for detecting cyclodextrins (which can be added to water for masking volatile nolecules responsible for bad tastes and odours);[18] CAD of the $[M+H]^+$ ion of γ-cyclodextrin resulted in successive losses of glucose residues. High performance tandem m.s. employing a four-sector instrument has been used in the characterization of disaccharides. High energy CAD allowed differentiation of linkage types irrespective of the monosaccharide subunits.[19]

Diaastereoisomeric carbohydrate 1,2-orthocarbonate derivatives [*cf.*, Vol. 24, p.277, compound (4)][20] and 1,2-*trans*-2-deoxy-2-iodoglycosyl azides,[21] and some *N*-acyl derivatives of D-ribofuranosylamine[22] have been characterized by FAB-m.s. and -m.s.-m.s. studies.

The fragmentation pathways and ion-molecule interactions of monosaccharides during positive and negative ion desorption chemical ionization (c.i.) m.s. with methane as reagent gas have been reported.[23] Two known linear oligosaccharides derived from bacterial capsular polysaccharides were analysed by positive and negative ion laser desorption F.t. ion cyclotron resonance m.s. The high resolution spectra, obtained on <1 nmol of sample, displayed prominent pseudo-molecular ions and fragment ions derived from glycosidic bond and ring cleavages. Structures were proposed for some of the frequently observed ring fragments.[24] An internal standard method, employing perfluorotributylamine, has been established for determining the accurate relative molecular masses and elemental compositions of several non-volatile and thermally labile compounds (*e.g.*, a natural flavone α-glucopyranoside) by laser desorption e.i.-F.t.m.s.[25]

On e.i.-m.s., per-*O*-benzylated 1,2-, 1,3-, and 1,6-anhydroaldopyranoses were found to fragment essentially according to the rules for glycosides, although some differences were observed for 1,3-anhydrides which could be useful in the characterization of new derivatives of this type.[26] The major m.s. fragmentation pattern observed for the Schiff base adducts of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose with four aldehydes has been discussed.[27] The e.i.- and c.i.(NH_3)-m.s. of a series of anomeric 4,6-di-*O*-benzyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl *C*-glycosides have been reported [*cf.*, Vol.24, p.277, compound (1)].[28]

The mass-analysed ion kinetic energy (MIKE) and CAD spectra of per-*O*-methylated β-xylotriose were recorded under c.i. conditions using ammonia or amines (especially $MeNH_2$, Me_2NH, and $H_2NCH_2NH_2$) as reagent gas; this methodology permitted a straightforward determination of relative molecular mass.[29] The influence of fluoroine atoms on the spontaneous fragmentation and CAD of the $[M\text{-}OMe]^+$ and $[M+NH_4]^+$ ions derived from per-*O*-acetylated methyl deoxyfluoro-α-D-glucopyranosides has been examined.[30]

Ion-spray (or electrospray) m.s. involves a mild new ionization technique in which the substrate for analysis is introduced into the spectrometer in solution through a charged capilliary. Positive and negative ions generated in this way from the four isomeric β-linked reducing gluco-disaccharides reflected the linkage positions.[31] For large molecules, this technique produces a range of multiply charged ions with *m/z* ratios in a range suitable for analysis on conventional m.s. instruments. Thus the non-covalent enzyme-substrate and enzyme-product complexes involved in the hydrolysis of chito-hexasaccharide with egg white lysozyme could be observed by ion-spray m.s.[32]

Further applications of coupled h.p.l.c. - m.s. systems have been reported. A thermospray interface proved best for packed column (amino-bonded silica) supercritical fluid chromatography - m.s. analysis, with a methanol-modified carbon dioxide eluant, of trace amounts of four veterinary drugs including lincomycin.[33] By using a chloroform-containing eluant in the h.p.l.c.-m.s. analysis in the negative ion mode of a range of unprotected sugars on a primary amine-bonded silica column, dominant $[M + Cl]^-$ ions with little fragmentation were observed.[34] Adenosine was used as a model compound to demonstrate the use of a thermospray h.p.l.c.-m.s. with an ion source utilizing corona discharge ionization, interfaced to a quadruple ion trap m.s.[35] Other thermospray h.p.l.c.-m.s. applications were to the analysis of iridoid glycosides,[36] urinary metabolites of lamotrigine including two *N*-glucuronides,[37] the aminoglycoside antibiotic gentamicin complex,[38] and *O*-methylated dinucleotides in enzymatic digests of RNA (confirming the natural occurrence of *O*-2 methylation on ribose).[39]

3 X-ray and Neutron Diffraction Crystallography

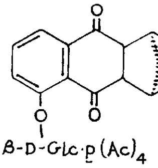
An X-ray and neutron diffraction study of the *O*-deuterated β-cyclodextrin ethanol octahydrate complex has been reported.[40] Published X-ray structures of seven nucleotide 3′,5′-cyclic phosphates and several related compounds have been compared, and the effects of substituents on phosphorus on the cyclic phosphate ring geometries examined.[41]

Specific X-ray crystal structures have been reported as follows (solvent molecules of crystallization are frequently not noted):

Free Sugars and Simple Derivatives Thereof. - Barium α-D-ribofuranose 5-phosphate (a reinvestigation).[42]

Glycosides, Disaccharides and Derivatives Thereof. - Methyl α-D-galactopyranoside 4-(sodium sulphate),[43] methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-altropyranoside,[44] methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside and methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside,[45] methyl 1-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-*manno*-octulopyranoside,[46] (2R)-2-(β-D-glucopyranosyloxy)-2*H*-1,4-benzoxazine-3(4*H*)-one,[47] a guaianolide lactone β-D-glucopyranoside,[48] the β-D-quinovoside jiocarotenoside A_1,[49] 6α, 8β, 15β-trihydroxy-3β,24(*R*)-di-(*O*-β-D-xylopyranosyl)-5α-cholest-22(23)-ene trihydrate,[50] rhododendrin [(2*S*)-4-(4-hydroxyphenyl)-butan-2-yl β-D-glucopyranoside],[51] 2,2,6,6-tetramethylpiperidin-1-oxyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside,[52] 2-*O*-α-D-galactopyranosyl-glycerol hexaacetate,[53] the cyclopentadiene - juglone glucoside cycloadduct (1),[54] bergenin pentaacetate (2),[55] the bis(gluco)crown ether (3),[56] and naringin hexahemihydrate [a 2-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl flavone].[57]

Oligosaccharides. - Panose [α-D-Glc*p*-(1→6)-α-D-Glc*p*-(1→4)-D-Glc*p* as an α,β-mixture in the ratio of 84:16],[58] stachyose tetrahydrate [α-D-Gal*p*-(1→6)-α-D-Glc*p*-(1→2)-β-D-Fru*f*] at 119 K to better refine a previous structure with disorder at some sites,[59] mono-2-*O*-[(*S*)-2-hydroxypropyl]cyclomaltoheptaose,[60] and cycloinulohexaose (4).[61]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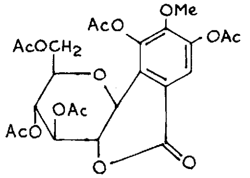
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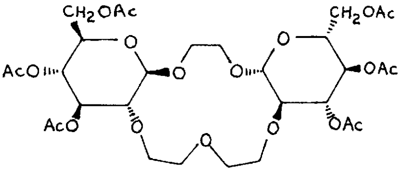
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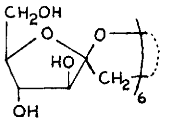
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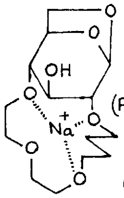
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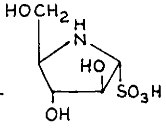
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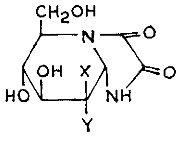

(7) X = OH, Y = H
(8) X = H, Y = OH

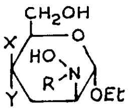
Anhydro-sugars. - The 1,6-anhydrogluco-crown ether (5).^{62}

Nitrogen- and Sulphur-containing Compounds. - The bisulphite adduct (6) of nectrisine (5-amino-5-deoxy-D-arabinose),^{63} kifunensine (7) which has a ${}^{1}C_{4}$ conformation,^{64} 8-*epi*-kifunensine (8) which has a ${}_{1}C^{4}$ conformation,^{65} 2-hydroxyamino-derivatives (9),^{66} (10),^{66} and (11),^{67} *N*-acetoxy-2,3,5,6-tetra-*O*-acetyl-*N*-methyl-α-D-mannofuranosylamine,^{68} the spirocyclic glycosylisoxazolidine (12),^{69} the isomeric hydantocidin derivative (13),^{70} the spirocyclic 1-amino-1-deoxy-fructose derivative (14),^{71} *N*-[2,2-bis(ethoxycarbonyl)vinyl]-α-D-ribofuranosylamine,^{72} the *lyxo*-oxazolidin-2-one (15),^{73} 3,4,6-tri-*O*-acetyl-2-deoxy-2-hydroximino-α-D-*arabino*-hexopyranoside,^{74} the isoxazoline (16),^{75} 2-deoxy-3,4-*O*-isopropylidene-2-*C*-nitro-6-*O*-pivaloyl-β-D-psicofuranose,^{76} the cyclic thiourea derivative (17)^{77} and its unsaturated analogue (18),^{78} 1,4-dimethyl-3-(D-*galacto*-pentitol-1-yl)-5-(*p*-tolyl)pyrazole,^{79} 7a-*epi*-alexaflorine (19),^{80} 6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-(*N*,*N*-dimethyldithiocarbamoyl)-α-D-galactopyranose,^{81} the dithioorthoformate derivative (20),^{82} and 1,6-anhydro-1(6)-thio-β-D-glucopyranose *S*-oxide.^{83}

Unsaturated Sugars. - 7,8-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*- and β-L-*glycero*-D-*galacto*-oct-7-enopyranoses,^{84} and 3-*O*-acetyl-5-deoxy-5-*C*-methylidene-1,2-*O*-(2,2,2-trichloroethylidene)-α-D-*xylo*-hexofuranurononitrile.^{85}

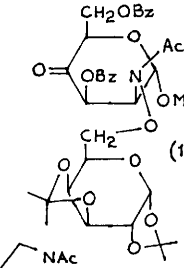
Branched-chain Sugars. - The cyclobutane derivative (21),^{86} the 2,3-fused pyranosides (22)^{87} and (23),^{88} the 2,3-fused-1,5-lactone (24),^{89} and the 2,4,6-tri-*C*-branched heptono-1,5-lactone (25).^{90}

Sugar Acids and their Derivatives. - D-*glycero*-D-*talo*-Heptono-1,4-lactone and its 2,3:5,6-di-*O*-isopropylidene derivative,^{91} 3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*altro*-heptono-1,5-lactone and 3,4-*O*-isopropylidene-D-altrono-1,5-lactone,^{92} *N*-tetradeca-6,8-diynyl D-gluconamide,^{93} ethyl 2-cyano-2,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-β-D-*manno*-2-octulosonate,^{94} sodium D-*arabino*-2-hexulosonate,^{95} and the *C*-ribofuranosyl glycine (26).^{96}



(9) R = Ph; X,Y = O

(10) R = Pr^i; X = H, Y = OH



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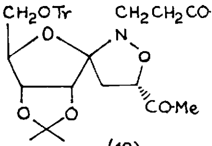

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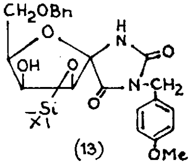

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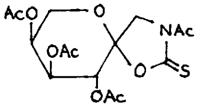

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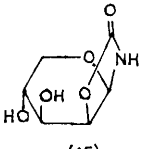
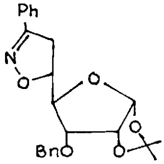
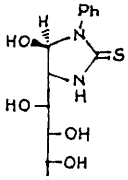


(15)



(16)



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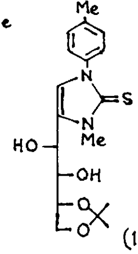

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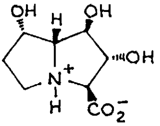

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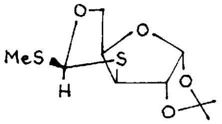

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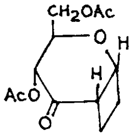

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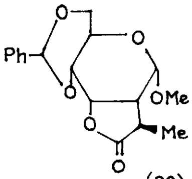

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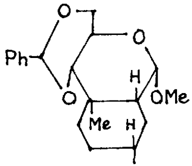

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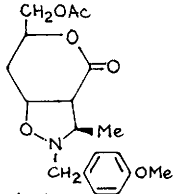

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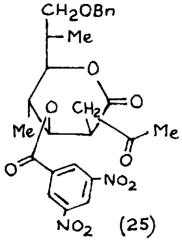

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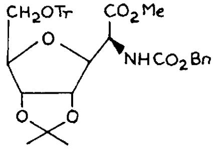

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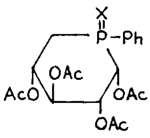
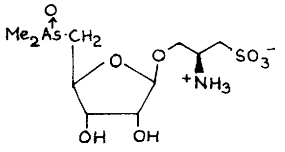


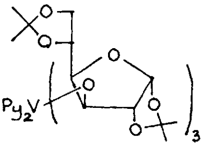
(27) X = O

(28) X = S



(29)

