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A Review of the Literature Published in 1989

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Carbohydrate Chemistry

Volume 23

A Specialist Periodical Report

Carbohydrate Chemistry

Monosaccharides, Disaccharides, and Specific Oligosaccharides

Volume 23

A Review of the Recent Literature Published during 1989

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ISBN 0-85186-172-5
ISSN 0951-8428

Published by The Royal Society of Chemistry
Thomas Graham House, Science Park, Cambridge CB4 4WF

Printed and bound in Great Britain by Bookcraft (Bath) Ltd

Preface

Our reviewing team has happily remained unchanged for Volume 23, and I acknowledge the great cooperation I have received from all members. Dr Neil Williams has continued to make his special contribution by again having done all of the drawings - a service that is much appreciated in a project which requires clear, unambiguous art work and does not lend itself especially well to computerised methods.

Despite our best intentions, the other responsibilities we hold have prevented our reducing the time required to produce the manuscript, and while continuing to aim to improve in this regard, we observe that for our own research purposes we place heavy reliance on back numbers as well as the most recent issue. It always, nevertheless, of course has particular significance.

We have to concede that our coverage is becoming less comprehensive as carbohydrate chemistry on the one hand diffuses still further into neighbouring sciences, and on the other becomes manifestly more complex (compare early volumes of this Report), but we hope we offer a wide-ranging and almost complete record of work published in this field in 1989.

We remain indebted to staff of the Royal Society of Chemistry and thank Dr P.G. Gardam and Mr A.G. Cubitt in particular for their cooperation and assistance.

R.J.Ferrier
April 1991

Contents

R E P R I N T S

In response to several queries, the situation regarding reprints of chapters of Specialist Periodical Reports titles is that they are not made available because even a relatively small consequent decrease in sales would have a disproportionately large adverse effect on the precarious finances of this specialist series of books.

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 1989 literature of mono- and oligo-saccharide chemistry illustrates continuing general advances on all fronts with strong emphasis on the development of synthetic methods and their application to problems with origins in biology. Many examples of this are clearly given in the Sections on oligosaccharides, nucleosides and antibiotics, while the role of carbohydrate chemistry in general organic chemistry is well illustrated by the many complex conversions of sugar derivatives into enantiomerically pure natural substances of a non-carbohydrate nature. Once again, however, biological issues - in this case medicinal - are commonly the driving forces behind the work.

Relevant reviews have appeared on recent developments in modern aspects of synthetic carbohydrate chemistry,[1] stereoselective chemical syntheses of sugar derivatives,[2] syntheses of unusual sugars by combinations of chemical and enzymic methods,[3] and purely enzymic syntheses.[4] Baer has surveyed recent synthetic studies of nitrogen-containing, deoxygenated sugars and related compounds,[5] and more specifically, the use of allylboronates in the synthesis of carbohydrates,[6] and the conversion of 7-oxanorbornenes to sugars and their derivatives[7] have been reviewed. The strategies for bonding sugars to proteins have been covered in a survey of neoglycoproteins,[8] and two Chinese reports have dealt with the applications of carbohydrates in the synthesis of other natural products,[9] and the effects of ultrasound on the reactions of derivatives of β-D-ribofuranose.[10]

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2
Free Sugars

1 Theoretical Aspects

The historic development of the understanding of carbohydrate stereochemistry has been briefly reviewed,[1] and a lecture with four references on the energetics and geometry of furanoid systems has been published. Two complementary descriptions of the conformational behaviour of furanose rings have been presented: (i) by quantum-mechanical energy calculations; and (ii) by a geometrical model of pseudorotation in five-membered rings.[2]

Molecular dynamic simulations of β-D-ribofuranose and 2-deoxy-β-D-erythro-pentofuranose in solution showed that their hydroxy groups are better hydrogen-bond donors, but worse acceptors, than water and that the ring oxygen atoms accept even less hydrogen-bonding.[3] In a similar study with α-D-glucopyranose, solvation was found to have little effect on the preferred conformation of the sugar molecule.[4] According to molecular dynamics simulation experiments both glucitol and mannitol have bent energy minima in vacuo; in aqueous solution mannitol is also bent, but glucitol prefers a planar zig-zag conformation.[5]

A computer program for molecular modelling which is part of the 3D-Molmaster system has been used to carry out computations of the energetics of monosaccharide, polysaccharide and glycoside conformations.[6] By use of the MM2 method a conformational energy map of β-laminarabiose has been constructed which makes allowance for the presence of several inter-converting conformers ("structural relaxation"). The finding that this map differs from one based on a fixed structure indicates the importance of "structural relaxation" within the glucose residue.[7] Newly developed computational methods for describing and understanding molecular motion and flexibility have been employed to describe the "relaxed" potential energy surface of maltose, which was chosen as a prototypical carbohydrate system.[8] Calculations to give solvent-specific "relaxed" energy surfaces have been applied to carbohydrate molecules, in particular to a mannobiose, with the aim of providing new insights into the conformational properties of sugars in solution.[9]

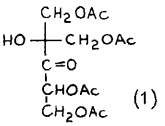
By an examination of optical rotation and n.m.r. measurements, a picture has

been developed of the potential energy surfaces of cellobiose and maltose in aqueous solution.[10]

2 Synthesis

The enzyme-catalysed synthesis of mono-, oligo- and poly-saccharides has been covered in a major review with 310 references,[11] and a review has appeared on the synthesis of saccharides uniformly labelled with ^{14}C, starting from D-[U-^{14}C]glucose.[12]

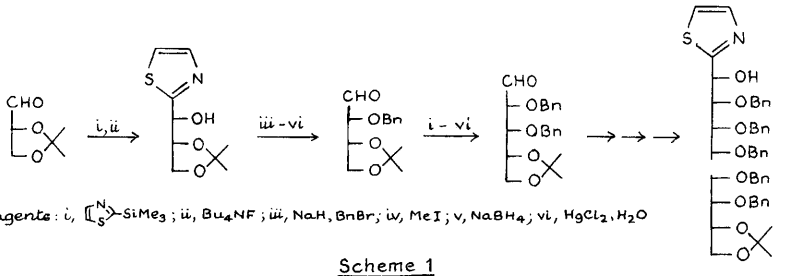
The distribution of products of the formose reaction carried out in aqueous DMF has been studied. Considerable control was possible by adjustment of the water content. When, for example, formaldehyde was heated at 75°C for 1 hour with triethylamine and thiamine hydrochloride in 8:1 DMF-H_2O, DL-2-C-



(1)