Inorganic Derivatives.- 1,6-Anhydro-2-chloro-2,4-dideoxy-4-(diphenylphosphoryl)-β-D-glucopyranose,[97] the P-in-the-ring sugar analogues (**27**) and (**28**),[98] the natural arsenic-containing riboside (**29**),[99] methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-triphenylstannyl-α-D-altropyranoside,[100] two isomeric chromium(III) complexes with 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol in the one structure,[101] the vanadium(III) complex (**30**),[102] and the platinum(II)-dithiocarbamate complex (**31**).[103]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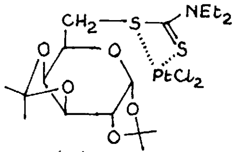
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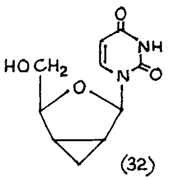
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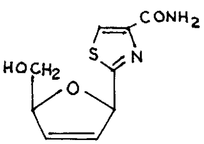
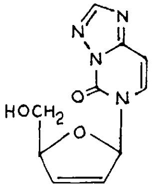

(33)

Alditols, Cyclitols and Derivatives Thereof.- D-Arabinitol,[104] D-altritol,[105] D-*glycero*-D-*manno*- and D-*glycero*-D-*gluco*-heptitols,[106] D-*glycero*-L-*galacto*-heptitol,[107] racemic perseitol (D-*glycero*-D-*galacto*-heptitol and its enantiomer),[108] 4-*O*-β-D-galactopyranosyl-D-glucitol dihydrate (lactitol),[109] hexa-*O*-acetyl-D-glucitol,[110,111] penta-*O*-acetyl-xylitol,[111] and methyl 1,5-di-*O*-acetyl-3,4-bis-*O*-(bicyclophosphoranylato)quinate.[112]

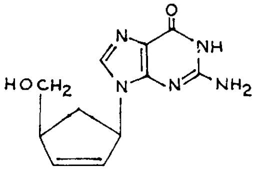
Nucleosides and their Analogues and Derivatives.- 2′-Deoxycytidinium phosphate salt,[113] 7-amino-4-β-D-ribofuranosyl-pyrazolo[1,5-*a*]pyrimidin-5-one,[114] 2-amino-7-methyl-9-β-D-ribofuranosyl-1*H*,9*H*-purine-6,8-dithione,[115] 7-methyl-4,5,7,8-tetrahydro-6*H*-3-β-D-ribofuranosyl-imidazo[4,5-*e*][1,4]diazepine-5,8-dione,[116] 5-carboxymethylaminomethyluridine monohydrate,[117] 1-(2-deoxy-β-D-*ribo*-hexopyranosyl)-5-iodouracil,[118] 5-bromouridine (a redetermination),[119] 2′-deoxy-5-azacytidine monohydrate (decitabine),[120] 2,2′-anhydro-5′-chloro-5′-deoxy-cytidinium chloride,[121] 2′,3′-anhydro-adenosine and its cyclopropyl-analogue (**32**),[122] 2′-*O*-(*S*)-tetrahydropyranyl-N^4-benzoylcytidine and 2′-*O*-(*S*)-tetrahydropyranyl-uridine,[123] (1*R*,6*R*)-2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-7,7,8,8-tetramethyl-*cis*-2,4-diazabicyclo[4.2.0]octan-3,5-dione (a photoadduct of 2′,3′-*O*-isopropylideneuridine with 2,3-dimethyl-2-butene),[124] 3′-*O*-acetylthymidine,[125] 2′,3′,5′-tri-*O*-acetyl-N^3-phenoxycarbonyluridine,[126] 2′-*O*-succinoyladenosine 3′,5′-cyclic phosphate,[127] 1-(2-deoxy-2-fluoro-β-D-arabinopyranosyl)-thymine and -5-ethyluracil,[128] 1-(2-deoxy-2-fluoro-α-D-arabinopyranosyl)-5-iodouracil,[129] 2′3′-dideoxy-3′-fluoro-cytidine,[130] - uridine and -5-bromouridine,[131] 3′-azido-2′,3′-dideoxy-5-bromouridine,[131] -5-methyluridine[132] and -5-chlorouridine,[133] 3′-amino-3′-deoxythymidine,[134] 1-(2,3-dideoxy-α-D-*erythro*-hexopyranosyl)thymine and the dioxane complex of its β-anomer,[135] 5-bromo-2′,3′-dideoxyuridine,[136] 1-(3-deoxy-β-D-*threo*-pentofuranosyl) cytosine,[137] the 2′,3′-unsaturated *C*-nucleoside (33) and its 2′,3′-dideoxy-analogue,[138] the unsaturated cytidine isotere (**34**),[139] 2′-deoxy-2′-methylidene-cytidinium chloride,[140] the carbocyclic nucleoside analogue (-)-carbovir (**35**),[141] 1-(2′-deoxy-3′-*C*-methyl-β-D-*erythro*-hexofuranosyl)thymine,[142] tetrakis(μ-acetato)-bis(1-methyladenosine)dirhodium(II),[143] and the dioxane nucleoside analogues (**36**).[144].

4 E.s.r. Spectroscopy

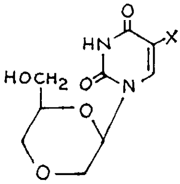
E.s.r. spectra recorded on aqueous alkaline solutions of 2-deoxy-sugars heated in the presence of



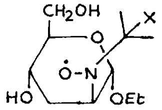
(34)



(35)



(36) X = H or Br



(37) X = H

(38) X = D

oxygen were interpreted in terms of the formation of enolate semiquinones.[145] Several radicals with semidione-like structures were observed by e.s.r. spectroscopic examination of the alkaline degradation products of some monosaccharides in DMSO containing tetrabutylammonium hydroxide, and a mechanism for their formation was proposed.[146]

Radicals induced by γ-irradiation of sucrose in the solid state at various temperatures and in aqueous solution, have been studied by spin-trapping, h.p.l.c., and e.s.r. techniques. Seven main radical species were identified, and chemical structures discussed for three of them.[147]

The e.s.r. spectra of the nitroxide (**37**) and its deuterio-analogue (**38**), formed by spontaneous oxidation of their hydroxylamine precursors, were recorded in 1,2-dimethoxyethane or diglyme solution at -50° to -120°C. Two conformers were frozen out at low temperatures, and their geometry was assigned from the observed spin coupling constants with the help of semi-empirical quantum mechanical calculations.[148]

The formation of free radicals from OH-radical attack on pyrimidine nucleotides has been investigated by a method combining spin-trapping, e.s.r., and h.p.l.c. with special emphasis on the detection of characteristic reactivity. For cytosine-related compounds, OH-radicals reacted with both the base and sugar moieties of the mononucleotides, but mainly with the sugar moieties of the polynucleotides to induce 4′-yl radicals. For uridine- and thymidine-related compounds, attack occurred on the base residues in both the monomer and polymer molecules. When DNA is attacked by OH-radicals, base damage occurs at the thymine base, while strand breaks are induced at the cytosine sugar residues.[149]

5 Polarimetry, Circular Dichroism and Related Studies

The calculated optical rotations of methyl β-D-arabinofuranoside, methyl β-D-fructofuranoside and sucrose as a function of ring conformations and, in the case of sucrose, of linkage conformation, has been described.[150] Anomeric *C*-(substituted)phenyl D-glucopyranosides can be distinguished on the basis of their Cotton effects at 260-280 nm.[151]

6 Electrochemistry

The electrochemical characteristics of synthetic derivatives of uridine, cytosine and their *arabino*-analogues, including deoxythio- and cyclo-analogues, have been examined and related to other properties (*i.e.*, h.p.l.c., biological, emymatic reactivity, and lipophilicity).[152,153]

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23

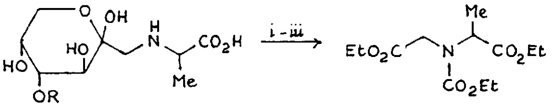
Separatory and Analytical Methods

1 Chromatographic Methods

General. - An extensive review on disaccharides has discussed their chromatography and analysis by both enzymic and non-enzymic methods.[1]

Gas-Liquid Chromatography. - All the following analyses were performed on capillary g.c. columns.

Amadori compounds, *N*-substituted 1-amino-1-deoxy-2-ketoses *e.g.* (**1**) in Scheme 1, formed by reaction of free sugars with the primary amino-groups in free amino acids, peptides or proteins can be determined by g.c. analysis of the *N*-(carboxymethyl)-amino acid derivatives *e.g.* (**2**) released by a protocol involving periodate oxidation of the sugar residue.[2]



(1) R = H or β-D-Gal*p*

(2)

Reagents : i, HIO_4 ; ii, H_3O^+ ; iii, EtO_2CCl, EtOH, Py, H_2O

Scheme 1

In a simple procedure that yields a mixture containing nearly equivalent amounts of all possible partially methylated, partially acetylated alditols from a given methyl glycoside, the sample is acetylated immediately following under-methylation. This ensures that all products can then be extracted into dichloromethane, and converted by hydrolysis, reduction ($NaBD_4$) and reacetylation into the alditol derivatives required as standards for g.c.-m.s. analysis.[3] The g.c.-c.i.m.s. (NH_3) analysis of the mycosamine (3-acetamino-3,6-dideoxy-β-D-mannopyranosyl) residues in antifungal heptaene antibiotics was achieved using alditol acetate derivatives.[4] In connection with the analysis of amino-sugar residues in marine triterpenoid oligoglycosides, 2-acetamido-1,5-di-*O*-acetyl-2-deoxy-2-*N*-methyl-3,4,6-tri-*O*-methyl-D-glucitol and -galactitol were synthesized from the corresponding free acetamido-sugars.[5]

The reductive cleavage methodology of Gray and co-workers has been applied to the analysis of commercial *O*-carboxymethylcellulose samples to determine the position of the substituents. Permethylation, reductive cleavage (Et_3SiH-MeOTf-$BF_3.OEt_2$), and acetylation yielded the eight possible 4-*O*-acetyl-1,4-anhydroglucitol derivatives bearing methyl or carboxymethyl substituents on O-2,3 and -6.[6]

The four isomeric 1,4:3,6-dianhydrohexitol mononitrates were determined in plasma without the need for derivatization by g.c. with electron capture detection.[7]

G.c.-m.s. analysis of partially methylated pertrimethylsilylated aldoses obtained from natural glycosides containing pentose, hexose and 6-deoxyhexose residues by permethylation, hydrolysis and silylation was claimed to be a reliable alternative to the more conventional analysis using partially methylated alditol acetate derivatives. Characteristic m.s. fragmentation patterns were obtained at an ionization potential of 20 eV and a reduced ion-source temperature (170°C), conditions chosen to enhance the proportion of structurally significant ions. These fragmentation patterns permitted the sites of methylation to be identified, and reference data for 25 derivatives were given.[8] To permit the diagnosis of various diseases, an automated procedure for screening urine samples for carbohydrates, organic acids, and amino-acids following urease treatment has been developed utilizing trimethylsilylation-g.c.-m.s. analysis.[9] 1-*O*-(2-Ethylhexanoyl)-β-D-glucopyranuronic acid was detected by trimethylsilylation-g.c.-m.s. (e.i. and c.i.) as a metabolite of the industrial chemical 2-ethylhexanoic acid.[10]

The simultaneous g.c. analysis of sugars (Ara, Rha, Fru, Gal, Glc, sucrose, maltose and raffinose), sorbitol, and nine organic acids in vegetables and strawberries utilized derivatives produced by oximation - trimethylsilylation.[11]

Thin-Layer Chromatography. - The mobility of sugars and sugar alcohols on thin-layer ion-exchange sheets (Polygam Ionex-25 SA) in various metal ion forms was used to assess their comparative ability to form complexes with these metal ions. The results, with some exceptions, confirmed previous findings.[12] Starch degradation products, e.g. glucose, maltose, malto-oligosaccharides and cyclodextrins present in complex fermentation broths, have been detected by a rapid h.p.t.l.c. method using silica plates.[13] Flavonoid *O*- and *C*-glucosides have been separated from their galactoside analogues on silica, cellulose and polyamide thin layers.[14] An examination of the t.l.c. behaviour of twenty-one 2′-deoxyuridines bearing various 5-*C*-alkyl substituents, on alumina layers with or without impregnated paraffin oil has led to the conclusion that a mixed absorption and reversed-phase retention mechanism is operative in both instances.[15,16] The acute toxicity of cardiac glycosides has been correlated with their lipophilic character, as determined by t.l.c. on silica impregnated with silicone DC200.[17]

High-Pressure Liquid Chromatography. - A new sensitive, selective amperometric detector has been developed, based on the oxidation in alkaline solutions of carbohydrates on a glassy carbon electrode onto which has been cast copper/copper oxide particles dispersed in a Nafion film. This system substantially lowers the overpotential for oxidation. Its use was demonstrated for the quantitation of various aldoses, sugar alcohols, and disaccharides in h.p.l.c. and flow injection analyses.[18]

The separation of aldoses, fructose and sucrose on h.p.l.c. columns with *N*-methyl-4-vinylpyridinium-divinylbenzene polymer packings has been reviewed.[19] The h.p.l.c. retention of various mono- and oligo-saccharides on silica modified with piperazine in the mobile phase has been reported in connection with a mathematical description of the molecular interactions in normal and reversed-phase chromatography.[20] The carbohydrates present in lichens (Glc, Fru, ribitol, arabinitol, and mannitol) and sugar cane juice (Xyl, Ara, Gal, Fru, Glc, and sucrose) were determined by h.p.l.c. on a bonded aminopropyl silica column eluted in a "reversed-phase mode" (*i.e.* with $MeCN-H_2O$) and with u.v.-detection. This method gave good separation of alditols, which can otherwise be difficult to achieve.[21] Analytical and preparative scale separations of 2-deoxyaldoses and 2-deoxy-2-fluoro-D-glucose, -mannose, and -galactose were achieved on a polystyrene-based strong cation exchange resin in the H^+ -form.[22] The analysis (on a strong cation exchange resin with an acidic eluant) of metabolites from the tricarboxylic acid cycle, glycolysis, ketogenesis, adenine nucleotide metabolism, and ethanol oxidation, that are present in organ perfusates is of interest, since the relative retentions of ribose, fructose, glucose and galactose were given with respect to several other compounds.[23] Reducing sugars were determined at trace levels by h.p.l.c. on a Ca^{2+}-form cation exchange resin column at 70°C with an aqueous calcium EDTA eluant and post-column fluorometric detection with benzamidine. Benzamidine has also been shown to be a selective reagent for sugars in complex mixtures because it does not react with amino acids, aldehydes, ketoacids, carboxylic acids, or nucleosides, and it reacts more rapidly with aldoses than do other fluorigenic reagents (M.Kai *et al*, *Anal. Sci.*, 1985, *1*, 59). Detection limits were 16-63 pmol at a signal to noise ratio of 3:1.[24]

For the analysis of the carbohydrate composition of glycoproteins, methods have been reported that: i) purify the glycoprotein in 90% yield on a Sephadex G25 column; ii) convert the glycoprotein constituent sugars into methyl glycosides in a methanolysis procedure that can be rapidly optimized for specific samples using a simplex optimization procedure (*e.g.*, 1.2 M HCl in MeOH, 66°C, 8.1 h for α_1-acid glycoprotein; 1.5 M HCl, 73°C, 12.5 h for tissue plasminogen activator); and iii) separate the methyl glycosides by reversed-phase h.p.l.c. analysis with light scattering detection. Retention data for the methyl glycosides of Glc, Gal, Man, Xyl, GlcNAc, Fuc, Rha, GalNAc, and Lyx were reported.[25]

Mono- and di-galactosyl diacylglycerols from barley leaves have been purified by h.p.l.c. on silica and used for monolayer and Langmuir-Blodgett film studies.[26] Complex natural mixtures of flavonoid glycosides have been assayed by reversed-phase h.p.l.c. with photodiode array u.v. detection.[27] The use of a computer software package for optimizing h.p.l.c. analyses was demonstrated for the reversed-phase separation of the flavonoid glycosides of marshmallow (*Althaea officinalis*).[28] The influences of the aglycone and the sugar moieties of red fruit anthocyanins on their reversed-phase h.p.l.c. retention has been distinguished and quantified.[29] Reversed-phase analyses of acidic saponins from ginseng on a porous glass support allowed the isolation of heat-unstable triterpene oligoglycosides bearing a 6-*O*-malonyl-β-D-glucopyranoside moiety.[30]

The content of α-linked glucodisaccharides in a mixture containing also D-glucose and trisaccharides was determined by reduction to the corresponding alditols and h.p.l.c. analysis on three different columns: polystyrene-based cation exchange resin, carbamoyl-silica, and cyano-silica.[31] An impressive separation of nine glucodisaccharides was achieved on a graphitized carbon column (Hypercarb) with gradient elution (molar aq. NaOH containing 1.5 - 5% MeCN), and pulsed amperometric detection. Eleven monosaccharides, three cyclodextrins and three glucosylcyclodextrins were also chromatographed on this column. Retention times for monosaccharides were too short to allow separation. Without alkali in the eluant, free sugars gave separate peaks for the anomers; this method was therefore suitable for determining anomerization rates.[32]

Selective determination of β-D-gluco-oligo- and poly-saccharides (of DP up to 30) in the presence of other oligo- and poly-saccharides, especially α-D-glucans, has been achieved. Impressive reversed-phase separations were followed by selective detection of the β-glucans using two post-column enzyme reactors and an electrochemical detector in sequence. The first reactor contained an immobilized commercial cellulose preparation capable of hydrolysing all β-linked glucans to β-D-glucose. The second reactor contained immobilised glucose oxidase, which produced hydrogen peroxide from oxygen in the oxidation of β-D-glucose. The hydrogen peroxide was then detected electrochemically.[33] Malto-oligosaccharides (DP 1-10) formed by digestion of dextrins by a membrane immobilized glucoamylase have been assayed by reversed-phase h.p.l.c.[34] The separation of malto-oligosaccharides (DP up to 7) on a strong anion exchange gel column and detection using a post-column oligosaccharide dehydrogenase reactor, wherein reducing terminal glucose residues are oxidized in the presence of 1-methoxyphenazine methosulphate which is reduced then detected electrochemically, is useful for the determination of trace amounts, the detection limit being 3 μM.[35] The fructo-oligosaccharides sucrose, raffinose and stachyose were separated (though only moderately well) on a cation exchange resin in the H^+-form with water as eluant, and determined using a novel coupled dual enzyme reactor and coulometric detection system. The fructose in the eluted oligosaccharides was first released by hydrolysis using an immobilized invertase, then oxidized with immobilized fructose dehydrogenase in the presence of hexacyanoferrate(III) ion. The hexacyanoferrate(II) ion so produced was detected electrochemically. The methodology proved to be of little practical value, however, due to difficulties in maintaining the immobilized invertase reactor which had to be renewed every eight days.[36]

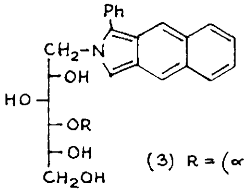
Further applications of h.p.l.c. on pellicular strong anion exchange resins with strongly alkaline eluants coupled with pulsed amperametric detection have been investigated because of the particularly good separations that can be attained and the high sensitivity of the detection system. In a thorough investigation of the separation of sugars and sugar alcohols, 93 compounds were examined including all tetroses, pentoses and hexoses, tetritols, pentitols and hexitols, and most of the common ketoses, di-, tri-, and tetra-saccharides. Correlations were made of retention times with structural and chemical features, and with chain length in homologous oligosaccharide series, of responses of the same compounds to pulsed amperometric and refractive index detectors, and of results reported from different laboratories.[37] Guidelines have been given for the selection of optimal potential and time parameters in the waveform to be used in pulsed amperometric detection following a study of the chromatography of D-glucitol, D-glucose, D-fructose, sucrose and maltose.[38]

In connection with a study of the branching patterns of amylopectins, the h.p.l.c. on pellicular anion exchange resins of linear and branched gluco-oligosaccharides has been examined. The response of malto-oligosaccharides as a function of degree of polymerization, and the effect of α-(1→6)-glycosidic linkages on retention times of linear pullulan oligosaccharides and glucosyl- and maltosyl-branched oligosaccharides from enzymatically degraded maize starch, were determined. The identities of peaks corresponding to pullulan fragments, singly branched malto-oligosaccharides (DP 6-14), and α-amylase limit dextrins from singly branched cyclodextrin were established.[39] Koizumi *et al.* have extended their earlier qualitative work on the h.p.l.c. of gluco-oligosaccharides (Vol.23, p.257) to the quantitative assay of malto-oligosaccharides released from amylopectins by the debranching enzyme isoamylase. Peak responses were determined using individual oligosaccharides (DP 6-17) isolated by h.p.l.c. on an amino-column (a vinyl alcohol copolymer with bonded polyamine groups) and a reversed-phase column. The chain length distributions in some typical amylopectins could be characterized in detail.[40]

Other studies utilizing pellicular anion exchange resin chromatography have reported the separation of xylose oligomers (DP 1-7) and some hexoses and hexosamines, and the analysis of monosaccharides in peat samples,[41] neutral sugars, amino-sugars and uronic acids, in plant residues, animal wastes, sewage sludge, microbial polymers, and soil,[42] saccharides in milk and dairy products,[43] high-mannose oligosaccharides isolated from yeast and mammalian glycoproteins,[44] and five acidic monosaccharides and a number of salic acid containing oligosaccharides.[45] In the development of an assay for plant sugars and starch digestion products (*i.e.* malto-oligosaccharides up to DP 30) in ruminal digesta of cattle, utilizing this h.p.l.c. methodology, the recoveries of sugars were evaluated by use of a variety of sample purification procedures, *i.e.* perchloric acid or ethanol precipitation, and solid-phase extraction on phenyl- or C_{18}-silica columns.[46]

The conversion of sugar mixtures to their fluorescent *N*-(2-pyridyl)-1-amino-1-deoxyalditol derivatives by reductive amination, and analysis by high performance anion-exchange chromatography, has been described.[47] Nine neutral and ten acidic oligosaccharides obtained by endoglycoceramidase hydrolysis of glycosphingolpids were derivatized as their oligoglycosyl *N*-2-pyridyl-1-amino-1-deoxyalditols by reductive amination (using $BH_3.NHMe_2$ as described by Kondo *et al*, *Agric. Biol. Chem.*, 1990, *54*, 2169) and separated by h.p.l.c. on reversed-phase or amide-silica columns. Retention on the reversed-phase column depended upon the number and position of sialic acid and *N*-

acetylhexosamine residues, while on the amide-silica column it depended on the total number of sugar residues. Retention data could thus be used to make 2D-maps for such oligosaccharides.[48] Complex tri- to octa-saccharide fragments obtained by cellulose digestion of xyloglucan were similarly converted to *N*-(2-pyridyl)oligoglycosylalditolamines and separated by reversed-phase h.p.l.c.[49] An alternative derivatization procedure was applied to malto-oligosaccharides (DP 1-18). These were converted into their corresponding 1-amino-1-deoxy-alditols by reductive amination under optimized conditions (dilute in 4 M ammonium salt solution, $NaBH_3CN$, 100°C, 2 h), reacted with 3-benzoyl-2-naphthaldehyde and potassium cyanide to yield the fluorescent derivatives (**3**), and assayed on a reversed-phase h.p.l.c. microcolumn (250 μm i.d., with 5 μm C_{18}-silica packing).[50] The electrophoretic separation of related derivatives is covered in section 2 of this chapter.



(3) R = $(\alpha\text{-D-Glc}p)_n$

Glycosylamines have proved to be useful derivatives in the separation of oligosaccharides. Conversion of oligosaccharides to their peracetylated *N*-[4-(pentafluorobenzyloxycarbonyl)phenyl]-glycosylamine derivatives permitted the evaluation of samples by h.p.l.c. (on an aminopropylsilica column) or supercritical fluid chromatography (s.f.c.). The derivatives were suitable for u.v. or fluorescence detection, and femtomole amounts could be detected by s.f.c. - negative ion c.i.-m.s.[51] A new reversible derivatization procedure for reducing oligosaccharides involved the formation of *N*-fluorenylmethoxycarbonyl-glycosylamines. These materials were stable at pH 7 for at least a month, but could be hydrolysed back to the free sugar form (with 15% aq. NH_3). Excellent h.p.l.c. separations were attained for milk oligosaccharides derivatized in this way.[52]

H.p.l.c. methods revealed the products and byproducts formed during a) the catalytic oxidation of lactose to lactobionic acid, and b) the alkaline oxidative degradation of lactose to 3-*O*-β-D-galactopyranosyl-D-arabinonic acid. Non-ionic sugar products were determined on series connected acetate-form anion and H^+-form cation exchange resin columns with water as eluant and refractive index detection. The anionic column adsorbed the anionic products. Lactose and lactulose co-eluted, so that a separate assay for lactulose using an ice-cooled reversed-phase column was employed when necessary. Anionic oxidation products were independently analysed on anion exchange resins either in the Cl^--form with an aqueous $NaCl$-$MgCl_2$ eluant, or in the SO_4^{2-}-form with an aqueous $(NH_4)_2SO_4$ eluant, with series u.v. and refractive index detection.[53] Both volatile and non-volatile organic acids, including gluconic acid, present in technical sugar solutions could be determined without prior isolation of the acids by h.p.l.c. on a strong acid exchange resin in the H^+-form, with an acidic eluent, and using a post-column anion-exchange micromembrane suppressor and a conductivity detector.[54]

Gluconolactone, galactonolactone and galactitol in the urine of galactosemic patients were determined by reversed-phase analysis of their per-*O*-(*N*-phenylcarbamate) derivatives (prepared by reaction with PhNCO in DMF, 100°, 1 h), with u.v. detection of as little as 0.05 ng. The separation of the two lactones has been a difficult problem, and this method provides a simple solution.[55]