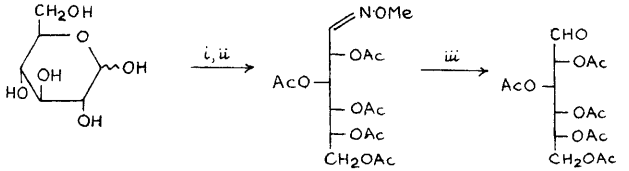
hydroxymethyl-3-pentulose, characterised as the tetraacetate (1), was produced in 28% yield. In the absence of water, the major products are dihydroxyacetone and DL-glycero-tetrulose (cf Shigemasa et al., Carbohydr. Res., 1987, 162, C1).[13] In the radiation-initiated formose synthesis in aqueous solution, pentaerythritol and ethylene glycol were the main products, their ratio depending on the initial formaldehyde concentration.[14]

An efficient new procedure for the general ascent of the aldose series, which lends itself to repetitive application and gives an all-anti configurated chain, is



Scheme 1

shown in Scheme 1.[15] The usefulness of this approach is further extended by the epimerisation referred to in Section 4, Scheme 11, of this Chapter. A new multigram method for trapping aldoses in their aldehydo-form is exemplified in



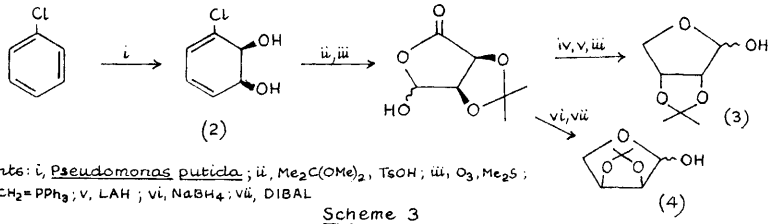
Reagents: i, NH_3OMeCl, Py ; ii, Ac_2O, Py ; iii, O_3, Me_2S

Scheme 2

Scheme 2. It exploits the discovery that oxime ethers are cleaved by ozone to give the parent aldehydes in high yields.[16]

In a study of the hydrolysis of cellulose to D-glucose by dilute sulphuric acid, the reversion products which represent 10% of the total yield have been analysed. The main components (>50%) were 1,6-anhydro-β-D-gluco-pyranose and -furanose (7:3). Isomaltose and gentiobiose were the major disaccharides, and (1→2)- and (1→3)-linked α-disaccharides predominated over their β-anomers.[17]

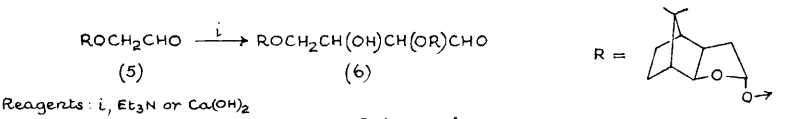
2.1 Tetroses.- The D- and L-erythrose derivatives (3) and (4), respectively, are available from chlorobenzene by the enantiodivergent route shown in Scheme 3, via



Reagents: i, Pseudomonas putida ; ii, $Me_2C(OMe)_2$, TsOH ; iii, O_3, Me_2S ; iv, $CH_2=PPh_3$; v, LAH ; vi, $NaBH_4$; vii, DIBAL

Scheme 3

the optically pure microbial oxidation product (2).[18] Small but significant asymmetric induction was observed in the aldolisation of the glycolaldehyde derivative (5) bearing an enantiomerically pure acetal-type protecting group

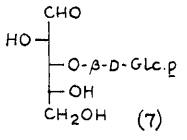


Reagents : i, Et_3N or $Ca(OH)_2$

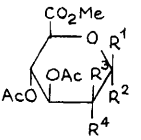
Scheme 4

(Scheme 4). The L-erythro-, D-erythro-, L-threo- and D-threo-isomers (6), present as a complex mixture of hemiacetals, were formed in a combined yield of 40-60% in the ratio 33:30:21:16. This was determined after reduction to the corresponding tetritols as mentioned in Chapter 18.[19]

2.2 Pentoses.- 3-O-Hexopyranosyl-D-arabinoses, such as compound (7), have been prepared by Zemplén degradation of aldonobiononitrile octabenzoates with



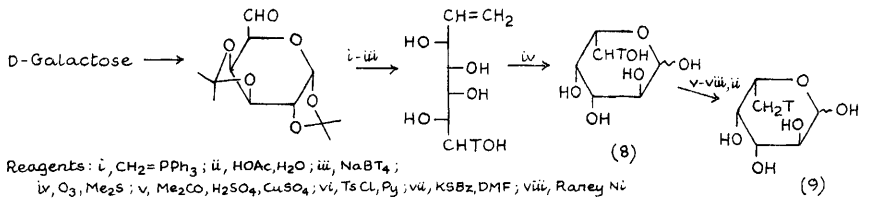
(7)



(10) $R^1 = R^4 = H$, $R^2 = OPr^i$, $R^3 = Br$
or $R^1 = OPr^i$, $R^2 = R^3 = H$, $R^4 = Br$

(1→4) glycosidic linkages. The products were obtained as α/β-pyranose/furanose mixtures and were reduced and benzoylated to the corresponding hexopyranosyl-D-arabinitol octabenzoates for easy characterisation by n.m.r. spectroscopy.[20] The conversion of derivatives of aldopentoses (e.g., arabinose) to stereoisomeric derivatives of pentonolactones (e.g., L-lyxonolactone) is covered in Chapter 16.

2.3 Hexoses.- A convenient procedure for the synthesis of D-[1-^{11}C]gluco- and D-[1-^{11}C]galacto-pyranose from D-arabinose and D-lyxose, respectively, and H^{11}CN uses diborane as highly effective and time saving reducing agent.[21]
UDP-[6-^{3}H]galactose of high specificity has been obtained by oxidation of the C-6 hydroxymethyl group of UDP-galactose by galactose oxidase and subsequent reduction with $NaBT_4$. Radiolabelled UDP-N-acetylgalactosamine has also been prepared by this method.[22] Economical access to [6-^{3}H]-labelled L-galactose (8) and L-fucose (9) starting from D-galactose is offered by the reaction sequence

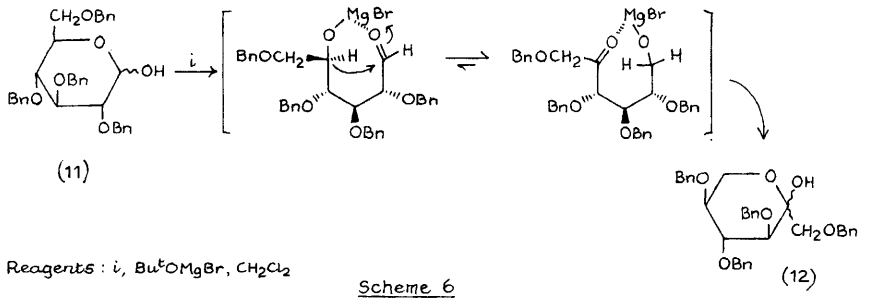


(8) (9)

Reagents: i, $CH_2=PPh_3$; ii, HOAc, H_2O; iii, $NaBT_4$;
iv, O_3, Me_2S; v, Me_2CO, H_2SO_4, $CuSO_4$; vi, TsCl, Py; vii, KSBz, DMF; viii, Raney Ni

Scheme 5

presented in Scheme 5.[23] A new tritiation method has been employed to synthesise [2,6,6'-^{3}H]-2-deoxy-D-glucose from a mixture of protected bromodeoxyglucose derivatives (10).[24]

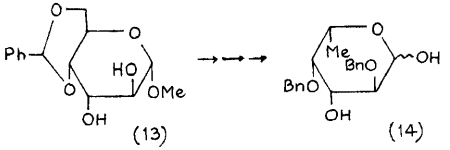


(11) (12)

Reagents: i, Bu^tOMgBr, CH_2Cl_2

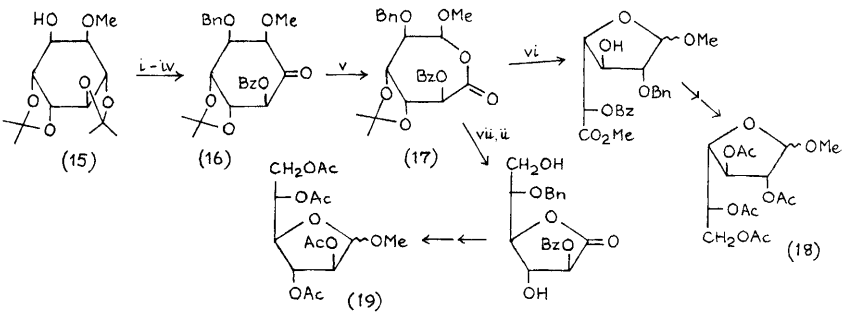
Scheme 6

2,3,4,6-Tetra-O-benzyl-D-glucopyranose (11) was converted to 1,3,4,5-tetra-O-benzyl-L-sorbose (12) in 94% yield in the presence of bromomagnesium salts of certain phenols and alcohols in dichloromethane. This reaction for which there is no precedent involves, at least formally, a hydride transfer from C-5 to C-1 of the starting material, a possible mechanism being indicated in Scheme 6.[25] A selectively protected fucose derivative (14), suitable for use in oligosaccharide synthesis, has



(13) (14)

been prepared from the known D-altrose derivative (13) in ten conventional steps and 33% overall yield.[26] 3,4,5,6-Di-O-isopropylidene-2-O-methyl-quebrachitol (15) served as the starting material for a multi-step synthesis of the peracetylated D- and L-galactofuranosides (18) and (19), respectively, as outlined in Scheme 7. The key step was the high yielding (>94%) Baeyer-Villiger oxidation of ketone (16) to the hemiacetal-lactone (17).[27]

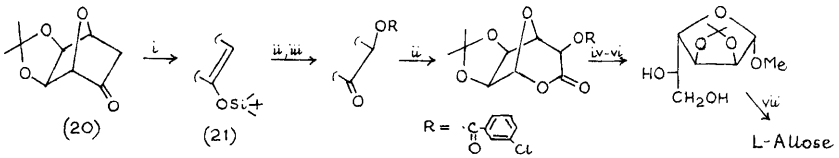


Reagents: i, BnBr, NaH, DMF; ii, MeOH, TsOH; iii, BzCl, Py; iv, PCC; v, MCPBA, $NaHCO_3$; vi, $HC(OMe)_3$, MeOH, TsOH; vii, $NaBH_4$

Scheme 7

In a newly patented process L-rhamnose has been produced from rhamnan sulphate by treatment with strong acid resin, followed by heating.[28]

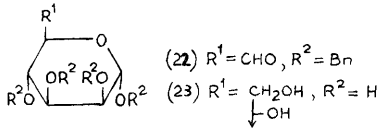
The enantiomerically pure oxabicycloheptane derivative (20) and its antipode, previously used in a total synthesis of D- and L-ribose (see Vol. 22, Chapter 2,



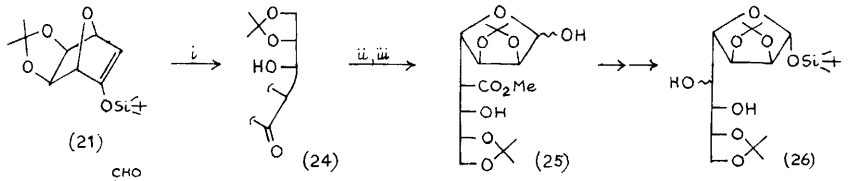
Reagents: i, $F_3CCONMeSi(CH_3)_3$; ii, MCPBA; iii, Δ(200°C); iv, MeOH, OH^-; v, MeOH, H^+; vi, LAH; vii, H_3O^+

Scheme 8

Scheme 1), were the starting compounds for new total syntheses of L-hexoses. Scheme 8 shows the steps leading from ketone (20) via the silyl enol ether (21) to L-allose. By a slightly different reaction sequence the enantiomer of compound (20) was converted to L-talose.[29]

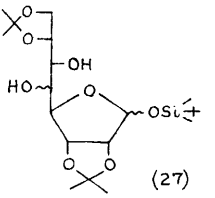


2.4 Higher Sugars.- L-glycero-D-manno-Heptopyranose (L-D-Hepp) (23) was the main product of the hydroxymethylation of the mannose-derived aldehyde (22) with (isopropoxydimethylsilyl)methylmagnesium chloride, followed by deprotection, the high stereoselectivity being consistent with the Cram cyclic model for 1,2-asymmetric induction.[30] Further use was made of the 7-oxabornane silyl enol ether (21) of Scheme 8 in the crossaldolisation with 2,3-O-isopropylidene-D-glyceraldehyde to give octoses as shown in Scheme 9. Under catalysis by $TiCl_4$



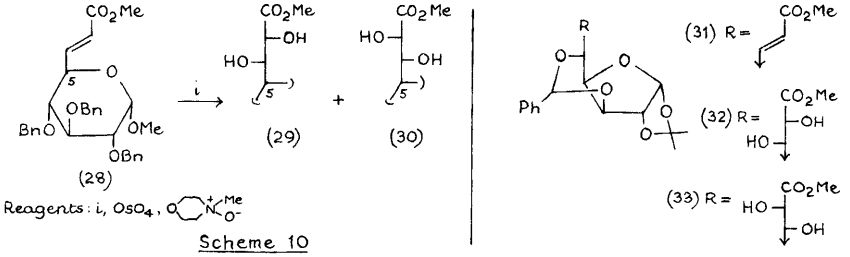
Scheme 9

the condensation product (24) was formed exclusively. This was transformed, by methods similar to those depicted above in Scheme 8, to the octofuranose derivative (25) and hence in seven steps to a mixture (26) of D-erythro-D-talo- and D-erythro-L-allo-octose derivatives. The enantiomer of silyl enol ether (21) gave analogously the D-threo-L-talo- and D-threo-D-allo-isomers (27).[31]