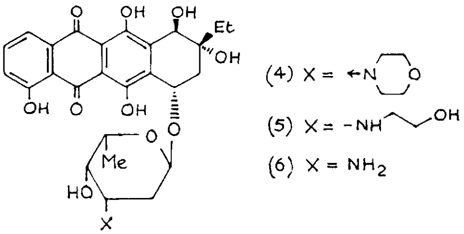
H.p.l.c assays of the following drugs and their metabolites in biological samples have been reported: morphine and its 3- and 6-glucuronide by reversed-phase[56] and ion-pair reversed-phase[57] methods, codeine, norcodeine, morphine, normorphine and their glucuronides by an ion-pair reversed-phase method with electrochemical detection,[58] aspirin, its phenolic and its ester glucuronide, and salicyluric phenolic glucuronide by reversed-phase chromatography on a phenyl-silica column,[59] and the anticonvulsant lamotrigine and its *N*-glucuronide.[60] A reversed-phase assay for 4-methylumbelliferone and its glucuronide and sulphate conjugates and their [^{3}H]-radiolabelled analogues in biological fluids has also been reported.[61]

A reliable simultaneous reversed-phase h.p.l.c. assay for ascorbic acid and dehydroascorbic acid in biological systems utilized sequential electrochemical and u.v. detection.[62] The determination of these acids in dairy foods was achieved by derivatization with 4-methoxy- or 4-ethoxy-1,2-phenylenediamine to form quinoxaline derivatives, reversed-phase chromatography and fluorescence detection. Detection limits were 50 and 70 fmol per 5 µl injection, respectively.[63] Simultaneous determination of ascorbic acid and sulphite in beer was achieved using a strong acid resin column, acid eluant, and pulsed amperometric detection.[64]

Homologous series of oligo-galacturonic, -guluronic, and -mannuronic acids have been separated by ion-pair reversed-phase h.p.l.c., using divalent-cation salt solutions containing 0.05% dodecyltrimethylammonium chloride as eluant. Separations were dependent upon the ionic strength of the eluant and the nature of the cation.[65] Oligogalacturonic acids (DP up to 7) from *endo*-polygalacturonase and pectate lyase depolymerisation of polygalacturonic acid were isolated in gram quantities by automated h.p.l.c. on a preparative 1-aminopropyl-silica column.[66] Tetra- and hexasaccharides from hyaluronidase digestion of sinovial fluid hyaluronic acid were assayed by ion-pair reversed-phase h.p.l.c. as a means of determining hyaluronic acid content.[67]

The aminoglycoside antibiotic spectinomycin was assayed in plasma by formation of its 2,4-dinitrophenyl hydrazone, reversed-phase chromatography and detection at 405 nm,[68] while neomycin in plasma and urine was assayed by ion-pair reversed-phase chromatography with post-column derivatization with *o*-phthalaldehyde and fluorescence detection.[69] The chemotherapeutic agent morpholino-anthracycline MX2 (**4**), its metabolites (**5**) and (**6**), and the deglycosylated anthracycline were determined in biological samples by reversed-phase h.p.l.c.[70]

The pool of purine bases, nucleosides and nucleotides on body fluids and tissues has been assessed by reversed-phase h.p.l.c. procedures.[71] The relationship between the retention parameters for



O-benzoylated pyrimidine nucleosides and their bases on reversed-phase h.p.l.c. and their antitumour activity has been studied.[72] Other reversed-phase analyses of nucleosides were of the drugs 2′,3′-dideoxyinosine,[73] 6-methylthiopurine riboside with 6-dimethylaminopurine riboside as internal standard,[74] 1-β-D-arabinofuranosyl-*E*-5-(2-bromovinyl)uracil, its base metabolite, and its chloro-analogue as internal standard,[75] 5-trifluoromethyl-2′-deoxyuridine,[76] all in biological samples, as well as 5-methylcytosine released from curcurbit DNA,[77] and purine dinucleoside polyphosphates.[78] 5-Fluoro-2′-deoxyuridine and its base, along with bromouridine as internal standard were analysed on a Zorbax RX column.[79] Reversed-phase separations were conducted on both the analytical and preparative scale for dideoxyribonucleosides, and for 3′-azido-3′-deoxythymidine (AZT) and AZT-5′-phosphate,[80] the guanosine-malonaldehyde adduct β-D-ribofuranosyl pyrimido[1,2-*a*]purin-10(3*H*)-one,[81] and the *N*-alkylated adducts formed by reaction of 2′-deoxy-cytidine and -guanosine with phenylglycidyl ether in methanol.[82]

Ion-pair reversed-phase h.p.l.c. with gradient elution separated all the nucleosides, nucleotides, and bases present in macrophages.[83] The metabolism of nucleosides in mitochondria was studied by using ^{14}C-labelled nucleosides and ion-pair reversed-phase h.p.l.c. analysis. Adenosine was predominately deaminated to inosine and subsequently converted to hypoxanthine, while guanosine was degraded to guanine.[84] The adenine metabolism in cells during tumour growth was similarly assessed, with separate analyses of nucleotides and of nucleosides and bases being conducted.[85] *S*-Adenosyl-L-methionine and -L-homocysteine in rat tissues were also assayed by ion-pair reversed-phase h.p.l.c.,[86] as were adenosine, inosine, and hypoxanthine in cell suspensions on a microbore column (2.1 mm i.d.).[87]

Useful separations of a variety of nucleosides and bases were achieved by h.p.l.c. on silica with an ethyl acetate eluant containing a polar modifier of poor solubility (ethylene glycol, triethylene glycol, or formamide). Under these conditions, a liquid stationary phase composed mostly of modifier is formed on the pores of the silica, leading to a mixed retention mechanism.[88] The retention of twenty-one 5-*C*-alkyl-2′deoxyuridines on alumina has been correlated with structural elements in the compounds.[15]

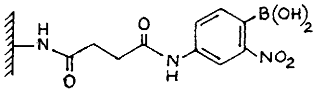
Applications of h.p.l.c. - thermospray m.s. techniques to the analysis of natural iridoid glycosides,[89] four components of the aminoglycoside gentamicin complex,[90] urinary metabolites of lamotrigine including two *N*-glucuronides,[91] and naturally occurring 2′-*O*-methylated dinucleotides in enzymatic digests of RNA[92] have been reported. By using a chloroform-containing eluant in the h.p.l.c. separation of aldoses, ketoses, and a variety of reducing and non-reducing disaccharides on a primary amine-bonded silica column, chloride ions are generated in the ion source during negative-ion m.s., leading to dominant $[M + Cl]^-$ quasimolecular ions with little fragmentation.[93] Adenosine was used as a model compound to demonstrate an h.p.l.c.-thermospray m.s. system utilizing corona discharge ionization and a quadrupole ion-trap m.s.[94] Lincomycin was one of four veterinary drugs detected in trace amounts by supercritical fluid chromatography on an amino-bonded silica column with a methanol-modified carbon dioxide eluent interfaced with a mass spectrometer.[95]

Partition Chromatography. - Applications of rotation locular and droplet counter current chromatography (RLCCC and DCCC) to the separation of natural products such as flavonone and stilbene glycosides and steroidal glycoalkaloids have been reported.[96]

Column Chromatography. - The separation of hexoses, pentoses, and polyols on polystyrene-based cation-exchange resins with water as eluant has been examined as a function of the bound cations (Ca^{2+}, Sr^{2+}, Ba^{2+}, Pb^{2+}, Y^{3+} and Pr^{3+}). The separations depend upon the extent of complexation. Aldoses form weak bidentate complexes, while polyols form tridentate complexes.[97] Pure xylitol can be separated from its mixture with L-arabinitol on a La^{3+}-form cation-exchange resin, due to its stronger complexation.[98] The mixture of epimeric 1-deoxy-1-nitroalditols and parent aldoses formed from addition of nitromethane to aldoses can in some instances be separated on such La^{3+}-form resin columns.[99]

D-Glucose was retained marginally longer than L-glucose on proteoliposomes containing red cell glucose transport protein immobilized on an octyl sulphide Sephacryl gel bead column.[100]

The binding of methyl β-D-ribofuranoside, cytidine and adenosine to a column bearing the substituted phenylboronic acid ligand (7) was examined. The nitro-group enhanced complexation between the boronic acid group and the *cis*-diol groups in these ribosides so that it occurred at less alkaline pH values and increased the speed of complexation - decomplexation.[101]



(7)

Neutral oligosaccharides in human milk, ranging from fucosyllactoses to trifucosyllacto-*N*-hexaoses, have been separated by gel permeation chromatography on a hydrophilic vinyl-polymer and quantified by refractive index detection.[102] The chromatographic behaviour of isomeric diglucosylated cyclomaltoheptaoses on an amino-bonded stationary phase column has been reported.[103]

A reversed-phase chromatography technique for the preparative separation of polar compounds has been demonstrated with the separation of a simple nucleoside mixture.[104] A group separation of the 2′-deoxyribonucleoside, nucleotide and nucleobase constituents of normal and modified nucleic acids was achieved by gel permeation chromatography, and further separation was achieved on a hydrophilic acrylate polymer operating in the partition mode.[105] Mononucleotides are selectively bound at low pH to Fe(III) immobilized on agarose gel due to their free phosphate ester group, and can be recovered with a neutral eluant. Nucleosides and molecules with phosphate diester groups are not retained.[106]

2 Electrophoresis

Glucose, sucrose and raffinose were analysed in 30 seconds or less by moving boundary electrophoresis as their borate complexes. Using a laser-based refractive index detector for concentration gradient detection, the detection limit was sub-millimolar.[107] A complete separation of all aldopentoses and aldohexoses, and good separations of gluco-oligosaccharide linkage isomers, were achieved by capillary zone electrophoresis of the borate complexes of the glycosylamine derivatives formed by their reaction with 3-methyl-1-phenyl-2-pyrazolin-5-one (in MeOH-NaOH).[108] Reductive amination ($NaBH_3CN$ - 4M ammonium salt) of oligosaccharides and condensation of the resulting oligoglycosylated-1-amino-1-deoxy-alditols with 3-(4-carboxybenzoyl)-2-quinolinecarboxaldehyde converted oligosaccharides into fluorescent derivatives suitable for open-tubular or polyacrylamide gel-filled capillary electrophoresis. Excellent separations of derivatives produced in this way from malto-oligosaccharides (of DP 1-18), and complex oligosaccharide mixtures produced by enzyme digestion of chondroitin sulphate A and hyaluronic acid, were achieved with the latter system.[50] Reducing mono- to oligo-saccharides could be separated by polyacrylamide gel electrophoresis (PAGE) of the charged fluorescent derivatives formed by reductive amination ($NaBH_3CN$) with the 8-aminonaphthalene-1,3,6-trisulphonic acid. This procedure effectively separated malto-oligosaccharides up to DP 7, certain isomeric disaccharides, and epimeric monosaccharides, and was applied to monitoring the enzymic degradation of picomolar quantities of complex oligosaccharides with neuraminidase and β-galactosidase.[109] A related method was developed for sequencing linear oligosaccharides. Samples were reductively aminated with 7-amino-1,3-naphthalenedisulphonic acid, purified by preparative gradient PAGE, and isolated by semi-dry electrotransfer onto positively charged nylon membrane and elution with aqueous sodium chloride. The oligosaccharide conjugates so obtained were degraded with a selection of *exo-* and *endo-*glycosidases and re-examined by gradient PAGE analysis.[110]

D-Gluconic and galactaric acids appear as analytes in a study of the application of capillary electrophoresis to the analysis of organic and inorganic anions using a chromate electrolyte, an electroosmotic flow modifier, and indirect u.v.-detection.[111] Gluconic acid was included amongst anionic substrates analysed by a "NICE-Pak" capillary electrophoresis system that uses a u.v.-chromophore in the electrolyte, so that the anions are detected by a lowered u.v.-absorption.[112] Seven water-soluble vitamins including ascorbic acid and two fat soluble vitamins were separated using micellar electrokinetic capillary chromatography.[113]

A new Z-shaped flow cell for u.v.-detection in capillary electrophoresis was shown to increase the sensitivity up to 14-fold over conventional on-column u.v.-detectors using the separation of nucleosides and nucleotides as a demonstration.[114] Cytosine β-D-arabinofuranoside, an antileukaemic agent, was detected down to 0.5 μM in plasma by capillary zone electrophoresis.[115] DNA damage in carcinogenisis studies could be assessed by an analysis of the 2′-deoxynucleoside 5′-monophosphates released through a sequence involving h.p.l.c. enrichment, dansylation, and micellar electrokinetic capillary chromatography with laser-induced fluorescence detection.[116]

3 Other Separatory and Analytical Methods

Sugars have been selectively removed from aqueous solution by adsorption onto precipitated iron(III) hydroxide. Under conditions in which about one-third of D-mannose and D-fructose were removed, 70-80% of the malto-oligosaccharides present in a starch hydrolysate were removed. Trehalose was unaffected, indicating a requirement for a hemiacetal function.[117]

The inclusion of 'sulphamate' (partially neutralised sulphamic acid) in the *m*-hydroxybiphenyl - sulphuric acid reagent used in the colourimetric analysis of uronic acids suppressed the unwanted colour formation from even relatively high concentrations of neutral sugars, significantly improving the selectivity of this assay.[118] A simple quantitative colourimetric assay for 2-deoxy-D-galactose in the presence of D-galactose and other aldohexoses used 2-thiobarbituric acid as reagent.[119] A study on the chromogens formed by hexoses with phenols in sulphuric acid has focused on the formation of 5-hydroxymethyl-furfuraldehyde and its condensation with resorcinol or orcinol.[120]