In accordance with Kishi's rule osmylation of the carbohydrate derived unsaturated ester (28) gave the D- and L-threo-D-gluco-configurated products (29) and (30) in the ratio 9:1 (Scheme 10), and similar selectivity was observed in the

osmylation of the manno analogue of alkene (28). In breach of Kishi's rule, however, methyl 3,5-O-benzylidene-6,7-dideoxy-1,2-O-isopropylidene-α-D-gluco-6-octenofuranuronate (31) afforded the β-L- and α-D-threo-derivatives (32) and (33) in the ratio 1:2.[32] The X-ray structure of the new compound (32) is referred to in Chapter 22. The selectivities of the osmylations represented in Scheme 10 and of



Scheme 10

two similar examples were greatly enhanced on addition of the "matching" Sharpless chiral auxiliary, either dihydroquinine p-chlorobenzoate or dihydroquinidine p-chlorobenzoate [e.g., (29):(30) = 20.5:1].[33]

3 Physical Measurements

As part of a study of the stability of enzymes in aqueous sugar solutions the solute-solvent interactions and water activities of small carbohydrates (D-glucose, D-galactose, D-fructose, D-glucitol, D-mannitol, sucrose and maltose) have been examined. D-Fructose was found to provoke the most noticeable perturbation of water structure, to cause denaturation (e.g., of lysozyme), and to lower the storage stability of enzymes (e.g., YADH).[34] Based on the finding that the relative increments of the sound velocities in aqueous sugar solutions (ribose, sucrose, raffinose and six others) correlate with the number of equatorial hydroxy groups in the solute molecules, the suggestion was made that molecules with a large proportion of equatorial hydroxy groups are particularly effective in stabilising the structure of water.[35]

The enthalpies of dilution at 25°C of binary and tertiary aqueous solutions containing the isomeric disaccharides cellobiose, maltose, and trehalose, were investigated, and an empirical relationship between saccharide solvation and solute - solute interactions was deduced.[36] The thermochemical properties of aqueous solutions of small carbohydrates as glasses and rubbers at sub-zero temperatures have been measured by differential scanning calorimetry (DSC),[37] and the thermodynamic properties of alcohols and monosaccharides in aqueous biuret solution at 25°C have been determined by flow microcalorimetry.[38] By use of DTG

and DSC-DTA techniques endothermic and exothermic reaction temperatures and enthalpies between 25 and 700°C have been recorded for 24 typical sugars. These data yield important information pertaining to the relation between molecular structure and thermal behaviour.[39]

The dehydration of xylose in aqueous solution catalysed by a Cp_2TiCl_2-protoporphyrin complex immobilised in a polyacrylamide gel has been studied, and rate constants activation parameters for this process have been determined,[40] and a thermodynamic investigation of the hydrolysis of sucrose by microcalorimetry and h.p.l.c. has been reported.[41]

In an investigation of the kinetics of isotope exchange between [1-^{3}H]saccharides and hydrogen on Pd catalysts it was found that the compounds examined could be arranged in a sequence of decreasing hydrogen-exchange rate which agreed with the order of decreasing relative mobility coefficients for the 1-H atoms.[42] Widely different polystyrene affinities are displayed by methyl glycopyranosides, deoxysugars and glucooligosaccharides as was demonstrated by measuring the coefficients K_{av} for partition between polystyrene gel and aqueous solvent systems for these three groups of carbohydrates. In combination with the accessible surface data of sugar molecules, the K_{av} values collected suggest that the hydrophobicity of sugars is determined, inter alia, by their surface area, the hydration effect of the hydroxy groups and molecular planarity and rigidity.[43]

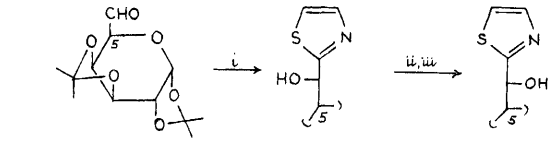
The non-isothermal kinetic parameters for the kinetically possible thermal decomposition steps of hydrated iron(III) and holmium(III) gluconates were evaluated. The values obtained for the Fe(III) derivative were sensitive to the rate of heating.[44] The association constants for the interaction of $CaCl_2$ and KCl with a number of standard monosaccharides are referred to in Chapter 17, and three kinetic studies of the anomerisation of D-glucose are covered in the next Section of this Chapter.

4 Isomerisation

A full report has been published on the newly discovered C-2 epimerisation of aldoses promoted by Ni(II) diamine complexes. The intermediate Ni(II) complex containing both diamine and sugar was investigated by use of ^{13}C-enriched D-glucose and by extended X-ray absorption fine structure (EXAFS) methods.[45] A procedure has been described for the epimerisation and rearrangement of D-[1-^{13}C]glucose to give a ca 1:1 mixture of starting material and D-[2-^{13}C]mannose.[46] The isomerisation of epimeric pairs of aldohexoses and the related ketohexose by aqueous KOH has been examined in detail. It is proposed that structures with the

hydroxy groups at C-1, -2 and -3 in ax/eq/ax or eq/ax/eq arrangements form particularly stable hydrogen-bonded ions or complexes, and that this influences the aldose - ketose equilibrium.[47]

Inversion α to the masked carbonyl group of sugar thiazoles by oxidation - reduction, as exemplified in Scheme 11, promises to be a very useful extension of



Reagents: i,  ; ii, $KMnO_4$; iii, K-Selectride

Scheme 11

the thiazole method of ascent in the aldose series which is described in Section 2 of this Chapter (see Scheme 1).[48] The synthesis of 6-deoxy-L-arabino-hexulose by isomerisation of L-rhamnose is covered in Chapter 12.

The "Glukometer GKM 01", an analytical tool based on a β-D-glucose-specific oxidase, has been used to measure the effects of pH, water content, water activity, and temperature on the mutarotation equilibrium of D-glucose. The equilibration rate showed a minimum value at pH 3 and increased with increasing water-content and -activity. The temperature dependence could be described by the Arrhenius equation, and an activation activity of 66.2 kJ mol^{-1} was calculated.[49] Similar experiments are reported in a Japanese publication.[50] The mutarotation of α- to β-D-glucose in DMSO over an alumina catalyst at 40°C has been investigated under various pressures in the range 0.1-90 MPa and with initial α-D-glucose concentrations of 2.8-12.0 x 10^{-2} mol dm^{-3}. The kinetic parameters (adsorption coefficients, rate constants for the surface reactions) were evaluated as a function of pressure. In sharp contrast to the negative adsorption volumes observed under homogeneous catalysis, fairly large positive activation volumes were found for the surface reactions, for which a formyl rotation step is thought to be responsible.[51]

An n.m.r. study of the kinetics of anomerisation of D-talose is covered in Chapter 21.

5 Oxidation

The mechanism of oxidation of D-glucose in alkaline media at gold electrodes has been investigated. Experiments using cyclic voltammetry at a rotating disc electrode indicated that the mass-transport-limited reaction proceeds via an enediol intermediate hydrogen-bonded to catalytic hydrous gold oxide. The enediol is

cleaved oxidatively and the primary hydroxy group is oxidised at the same time.[52]

In continuation of earlier work (Vol. 22, Chapter 2, ref. 53), three papers on the oxidation of monosaccharides and model compounds by vanadium(V) in the presence of perchloric acid have been published by Finnish researchers. From their results they conclude that the oxidations proceed in three steps and involve open chain forms. In the rate determining step a carbon-bound hydrogen atom is transferred from the substrate to $V(OH)_2^{3+}$ as the main oxidising species. Oxidation is facilitated by a neighbouring carbonyl group which stabilises the initially formed carbon-centred carbohydrate radical. The experimental order of reactivity was acetoin>hydroxyacetone>>D-gluconic acid>standard ketohexoses>> standard aldopentoses>standard aldohexoses>D-glucitol;[53] D-fructose and L-sorbose gave dicarbonyl compounds as the primary products[54] and aldopentoses furnished aldotetroses.[55]

A spectrophotometric study of the oxidation of aldoses by Ce(IV) in dilute sulphuric acid showed that the reactions are first order in both Ce(IV) and sugar. Similar kinetics for D-glucose, D-ribose and D-erythrose indicate a common oxidation mechanism involving cyclic (furanoid or pyranoid) forms in the rate determining radical formation step. Dissimilar kinetic and thermodynamic data for glyceraldehyde, on the other hand, point to a different oxidation pathway for the triose.[56] Formation of an intermediate free radical species in the rate determining step has also been proposed for the Ce(IV) oxidation of L-rhamnose.[57]

The kinetics of oxidation of D-glucose, D-galactose and D-fructose by $K_2Cr_2O_7$ have been studied by u.v. spectroscopy, and oxidation mechanisms were discussed. Whereas first order dependency in oxidant and substrate was readily demonstrated, the order with respect to $[H^+]$ was complex.[58] In the oxidation of monosaccharides by Mn(VII) in acidic pyrophosphate solution the orders of reactivity were D-galactose>D-glucose>D-mannose and L-arabinose>D-xylose>D-ribose in the aldo-hexose and -pentose series, respectively, and it is thought that the relative configurations at C-2 and C-3 affect the reaction rate.[59]

The oxidising action of hexachloroiridate on D-ribose, D-erythrose and DL-glyceraldehyde has been studied and the results compared with those reported for D-glucose.[60]

6 Other Aspects

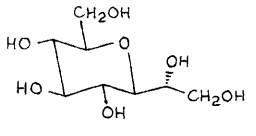
D-gluco-L-glycero-3-Octulose (34), the first naturally occurring 3-octulose reported, was identified as the main constituent in aqueous extracts from Laurus nobilis leaves and buds,[61] and evidence has been presented that 1-deoxy-D-threo-pentulose

is a biosynthetic precursor of pyridoxal (vitamin B_6).[62]

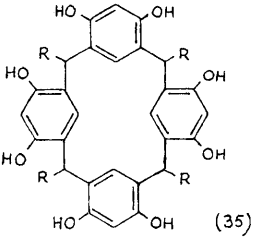
A review with 32 references has been published on capto-dative radical stabilisation and its importance in organic synthesis and especially in the radical halogenation of carbohydrates.[63]

The radiolysis-induced degradation of 2-deoxy-D-erythro-pentose has been investigated. In the presence of iron ions prolonged post-irradiation release of malondialdehyde, a major degradation product, was observed. It is thought that this is due to iron ions catalysing the formation of hydroxy radicals from H_2O_2 and stimulating the breakdown of intermediate carbohydrate-derived radical species.[64]

The conversion of fructose and glucose and their isopropylidene derivatives into hydrocarbons over zeolite catalysts at ≥350°C has been examined,[65] and the decarbonylation - dehydration of ketoses mediated by complexes of rhodium and palladium has been reported.[66] Procedures for the selective reductive cleavage of C - C bonds in sugars under catalysis by $RuH_2(PPh_3)_4$ is referred to in Chapter 18.



(34)



(35) R = $(CH_2)_{10}Me$

The cyclic tetramer (35) acting as a lipophilic host solubilises certain sugars (e.g., fructose) as polar guests in CCl_4, whilst other sugars (e.g., glucose) are not accepted at all. The relative affinities of various hexoses with compound (35) have been explained in terms of stereochemistry at C-3 and C-4 and lipophicility of the substituents at C-2 and C-6.[67,68]

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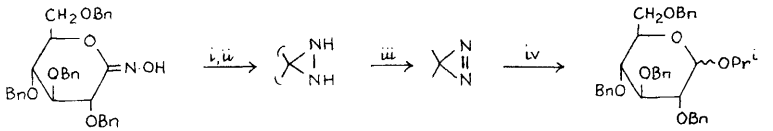
3
Glycosides

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.- A new procedure for glycosylating unreactive alcohols or phenols involves the treatment of perbenzylated S-phenyl 1-thioglycoside sulphoxides with triflic anhydride followed by the hydroxy compounds at -78°C. The α,β ratios depend strongly on the solvent, and the procedure appears to be the first to allow the direct N-glycosylating of amides.[1]

An entirely novel approach to glycosylation uses glycosylideneaziridines which can be oxidised to the relatively unstable diazirines from which glycosylidene carbenes are produced on warming to room temperature. In the presence of alcohols these give glycosides by insertion reactions (Scheme 1); attempts to



Reagents: i, MsCl, Et_3N; ii, NH_3, MeOH; iii, Br_2, Et_3N, MeOH; iv, Pr^iOH

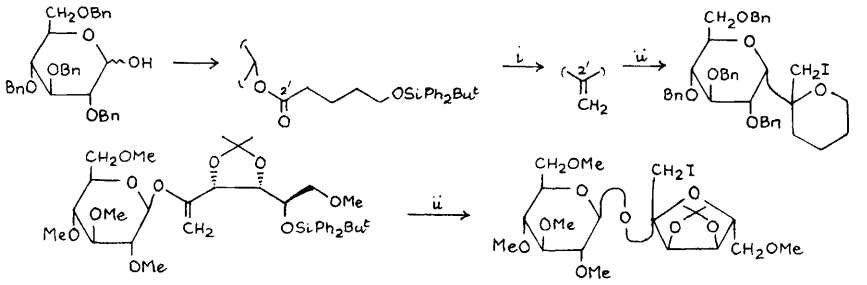
Scheme 1

repeat these processes with furanoid analogues were not successful.[2] Glycosyl carbonates treated with alcohols in the presence of p-toluenesulphonic acid afford a new way of making glycosides,[3] and a more sophisticated, related method for making cyclic glycosides involves acylation of anomeric hydroxyl groups followed by Tebbe methylenation of the resultant esters and ring closures (Scheme 2).[4]