The development and use of glucose detecting electrodes based upon composites of glucose oxidase with the conducting polymer polypyrrole have been pursued.[121,122]

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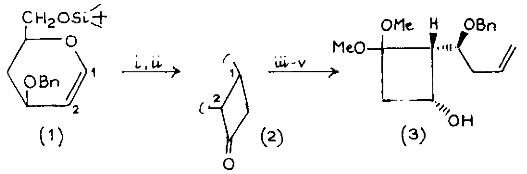
24

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

Two reviews have appeared which discuss the synthesis of enantiomerically-pure insect pheromones from carbohydrates,[1,2] and in a discussion of the kilogram-scale synthesis of chiral materials, some uses of carbohydrate precursors are covered.[3]

1 Carbocyclic Compounds

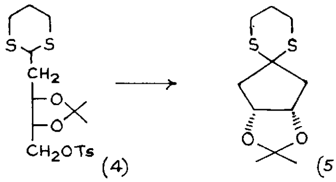
Various chiral cyclobutanone derivatives have been prepared by cycloaddition of dichloroketene to the glycal (1), as shown in Scheme 1. A number of other reactions of (2) and (3) were also reported, including Baeyer-Villiger oxidations to γ-lactones.[4,5]



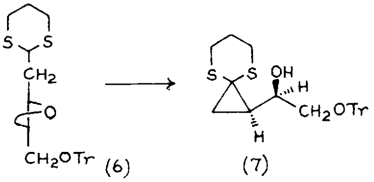
Reagents: i, Cl_3CCOCl, Zn, ultrasound; ii, Bu_3SnH; iii, TsOH, MeOH; iv, PPh_3, imidazole, I_2; v, Zn, EtOH

Scheme 1

As regards routes from sugars to cyclopentanes, the dithiane (4), derived from 2-deoxy-D-ribose, undergoes cyclization to (5) in good yield on treatment with BuLi. Related reactions, in which O-3 or O-4 was activated, were used to make dithioacetals of chiral cyclopropanones and cyclobutanones, as in the formation of (7) from epoxide (6).[6] The cyclopentanone



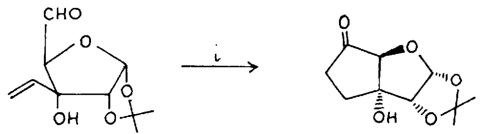
(4) (5)



(6) (7)

(8) was prepared by the intramolecular hydroacylation shown in Scheme 2, and cyclohexanones were also accessible from *C*-allyl derivatives.[7] An interesting reductive aldol strategy for making highly-substituted cyclopentanes is ilustrated in Scheme 3,[8] and the known cyclopentene chiron (9),

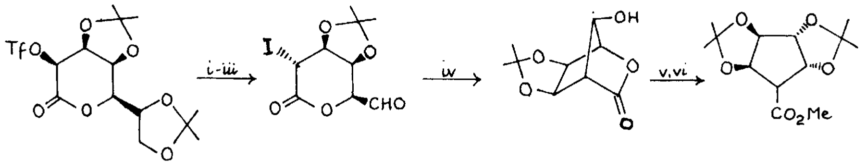
made from D-ribonolactone (Vol. 22, p. 258), has been used in a synthesis of mannostatin A (10).[9]



(8)

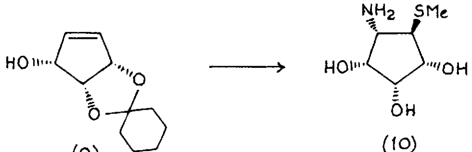
Reagents: i, $[(Ph_3P)_2RhCl]_2$, $CH_2=CH_2$, CH_2Cl_2

Scheme 2



Reagents: i, Bu_4NI, THF; ii, HOAc, H_2O; iii, $NaIO_4$; iv, LiI; v, K_2CO_3, MeOH; vi, Me_2CO, H^+

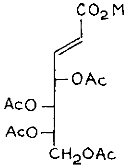
Scheme 3

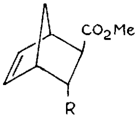


(9) (10)

There have been further reports from Horton's laboratory on the Diels-Alder reactions of cyclopentadiene and the L-*arabino*-α,β-unsaturated ester (11) (see Vol. 17, p. 250). Appropriate choice of thermal or Lewis acid-catalysed conditions can give preparative access to each of the stereomers (12) - (14), and periodate cleavage of the sugar chain and, if required, rhodium-catalysed decarbonylation gives a route to chiral bicyclo[2,2,1] heptenes.[10] Alternatively, cleavage of the alkene in (14) followed by decarbonylation gives chiral cyclopentanes.[11] In somewhat similar work, isomer (15) was the major product from cycloaddition of 2,3-dimethylbutadiene to the nitroalkene derived from D-galactose. Side-chain cleavage then gave the chiral cyclohexene (16), the enantiomer of which could be obtained if the starting nitroalkene was of D-*manno*-configuration.[12]

Intramolecular Diels-Alder reactions have been used to make chiral naphthopyrans, as illustrated by the conversion of (17) into (18) on thermolysis. Intermediate (17) was prepared from di-*O*-acetyl-D-xylal by a sequence involving a 'carba-Ferrier' reaction, and the epimer of (17) at the asterisked stereocentre gave the analogous epimer of (18), with the same stereochemistry at the ring junctions.[13] The glucose-derived diene (19) reacts with 2-methoxycarbonyl-*p*-benzoquinone to give the cycloadduct (20), and a number of other similar reactions were also studied.[14,15]


(11)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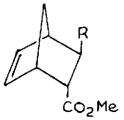
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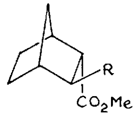
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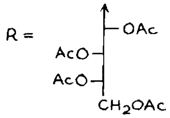
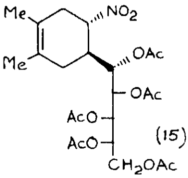
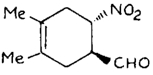



(15)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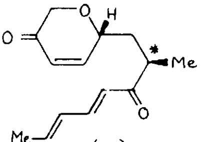
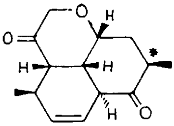
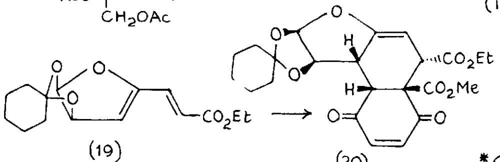
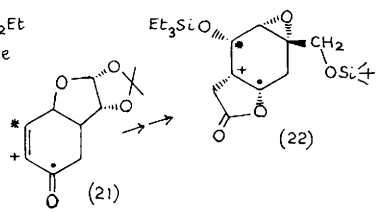

(17)

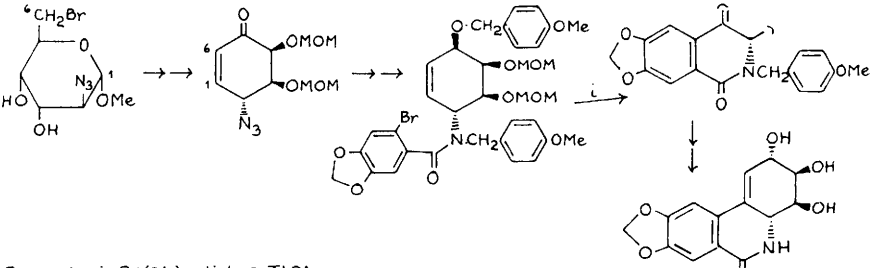

(18)


(19) (20)


(21) (22)

Shikimic acid, and its phosphonic acid analogue, have been made from a D-lyxose derivative by sequences involving intramolecular Wadsworth-Emmons reactions, in a manner very reminiscent of that employed earlier by Fleet and Shing (Vol. 17, p. 165; Vol. 18, p. 172),[16] and the previously-reported enone (21), made from di-*O*-isopropylidene-α-D-glucofuranose (Vol. 21, p. 180), has been converted into the known intermediate (22) in a prior synthesis of paniculide B.[17]

In a synthesis of the Amaryllidaceae alkaloid (+)-lycoricidine (23), the hydroxylated cyclohexene ring was constructed, ultimately from D-glucose, using a Ferrier rearrangment; the key intermediates in this synthesis are indicated in Scheme 4.[18] In an alternative approach to compounds such as


(23)

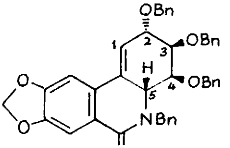
Reagents: i, $Pd(OAc)_2$, diphos, TlOAc

Scheme 4

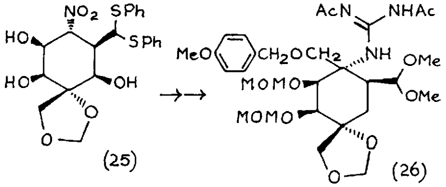
(+)-lycoricidine and other narciclasine-type alkaloids, the tetrabenzyl derivative (24) of (+)-lycoricidine has been made from L-arabinose (sugar carbons numbered), using an intramolecular aldol reaction to construct the cyclohexene ring.[19]

In an approach to tetrodotoxin, the triol (25), derived from D-glucose as for the dithianyl analogue (see Vol. 14, p. 149-150), has been converted to the more advanced intermediate (26).[20]

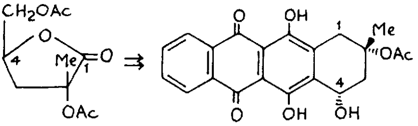
In the area of anthracyclinones, the lactone (27), prepared from isosaccharinic acid (Vol. 21, p. 258), has been used as a precursor for the chiral centres of 4-demethoxyfeudomycinone (28),[21] whilst the synthon (29), made from α-D-glucosaccharino-1,4-lactone, was used to make (30), and some related compounds.[22]



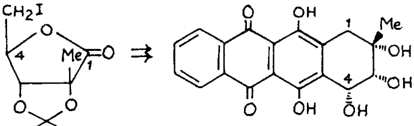
(24)



(25) (26)



(27) (28)

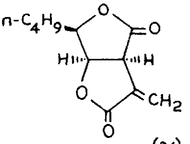


(29) (30)

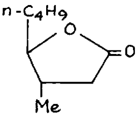
Some other papers dealing with the formation of cyclopentanes and cyclohexanes from sugars, including syntheses of (-)-allosamizoline, are mentioned in Chapter 18, a cyclopropane derivative of relevance to chrysanthemic acid is covered in Chapter 14, and a route to the cyclohexane unit of the macrolide rapamycin is discussed in Section 3.

2 γ- and δ-Lactones

A free-radical cyclization similar to that reported last year in a synthesis of (-)-avenaciolide (Vol. 24, p. 305, Scheme 6) has been used by the same team in a route to (-)-canadensolide (31) from D-glucose.[23] Intermediates in this synthesis could also be used to make the lactone (32).[24] The regioselective

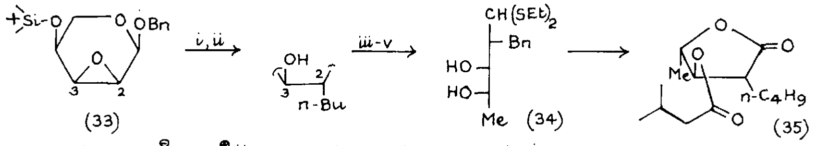


(31)



(32)

opening of epoxide (33) was used in a synthesis of (+)-blastmycinone (35) (Scheme 5),[25] and the D-lyxose derivative (36) was employed to make neopatulin (37).[26]

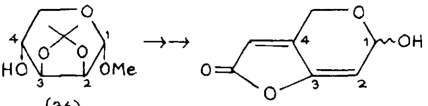


Reagents: i, $Et-\equiv-\overset{\ominus}{A}lMe_3Li^{\oplus}$; ii, H_2, $(Ph_3P)_3RhCl$; iii, EtSH, $ZnCl_2$; iv, MsCl, py; v, LAH

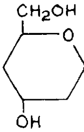
Scheme 5

A review of syntheses of the Prelog-Djerassi lactonic acid includes carbohydrate-based routes,[27] and there have been two further reports of syntheses of the β-hydroxy-δ-lactone unit (38) of mevinic acid and its congeners.[28, 29] In a synthesis of the mosquito oviposition pheromone (39), the chiral centres were derived from those of 2,3-*O*-ethylidene-D-erythrose, with this chiron being extended by Wittig reactions,[30] in a similar manner to the use of 2-deoxy-D-ribose in an earlier approach to the same target (S.-K. Kang and I.-H. Cho, *Tetrahedron Lett.*, 1989, **30**, 743).