1-O-Acetyl-2,3,5-tri-O-benzyl-β-D-ribofuranose can be converted into α-glycosides with good stereoselectivity (Scheme 3).[5]

2-Chloro-1,1,2-trifluoroethyl α-D-glucopyranoside was prepared and found to inhibit yeast α-glucosidase irreversibly, probably because the released 2-chloro-1,1,2-trifluoroethanol

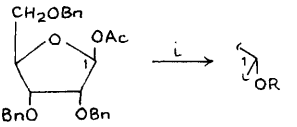
decomposed to hydrogen fluoride and 2-chloro-2-fluoroacetyl fluoride which acylates the nucleophilic centre of the enzymic



Reagents: i, $(Cp)_2Ti(Cl)(CH_2AlMe_3)$; ii, I_2, $KOBu^t$

Scheme 2

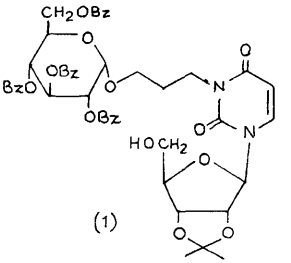
active site.[6] Tetra-O-benzyl-α-D-glucopyranosyl chloride has been used to prepare (1R,2R) - and (1S,2S)-2-hydroxylcyclohexyl α-D-



Reagents: i, ROTMS, $SnCl_4$, $Sn(OTf)_2$, $LiClO_4$

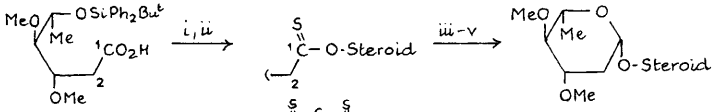
Scheme 3

glucopyranoside (from trans-1,2-dihydroxycyclohexane),[7] and 3-iodopropyl α-D-glucopyranoside tetrabenzoate has been made from the corresponding pentabenzoate and converted into the uridine diphosphate glucose analogue (1).[8]



(1)

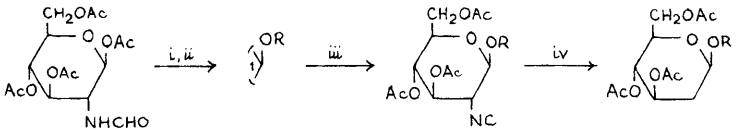
A review on free radical reactions has included a description of the synthesis of 2-deoxy-β-D-glycosides,[9] and an extension of work referred to above[4] has used an interesting new glycosylation method involving thionoaldonates to obtain a 2,6-dideoxy steroidal glycoside (Scheme 4).[10] A further novel and general route to 2-deoxyglycosides starts with 2-deoxy-2-



Reagents: i, DCC, steroid; ii, MeO-(P,S,S,P)-OMe; iii, LiBHEt$_3$, MeI; iv, Bu$_4$NF; v, AgBF$_4$

Scheme 4

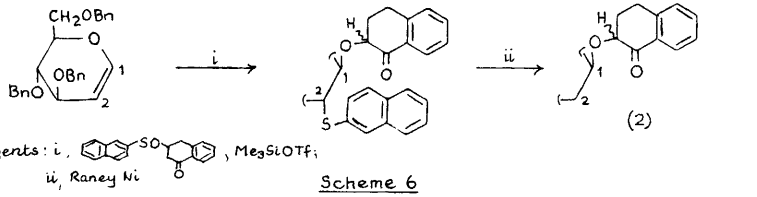
formamido-compounds and proceeds by reduction of derived isocyanides (Scheme 5).[11] In related work Ogawa's synthesis of



Reagents: i, AcCl, HCl; ii, ROH, AgOTf; iii, $POCl_3$, NEt_3; iv, Bu_3SnH

Scheme 5

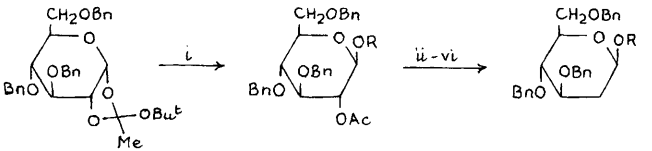
2-deoxy-β-glycosides from glycals by addition of arylsulphenyl esters of the aglycone has been modified by use of the less volatile 2-naphthylsulphenyl chloride and extended to the synthesis of (2), a model of aureolic acid antibiotics (Scheme 6).[12] A further route to 2-deoxy-glycosides involves the specific



Reagents: i, , Me_3SiOTf; ii, Raney Ni

Scheme 6

ring opening of 1,2-orthoacetates and the subsequent reductive cleavage of the ester group at C-2 (Scheme 7).[13] A route to



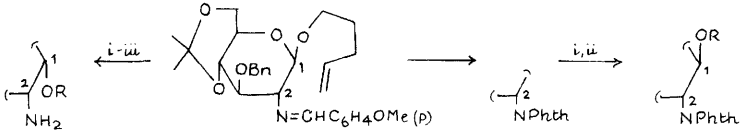
Reagents: i, ROH, collidine perchlorate; ii, MeO^-; iii, NaH; iv, CS_2; v, MeI; vi, Bu_3SnH, AIBN

Scheme 7

2-deoxy-D-<u>lyxo</u>-hexopyranosides from ulosonic acid glycosides is mentioned below.

In the field of glycosides of 2-amino-2-deoxy sugars Mootoo and Fraser-Reid have found an ingenious method for controlling the

stereochemistry at the anomeric position by opting for specific amino-protecting groups. With monohydroxy sugar derivatives they were able to obtain yields of about 65% and 80-90% of α- and β-linked disaccharides respectively (Scheme 8).[14]



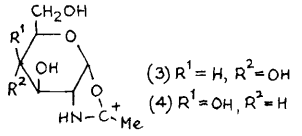
Reagents: i, I(collidine)$_2$ClO$_4$; ii, ROH; iii, H$^+$

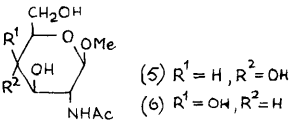
Scheme 8

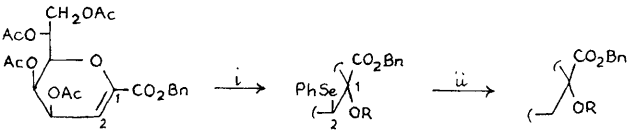
A novel method of synthesis of β-glycosides (including disaccharides) of 2-acetamido-2-deoxy-D-glucose uses 2-deoxy-2-iodo-D-mannosyl azide (prepared from tri-O-acetyl-D-glucal) which gives access to the glycosides (via aziridine intermediates) on treatment with triphenylphosphine and alcohols in dichloromethane. In similar fashion, the D-gluco-iodoazide affords the 2-acetamido-2-deoxy-α-D-mannopyranosides.[14a]

When 2-acetamido-2-deoxy-D-glucose or -galactose was dissolved in anhydrous hydrogen fluoride, the oxazolinium ions (3) and (4) were produced; addition of methanol gave the methyl β-glycopyranosides (5) and (6) in high yield. The former glycoside was also obtained by treating chitin under the same conditions. If, instead of treating the intermediates with methanol, the acid was allowed to evaporate, β-(1→6)-linked oligomers ranging from the di- to hexa-saccharides were formed.[15] Some N-acrylyl derivatives from which β-glycosides can also be produced are referred to in Chapter 9. Specific 2-amino (or 2-acetamido-)-2-deoxy-β-D-glucopyranosides or -galactopyranosides have been made from the "spacer arm" compound 3,6-dioxa-non-8-en-1-ol,[16] 6-aminohexanol bonded through the amino-group to 2'-deoxyuridine,[17] and 4-methylumbelliferol.[18] In this last report the α-anomer was also isolated, and analogous 2-acetamido-2-deoxy-α-D-glucosides and -galactosides having "spacer arm" aglycones were made following Wittig reactions applied to 3-hydroxyacraldehyde glycosides.[19]

In the area of ulosonic acid glycosides a stereospecific route to α-glycosides of KDO derivatives has been described (Scheme 9),[20] and a related route involves addition of hydrogen chloride to the glycal, conversion of the adduct via the phenyl thioglycoside to the sulphone and C-1 carboxylation of the latter. The products could be reduced to the ulosonic acid thioglycosides and



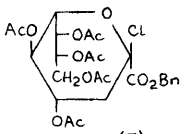


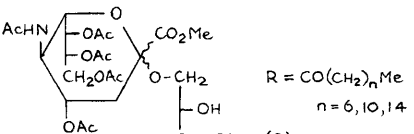


Scheme 9

hence converted to glycosides; radical decarboxylation of these last products afforded a novel route to 2-deoxy-D-galactopyranosides.[21]

The sodium salts of the phenyl, p-nitrophenyl and 4-methylumbelliferyl α-glycosides of 3-deoxy-D-glycero-D-galacto-2-nonulopyranosonic acid have been synthesised using compound (7),[22] as have the 4-methylumbelliferyl α-glycosides of N-acetylneuraminic acid, its 7-, 8- and 9-deoxy and 4,7-dideoxy-analogues and its 7-, 8- and 7,8- epimers, also from the corresponding glycosyl chlorides.[23] α- and β-Thioglycosides if N-acetylneuraminic acid have been made from the acetylated β-glycosyl chloride and from the β-glycosyl acetate, respectively,[24] and the β-chloride was used in the preparation of anomeric sialyl glycerol lipids (8) from


(7)



(8)

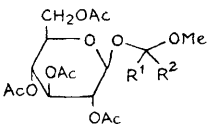
both (R)- and (S)-glycerol-lipid precursors. The products, after deacetylation, especially those incorporating the palmitoyl residue, are inhibitors of phospholipase A_2 and C.[25]

Continuing their studies on acetal glycosides Tietze and coworkers have made various compounds with general structure (9) (R, alkyl or chloromethyl) by treatment of trimethylsilyl tetra-O-acetyl-β-D-glucopyranoside with different ketones and (trimethylsilyl)methyl ether.[26] Related aldehyde methyl acetals (10) have been tested as substrates for β-D-glucosidase from sweet almond emulsin. Some of the amino-compounds were particularly

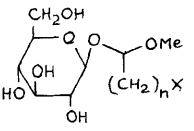
resistant to hydrolysis - especially (R)-3-amino-1-methoxypropyl β-D-glucopyranoside. The significance of the findings was discussed in terms of the special orientation of functional groups in the active site.[27]

Condensation of protected glycosyl fluorides with phenols in the presence of Cp_2HFCl_2 and silver perchlorate generally affords the thermodynamically favoured aryl glycosides, but in some cases such factors as solvent can determine which anomers are favoured.[28] Specific aryl glycosides to have been made and studied are the β-glucopyranoside of p-hydroxybenzaldehyde,[29] the β-D-mannopyranosides of o-nitrophenol, methylumbelliferol and α-naphthol (Mitsunobu condensation),[30] the α-D-xylopyranoside of p-chloro-5'-bromosalicylanilide[31] and the β-D-glucuronide of fluorescein (enzymic procedure).[32] A series of tetra-O-acetyl-β-D-glucopyranosides of hydroxy-substituted benzaldehydes have been made and condensed with 3-methylpyrazolin-5-(4H)-ones to give potential anti-inflammatory products.[33]

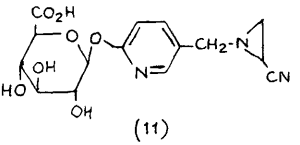
Several biologically significant products which are alkaryl glycosides have been synthesised: the metabolite (11) of the diabetes therapeutic ciamexon;[34] potassium lespedezate (12) which is involved with the circadian rhythm in plants,[35] and salidroside (13).[36]



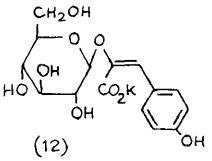
(9)



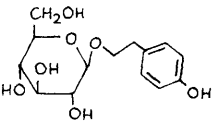
(10) X = N_3, NH_2; n = 1-4



(11)

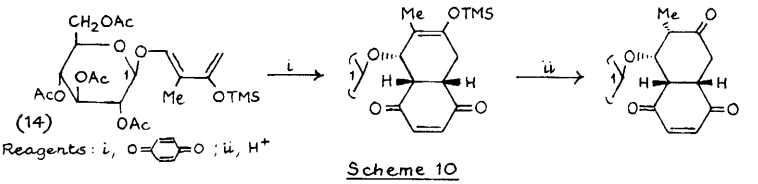


(12)



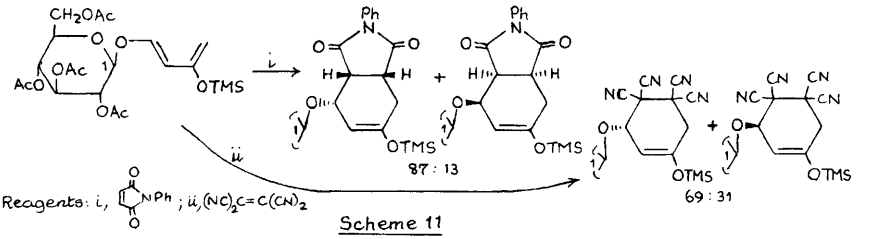
(13)