The 3-*O*-methyl enol ether (41) of ACRL toxin I has been prepared by a route in which the glucose-derived intermediate (40) was converted into two building blocks that were linked in a Julia reaction about the central alkene unit (sugar carbons numbered).[31]



(36) (37)



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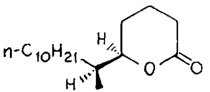
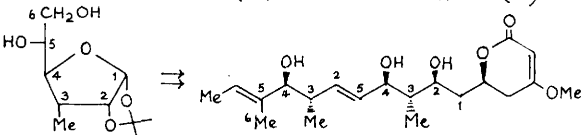
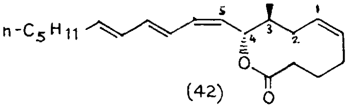


(39)



(40) (41)

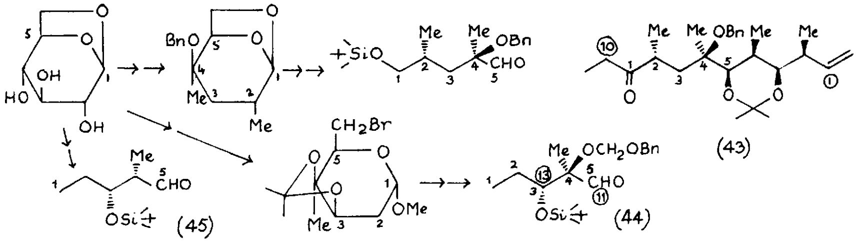


(42)

3 Macrolides, Macrocyclic Lactams, and their Constituent Segments

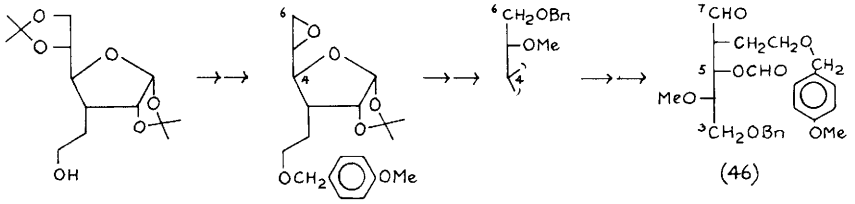
The enantiomer (42) of neodidemnilactone, a natural product from a tunicate, has been made by Wittig extension of 2-deoxy-D-ribose (sugar carbons indicated).[32]

The team at the Zelinsky Institute have developed a route to erythronolides A and B using a new strategy in which levoglucosan served as a source of chirality. The anhydride was converted (Scheme 6) into (43), representing C(1)-C(10) of the erythronolides, and also into the C(11)-C(13) synthon (44) for erythronolide B (sugar carbons shown, and macrolide numbering circled). The unit (45) needed for C(11)-C(13) of erythronolide A



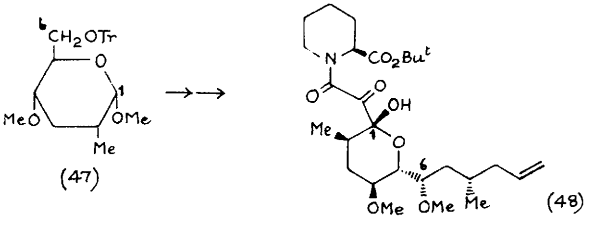
Scheme 6

was similarly prepared,[33] and the building blocks were linked together in diastereoselective aldol condensations to complete the syntheses.[34] The 16-membered macrolide aglycone carbonolide B has been synthesized, the chiral array of C(3) - C(7) being generated from diacetone glucose by way of the intermediates indicated in Scheme 7 [macrolide numbers indicated in (46)].[35] Two papers have described routes to acyclic 1,3-diol derivatives of potential application in the synthesis of amphotericin B.[36,37]

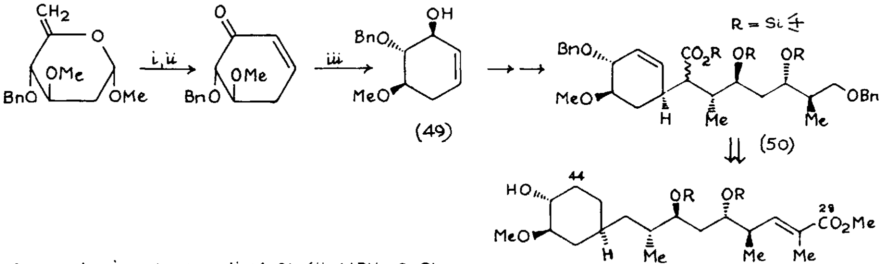


Scheme 7

In a route to the 'bottom half' of FK-506, the known intermediate (47), made from D-glucose,has been elaborated to (48), where the stereochemistry at C-6 (sugar numbering) was derived through chelation-controlled addition of an organometallic containing the other exocyclic stereocentre.[38]

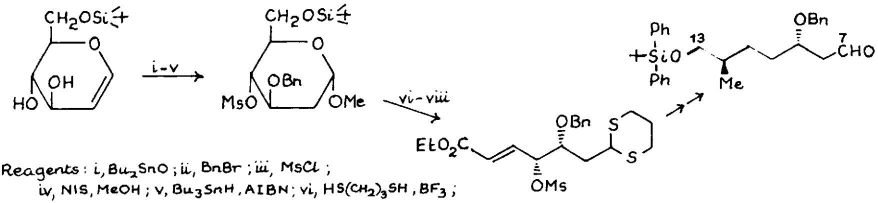


Meanwhile, Danishefsky's group has been developing a route to the related macrolide rapamycin. The cyclohexene alcohol (49) was prepared from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside via the intermediates indicated in Scheme 8, and then linked to an acyclic carboxylic acid (not sugar-derived) by means of an Ireland ester-enolate rearrangement to give (50), further converted to (51), representing C(28) - C(44) of the target.[39] Scheme 9 indicates a route to a C(7) - C(13) synthon, which was then combined with other segments to make a C(13) - C(30) unit.[40]



Reagents: i, HgCl$_2$, H$_2$O ; ii, MsCl ; iii, LiBH$_4$, CeCl$_3$

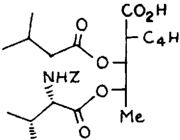
Scheme 8

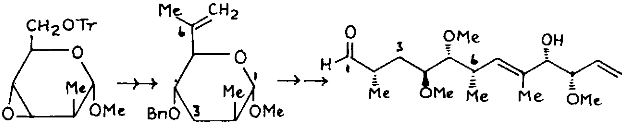


Reagents: i, Bu$_2$SnO ; ii, BnBr ; iii, MsCl ; iv, NIS, MeOH ; v, Bu$_3$SnH, AIBN ; vi, HS(CH$_2$)$_3$SH, BF$_3$; vii, Pb(OAc)$_4$; viii, Ph$_3$P=CHCO$_2$Et

Scheme 9

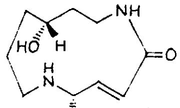
An intermediate (52) in a previous route to the 9-membered dilactone antimycin A3 has been made from (34) (Scheme 5).[25]


(52)



(53) (54) (55)

In a total synthesis of the macrolactam herbimycin A, the known mannose-derived epoxide (53) (Vol. 22, p. 150) was converted to (54), and hence to the ansa-chain unit (55). The epoxide ring in (53) was opened regioselectively using disiamyl borane/NaBH$_4$.[41] In a route to glidobamine (56), the core structure of the antibiotic glidobactin, the chirality of the allylic amine unit was derived from C-5 of D-arabinose, with inversion of configuration,[42] and, during a total synthesis, the C(7)- C(11) segment or the macrolide-macrolactam (+)-myxovirescine M2 was prepared from D-ribonolactone.[43]



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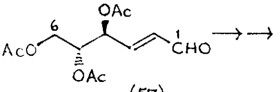

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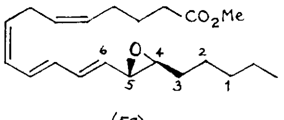
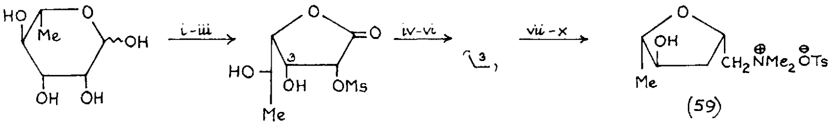


(58)

4 Other Oxygen Heterocycles

There has been a further carbohydrate-based synthesis of the epoxide (+)-disparlure, the gipsy moth pheromone, using 2-deoxy-D-ribose as starting material and epoxyalcohol intermediates.[44] (14*S*, 15*S*)-Leukotriene A4 methyl ester (58) has been prepared using the synthon (57), derived from D-glucal, as precursor, and epoxy alcohols were again used as intermediates.[45]

A synthesis of (+)-muscarine (59) from L-rhamnose is outlined in Scheme 10.[46]

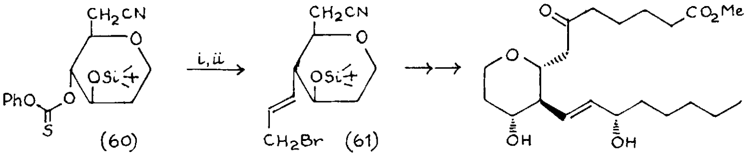


(59)

Reagents: i, Br_2, H_2O, $BaCO_3$; ii, TFA, H_2O; iii, MsCl, py, DMAP; iv, TFAA, Et_3N; v, MeOH, AcOH; vi, H_2, Pd/C; vii, $LiBH_4$; viii, NaOAc, MeCN; ix, TsCl, py; x, Me_3N

Scheme 10

Structure (62) is the methyl ester of 'Stable Metabolite X', a reported metabolite of PGI2. In a synthesis of (62) (Scheme 11), D-glucal was converted to (60), which led to (61) as the major epimer on free-radical *C*-allylation. The ester (62) produced did not show platelet aggregation or fibrinolytic activity, however.[47]

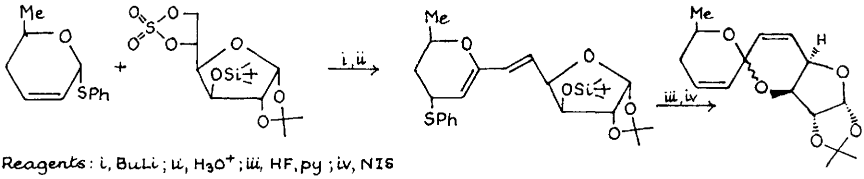


(60) (61) (62)

Reagents: i, $Bu_3SnCH_2CH{=}CH_2$, hν; ii, NBS, AIBN

Scheme 11

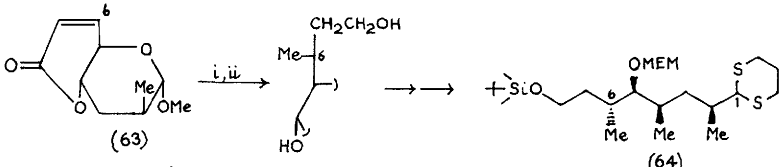
A route to unsaturated spiroketals, involving a 1,3-sigmatropic thioallylic rearrangement, is outlined in Scheme 12.[48]



Reagents: i, BuLi; ii, H_3O^+; iii, HF,py; iv, NIS

Scheme 12

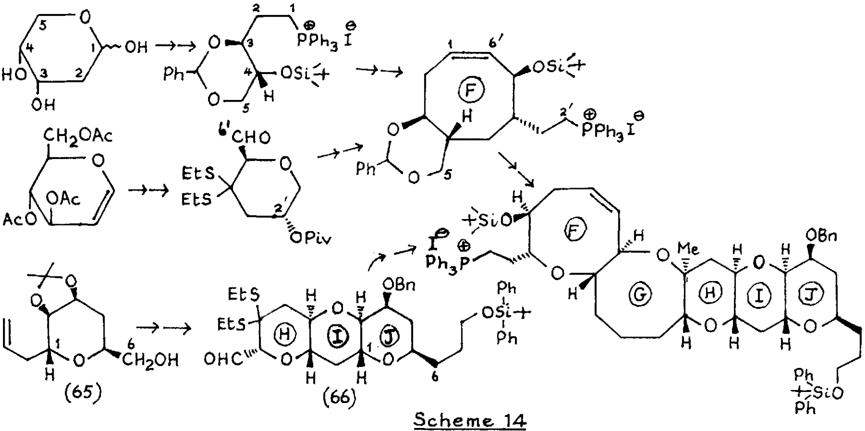
In a synthesis of the C(2) - C(9) fragment (64) of the polyether ionomycin (Scheme 13), enone (63), produced by intramolecular Wadsworth-Emmons reaction, underwent stereoselective introduction of a methyl group by use of a higher-order cuprate.[49]



Reagents: i, $Me_2Cu(CN)Li_2$; ii, DIBAL

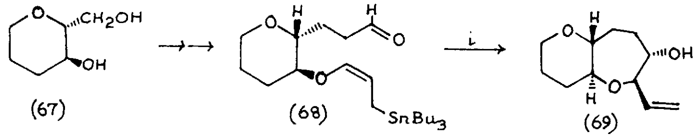
Scheme 13

A further significant advance in Nicolaou's work on brevetoxin synthesis comes with the synthesis of the FGHIJ framework of brevetoxin A from 2-deoxy-D-ribose, D-glucal, and the known mannose-derived *C*-glycoside (65), as outlined in Scheme 14, the other chiral centres in (66) being derived from asymmetric epoxidation.[50] In model work on brevetoxin



Scheme 14

B, other workers have converted (67), made from D-glucal, into allyl stannane (68) and thence to (69) (Scheme 15). Two other trans-fused 7-membered rings were subsequently annulated onto (69) using similar methods.[51,52]

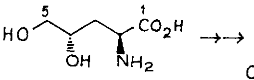


Reagent: i, $BF_3 \cdot Et_2O$

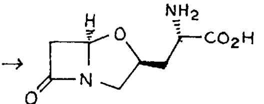
Scheme 15

5 Nitrogen Heterocycles

In the area of β-lactams, full details have been given of a glucose-based synthesis of thienamycin (see Vol. 16, p. 263-4).[53] The aminoacid (70) has been prepared from D-ribonolactone (sugar carbons as indicated), which constitutes a formal total synthesis of clavalanine (71).[54]



(70)



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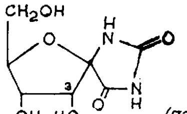
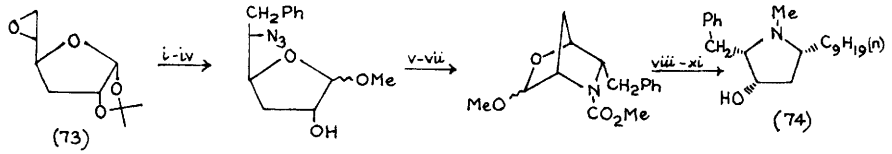


(72)

The antibiotic hydantocidin (72) has been made from D-fructose, with configurational inversion at C-3 by a redox sequence,[55] and some acyclic *O*-methyl analogues of the antitumour agent sesbanimide A have been prepared from D-xylose by a route analogous to that used for sesbanimide itself (see Vol. 20, p. 265).[56]

There is continued interest in chiral syntheses of pyrrolidines, piperidines, and related bicyclic systems. A review has appeared, in Russian, on the stereoselective synthesis of proline and pipecolic acid derivatives from sugars.[57] The antifungal pyrrolidine (+)-preussin (74) has been made from the glucose-derived epoxide (73) as indicated in Scheme 16,[58] whilst full details have been given on the synthesis of the fungal metabolite nectrisine (75) from D-glucose, and of its reduction to 1,4-dideoxy-1,4-imino-D-arabinitol (see Vol. 22, p. 265).[59]

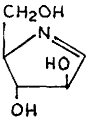


Reagents: i, PhMgCl; ii, TsCl; iii, NaN_3; iv, MeOH, H^+; v, Tf_2O, py; vi, H_2, Pd/C; vii, $ClCO_2Me$, py; viii, H_3O^+; ix, $C_8H_{14}\overset{+}{P}Ph_3I^-$, BuLi; x, H_2, Pd/C; xi, LAH

Scheme 16

The tetrahydropyrrolizidine (76) has been made from 2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,4-lactone by introduction of an azide at C-7 and subsequent cyclization onto C-1 and C-4 (see Chapter 16 for the preparation of the lactone),[60] and the known intermediate (77) (Vol. 21,

p. 176), made from D-glucose, has been converted into the necine base platynecine (78) by deoxygenation at C-5 and two-carbon extension at C-2 by a Wittig-reduction procedure (sugar carbons numbered).[61] Both (+)-7-epiaustraline (79) and (-)-7-epialexine (80) have been obtained by a reaction sequence beginning with 2,3,5-tri-*O*-benzyl-L-xylofuranose. The stereochemistry at C-7 and C-7a in both products was established by ring opening of epoxide intermediates, and the formation of (79), rather than australine itself, was unexpected (alkaloid numbers are circled, whilst sugar carbons are indicated by non-circled numbers).[62] In somewhat similar work, the azidolactone (81) was used to make 1,7-di-epiaustraline (82), where again a 5,6-epoxide (sugar numbering) was used to introduce nitrogen as C-5 with overall retention of configuration. Inversion of configuration at C-7 of the alkaloid (C-6 of the sugar) in a late intermediate gave rise to 1-epi-australine.[63]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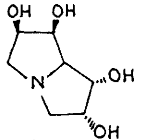
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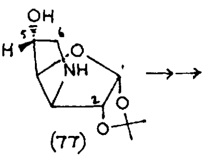
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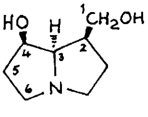
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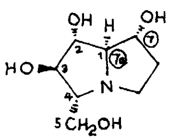
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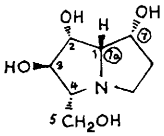
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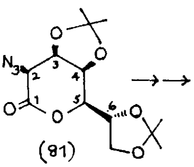
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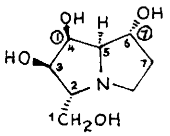
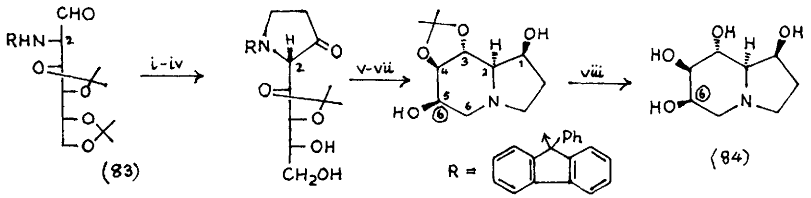

(82)

In a synthesis of (+)-6-epicastanospermine (84), the intermediate (83), made from D-glucono-1,5-lactone by an extension of the chemistry of Vol. 22, p. 163, was manipulated as indicated in Scheme 17. Castanospermine itself was also prepared by introducing an inversion of configuration at C-5 of the sugar (C-6 of the alkaloid).[64] Vogel's group have used the 'naked sugar'

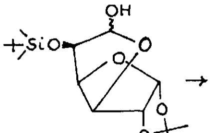


Reagents: i, $\text{CH}_2{=}\text{CHMgBr}$; ii, NCS, Me_2S ; iii, HBr ; iv, NaHCO_3 ; v, NaBH_4 ; vi, $\text{TsN}\frown\overset{+}{\text{N}}\text{Me}$; vii, H_2, Pd/C ; viii, H_3O^+

Scheme 17

approach in syntheses of castanospermine, (+)-6-deoxycastanospermine, and 6-deoxy-6-fluorocastanospermine.[65]

The L-*ido*-intermediate (85), accessible from D-glucofuranurono-6,3-lactone, has been used to make the quinolizidine analogue (86) of castanospermine, by a sequence involving stereorandom addition of a C_3 Grignard reagent to (85) and insertion of nitrogen at C-5 (sugar numbering) with inversion of configuration.[66] The piperidine (87), made from D-glucose (Vol. 21, p. 29-30), has been converted into the quinolizidine (88) and the indolizidine (89), both of which were inhibitors of α-glucosidase I, comparable with castanospermine.[67]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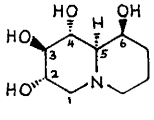
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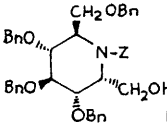
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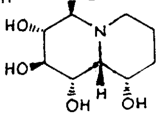
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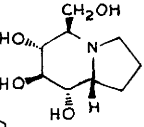
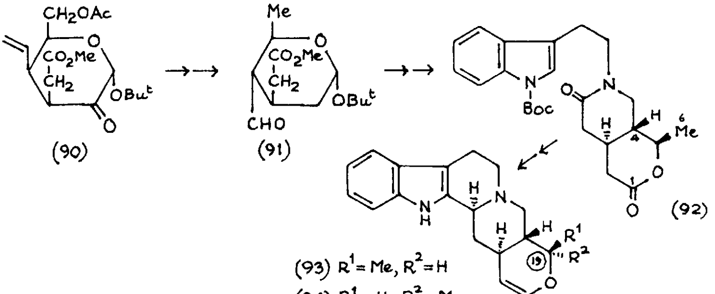
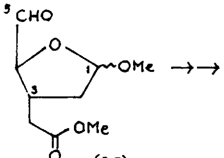

(89)

There have been a number of papers dealing with the synthesis of indole alkaloids from carbohydrates. In a route to (-)-ajmalicine (94) (Scheme 18), the known intermediate (90) (Vol. 24, p. 313-4) was converted to (91), with base-catalysed epimerization at C-4, and then by reaction with tryptamine to (92). Bischler-Napieralski cyclization then led to (+)-19-epi-ajmalicine, and by including a Mitsunobu inversion at C-19, (-)-ajmalicine was accessible.[68] French workers have used Pictet-Spengler condensations with tryptamine to make tetracyclic systems, as in the conversion of the D-mannose-derived intermediate (95) to (96) (sugar carbons indicated),[69] and in the route from (97), also from D-mannose, into (98).[70] A similar sequence to this latter, but using a pentose synthon, led to the synthesis of antirhine (99),[71] whilst (100), made by Pictet-Spengler reaction with a branched-chain anhydrohexopyranose, was used to make (+)-ajmalicine [enantiomer of



Scheme 18

(94)].[72] For earlier work by this group leading to (-)-ajmalicine (94) see Vol. 17, p. 251.



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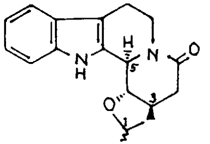

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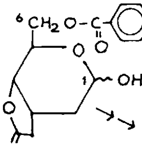

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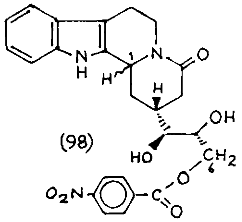

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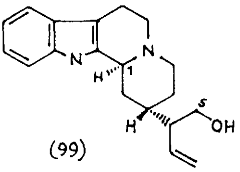

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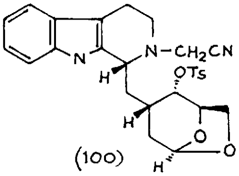
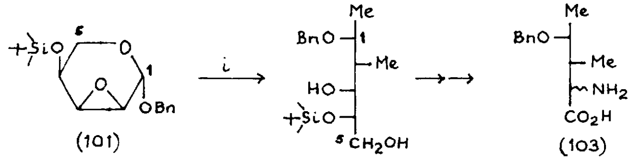


(100)

6 Acyclic Compounds

The use of carbohydrates in the synthesis of α-aminoacids, covering both situations in which the sugar is used as a chiral precursor, and where it acts as a chiral auxiliary, has been reviewed.[73] Reviews have also been published, in Russian, on the stereoselective synthesis of β- and γ-aminoacids and polyoxins,[74] and of uncommon aminoacids such as streptothricin components,[75] from sugars.

In this area of aminoacid synthesis, it was found that treatment of the epoxide (101) with excess of AlMe3 caused stereoselective opening of both the epoxide ring and the pyranoside to give (102), which was convertible by appropriate manipulation to either isomer of the γ-hydroxyisoleucines (103) (Scheme 19).[76] The dihydroxy-γ-aminoacid (104) occurs as a peripheral unit

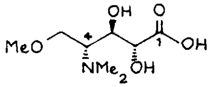


Reagent: i, Me3Al (6 equiv.)

Scheme 19

in the spiroketal calyculin A, and it has been made in protected form and incorporated into a larger fragment, with 2,3-*O*-isopropylidene-D-erythronolactone as chiral precursor (sugar carbons indicated).[77] (-)-Galantinic acid (106), with revised structure, has been made from the differentially-protected ribonolactone derivative (105),[78] and L-[4-^{13}C]-carnitine (107) has been prepared from [1-^{13}C]-3-deoxy-D-glucose.[79] A new route to polyoxamic acid is discussed in Chapter 19.

There have been a number of reports on the synthesis of oligopeptide isosteres from sugars. There has been a full description of the preparation of dipeptide analogue (108) from D-glucal (Vol. 23, p. 275), and its incorporation into potent renin inhibitors,[80] whilst the simpler analogue (109) has been made from 2,3-*O*-isopropylidene-L-erythrose (sugar carbons numbered) by use of Wittig reactions and the introduction of nitrogen with inversion of configuration.[81] The related analogue (111) has also been made from the known epoxide (110).[82] The aminoacid derivative (113), of relevance in the synthesis of inhibitors of the HIV protease, has been prepared from (112), with the introduction of nitrogen at C-5 by the involvement of a 5,6-aziridine.[83] Two groups have independently reported very similar use of the diepoxide (114), derived from D-mannitol, for making the HIV protease inhibitor (115), with the C_2-symmetry which has proved very effective in this field,[84,85] and one team also prepared the pseudosymmetric structure (116) from D-arabinitol, using the 1,2:4,5-dianhydroderivative as an intermediate.[85]



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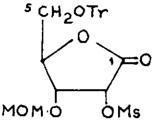

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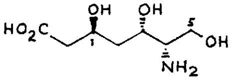

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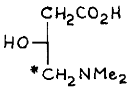

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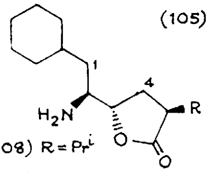
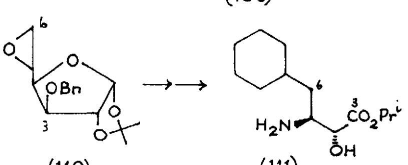
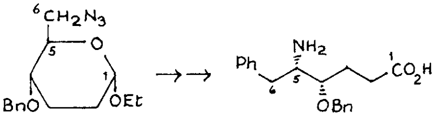


(108) R = Pr^{i}

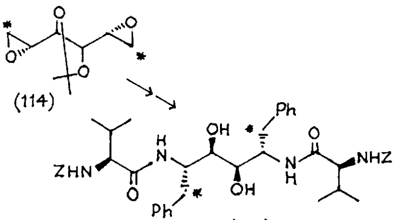
(109) R = H



(110) (111)



(112) (113)

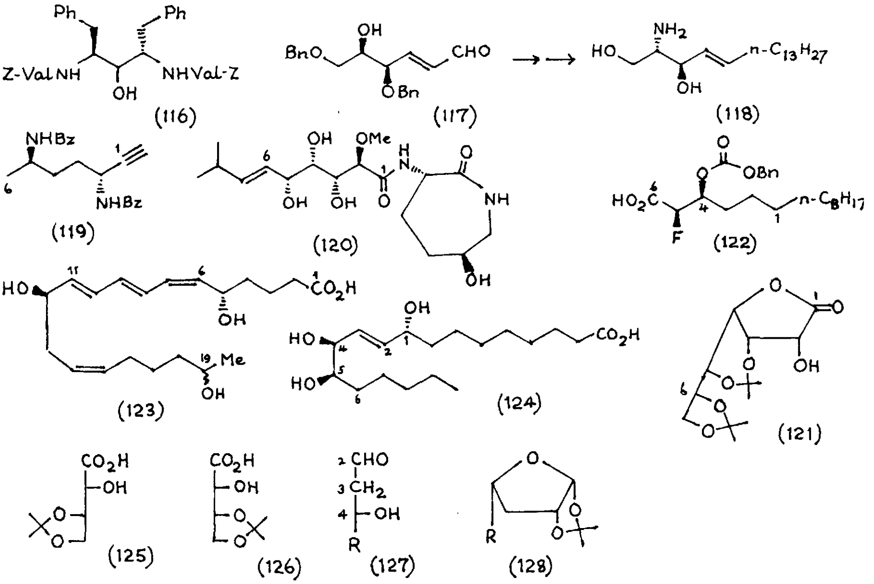


(114) (115)

The enal (117) is easily obtained from tri-*O*-benzyl-D-galactal by mercuric-ion catalysed ring opening, and has been used to make D-*erythro*-sphingosine (118).[86] Sphingosine and ceramide stereoisomers with (3*S*)-configuration have been made from D-glucose, with the intermediacy of 2,4-*O*-benzylidene-D-erythrose.[87]

The dibenzyl derivative (119) of an ornithine decarboxylase inhibitor has been prepared from D-glucosamine in a multistep process (sugar carbons indicated).[88]

The side-chain unit of the bengamides, such as bengamide E (120), has attracted carbohydrate-based syntheses. One team has recognized the suitability of the D-heptonolactone derivative (121) as a precursor (sugar carbons indicated),[89] whilst others have used L-glucose as starting material; in this approach C-6 of the sugar corresponds with the carbonyl group of the side-chain and C-1 with the alkene carbon.[90]



(116) (117) (118) (119) (120) (122) (123) (124) (121) (125) (126) (127) (128)

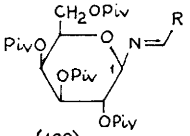
The fluoroacid (122), required for incorporation into Lipid A analogues, has been prepared from tri-*O*-acetyl-D-glucal (sugar carbons numbered).[91]

In the eicosanoid field, D-galactal derivatives were used to prepare (14*R*,15*R*)-lipoxin B, C-4 and C-5 of the sugar becoming the chiral centres of the target, after the glycal ring had been opened by acid and mercuric ions.[92] Depezay's group have extended their approach to arachidonic acid metabolites (see Vol. 20, p. 270, and earlier) to the preparation of 19-hydroxyleukotriene B_4, a metabolite of LTB_4. Both the C(1) - C(6) and C(11) - C(20) units were derived from diepoxides such as (114) by organometallic attack and central cleavage to give α-hydroxyaldehydes.[93] Two trihydroxylated C_{18} fatty acids, (124) and its C-9 epimer, have been made from tri-*O*-acetyl-D-glucal, which after chain extension at C-6 underwent acidic Hg^{2+}-catalysed opening to an enal (sugar carbons numbered). These acids are stereoisomers of a compound isolated from rice plants with rice-blast disease.[94]

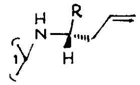
The chiral C_4 synthons (125) and (126) can be prepared by degradation of L-ascorbic acid and D-isoascorbic acid respectively using alkaline H_2O_2, and further oxidation gave the isopropylidene derivatives of L- and D-glyceric acids.[95] Chiral units of type (127, R=alkyl) have ben obtained from 3-deoxy-D-glucose derivatives, and hydrolysis and periodate cleavage of compounds (128), also obtained from diacetone glucose, via a 3,4-ene, gave the enantiomers of (127).[96] Some chiral units obtained from *N*-acetylglucosamine are mentioned in Chapter 9.

7 Carbohydrates as Chiral Auxiliaries

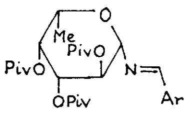
There have been further developments, principally from Kunz's group, concerning the use of imines derived from glycosylamines. Full accounts have been given of the synthesis of D-aminoacids using D-galactosylamine derivatives (Vol. 22, p. 110-111),[97] and of the use of the 'enantiomeric' D-arabinopyranosylamine and L-fucosylamine derivatives in Strecker and Ugi reactions giving L-aminoacids (Vol. 23, p. 277).[98] Ugi's group have themselves described four-component-condensation reactions involving D-glucosylamine systems, which lead predominantly to D-aminoacid derivatives.[99] D-Galactosylamine imines of type (129, R=aryl) react with allyl trimethylsilane in the presence of $SnCl_4$ to give predominantly products (130) of (*S*)-configuration, which could be hydrolysed to chiral homoallylamines[100,101] or, after oxidative cleavage of the alkene, to β-aminoacids. Use of allyl stannanes permitted extension of this chemistry to cases of (129, R=alkyl),[101] whilst homoallyl amines of (*R*)-configuration could be obtained by moving to β-L-fucosylamine derivatives (131).[102]



(129)



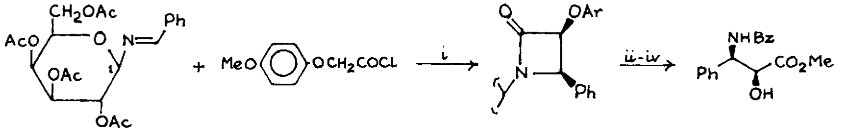
(130)



(131)

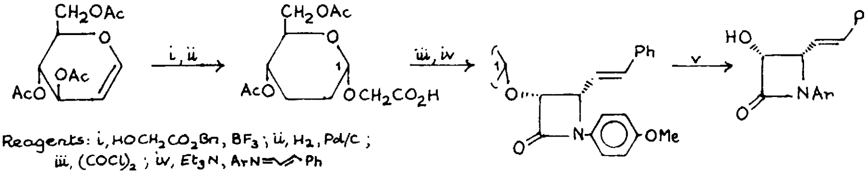
Other workers have carried out the Staudinger β-lactam synthesis on a D-galactosylamine derivative as a route to homochiral α-hydroxy-β-amino-acids (Scheme 20),[103] whilst a similar ketene-imine cyclization has been reported in which it is the acyl chloride component which is tethered to a sugar unit (Scheme 21).[104]

In the area of chirally-selective Diels-Alder reactions, the acryloyl derivative (132) underwent predominant *re*-face attack by dienes, catalysed by $SnCl_4$, to give, after disconnection of the auxiliary, products such as the



Reagents: i, Et_3N; ii, MeOH, HCl; iii, BzCl, Et_3N; iv, $Ce(NH_4)_2(NO_3)_6$

Scheme 20



Reagents: i, $HOCH_2CO_2Bn$, BF_3; ii, H_2, Pd/C; iii, $(COCl)_2$; iv, Et_3N, $ArN{=}\diagdown\!\diagup\!\!{=}\!\diagdown Ph$

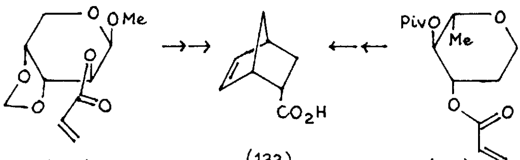
Scheme 21

(*S*)-acid (133) from cyclopentadiene.[105] The same product (133) was obtained by the use of the L-rhamnal-derived acrylate (134), the cycloaddition proceeding with 88% d.e. Use of an 'enantiomeric' acrylate originating from D-glucal gave the (*R*)- adduct with 96% d.e.[106] Stoodley and coworkers have made the juglone glucoside (135) and shown that it produces single cycloadducts, such as (136) with Danishefsky's diene. The sugar thus exerts a remarkable long-range stereodirecting effect.[107]

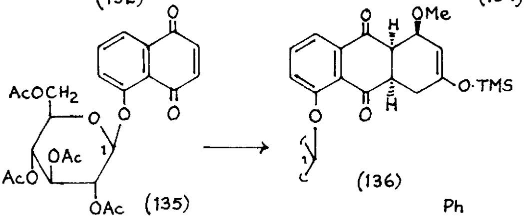
The adduct (137) was obtained diastereoselectively by reaction of cyclohexa-1,3-diene with the *N*-acylnitroso-compound derived from a chiral pyrrolidine, itself made from D-mannitol (Vol. 22, p. 181).[108] An ene reaction between the 1-chloro-1-nitrososugar and cyclopentene gave the nitrone (138), which could be used as a precursor of the chiral hydroxylamine or amine.[109]

When α,β-unsaturated esters of type (139) underwent reaction with Grignard reagents R'MgBr under Cu^I catalysis, the major adducts had the stereochemistry indicated in (140), a result that was attributed to a π-stacking interaction of the benzene ring and enoate helping to fix the conformation of (139).[110] Trimethylsilyl ketene acetals (141) reacted stereoselectively with NCS to give products (142), and hence (*S*)-α-chloroacids.[111]

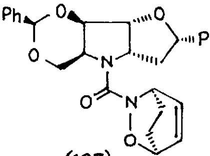
Thermolysis of the trichloroacetimidate (143) led stereospecifically to (144), in which the [3,3]-sigmatropic rearrangement had occurred on the rear (*re*) face of the alkene. This result was attributed to the steric repulsion of the bulky groupings on both the α- and β-faces of (143) which make the observed stereochemical outcome more likely. Oxidative cleavage of the alkene in (144) gave *N*-trichloroacetyl-D-alanine, and use of a similar sequence gave a route to chirally-deuteriated glycine.[112]



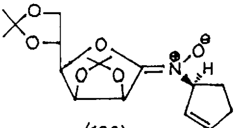
(132) (133) (134)



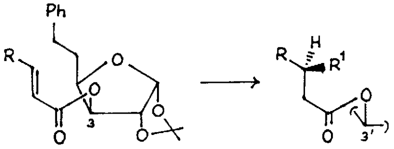
(135) (136)



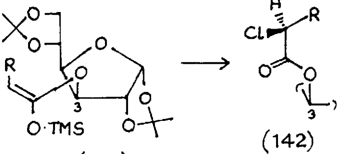
(137)



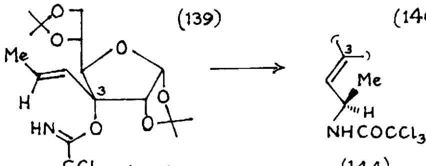
(138)



(139) (140)

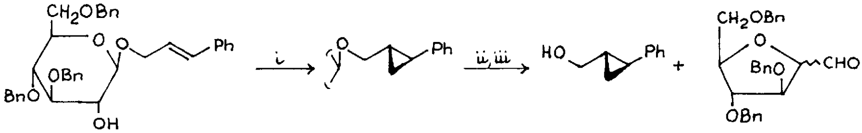


(141) (142)



(143) (144)

The diastereoselective hydroxyl-directed cyclopropanation shown in Scheme 22 was one of a number studied which proceed with high stereoselectivity. The chiral auxiliary could be removed as indicated, and use of the equivalent derivative of 6-deoxy-L-glucose gave the enantiomeric cyclopropylmethanols.[113]

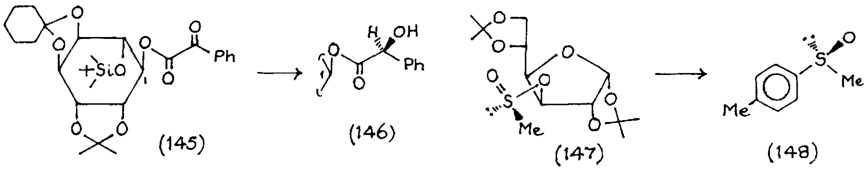


Reagents: i, Et_2Zn, CH_2I_2; ii, Tf_2O; iii, DMF, H_2O, py.

Scheme 22

Reduction of the *chiro*-inositol derivative (145), made from quebrachitol, with K-selectride in THF and HMPA gave a high preponderance of the (*S*)-diastereomer (146). Surprisingly, replacement of the HMPA with 18-crown-6 led to reversal of the diastereoselectivity with up to 92% d.e. of the (*R*)-product.[114]

Diacetone glucose has been used as a chiral auxiliary in the synthesis of enantiomeric sulfoxides. Treatment of the sugar derivative with methanesulfinyl chloride in the presence of $(i\text{-Pr})_2$NEt gave predominantly the (*S*)-sulfinate (147), which gave the (*R*)-sulfoxide (148) with *p*-tolyl magnesium bromide. Use of pyridine as base gave the (*R*)-sulfinate in 86% d.e., and hence the enantiomeric sulfoxide.[115]



(145) (146) (147) (148)

A paper on the use of carbohydrate-based bis-phosphines as ligands for asymmetric homogeneous hydrogenation is mentioned in Chapter 17.

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