Further interesting work has continued on the synthesis of glycosides of functionalised cyclohexanes formed by Diels-Alder reactions of glycosyloxybutadienes. The detailed structure of (14) was examined crystallographically and in solution by n.O.e. methods, and its reactions with various dienophiles, e.g. quinones, N-methyl maleimide and tetracyanoethylene, were reported. The final product (Scheme 10), formed after a specific cycloaddition process, was again structurally characterised by crystallography.[37] Results obtained in an extension of this work



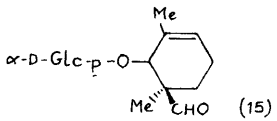
Scheme 10

are summarised in Scheme 11.[38] An important related study was carried out with 2-methylbutadienyl α-D-glucopyranoside and 2-methylacrolein to give (15) using aqueous media and no catalyst. The reaction proceeded with 20:1 endo:exo selectively. The

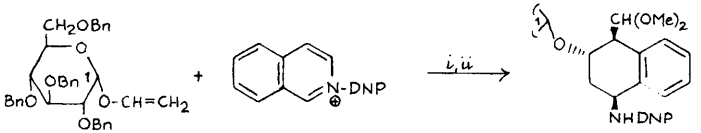


Scheme 11

effects of substitution of a benzyl group at O-2 and O-6 were also examined.[39] A reverse type of Diels-Alder reaction involving a



vinyl glycoside is illustrated in Scheme 12.[40]



Scheme 12

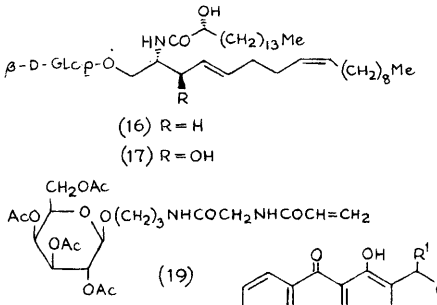
In the area of glycosylinositols, 1-O-(1,2-di-O-palmitoyl-SN-glycero-3-phosphoryl)-2-O-α-D-mannopyranosyl-D-myo-inositol has been synthesised by way of a substituted derivative of the corresponding 2-O-α-D-mannopyranosyl-D-myo-inositol.[40a]

1.2 Synthesis of Glycosylated Natural Products.- Several of the compounds mentioned above have biological chemical significance; this section notes the synthesis of natural glycosides (or related

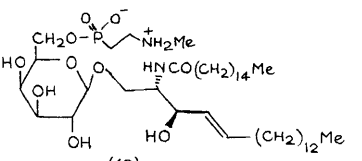
substances) grouped according to the type of aglycone employed.

A review has appeared on the total synthesis of neutral glycosphingolipids, one of the topics being the preparation of optically active ceramide from D-glucose.[41] The first total synthesis of optically active cerebroside B_{1b} (16) and its aglycone stereoisomers used the trichloroacetimidate methods,[42] as did the preparation of the hydroxy analogue (17),[43] and the related phosphonophingoglycolipid (18) has been reported, the aglycone having been derived from 2,4-O-benzylidine-D-threose,[44] as was the case for (17).[43] Palmityl β-D-glucosiduronic acid and β-D-glucopyranoside have been produced in connection with studies of liposome stability,[45] and compound (19) was coupled with a 3-aminopropylthioglycolate and the product condensed via the terminal amino group with fluorescein isocyanate to give a compound used for fluorescence studies of membrane lectins.[46]

In the field of anthracycline chemistry the alcohols (20)-(22) were glycosylated by use of derivatives of 2,6-dideoxy-L-lyxo-hexopyranose,[47] 2,6-dideoxy-2-iodo-L-hexoses[48] and 3-amino-2,6-dideoxy-L-lyxo-hexopyranose,[49] respectively. Likewise daunosamine and related sugars have been bonded to the dihydropyran analogues (23)-(25).[50]

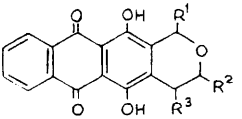


(16) R = H
(17) R = OH

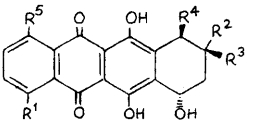


(18)

(19)



	R¹	R²	R³
(23)	H	H	OR
(24)	H	CH_2OH	H
(25)	Me	CH_2OH	H



	R¹	R²	R³	R⁴	R⁵
(20)	H	NH_2	COMe	H	H
(21)	OH	OH	Et	OH	H
(22)	OH	OH	Et	CO_2Me	OH

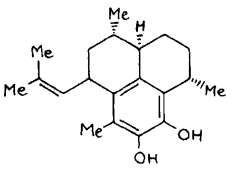
In the area of simple terpene glycoside farnesyl β-D-galactopyranoside and α- and β-D-mannopyranoside have been reported[51] as have eighteen monoterpene β-D-glucopyranosides for an investigation of β-glucosidase specificity. The soluble silver trifluoroacetate gave appreciably enhanced yields.[52,53]

Glycosylation of various steroids by use of tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride gave predominantly the β-glycosides,[54] and β-galactosylation of ethyl cholate at O-7 was most effective with trimethylsilyl triflate as catalyst.[55] A review has been produced on the preparation of potent unnatural digitalis derivatives - cardioactive steroid glycosides - having improved safety margins.[55a]

A review has been published on flavone and flavonol glycosides.[56] Specific reports have appeared on the preparation of several sets of α- and β-4-trifluoromethylumbelliferone glycosides,[57] and on the β-D-glucopyranosides of several isoflavones.[58]

Allyl esters have been used for carboxyl group protection in O-glycopeptide synthesis. Standard glycosylation procedures were used to substitute the hydroxyl groups of serine and threonine N-Cbz esters, and the peptide chains were extended following dealkylation using Pd(0)-catalysed allyl transfers.[59] Specifically, glycosylated threonine derivatives have been extended by solid phase peptide methodology to glycosylated hexapeptides related to oncofetal fibronectin; the sugars involved were β-D-GlcNAc and the (1-3)-linked β-D-Gal derivative of it.[60]

Complex polycyclic compounds to have been glycosylated are several gibberellins (β-D-glucosylation),[61] pseudopterosin (26) (α-L-fucosylation),[62] normorphine (27) (3- and 6-β-D-glucuronides),[63] 9α-methoxymitosane (28) (7-substitution by β-D-glucopyranose, β-lactose, β-D-N-acetyl-glucosamine and -galactosamine),[64] and streptazoline (29) (β-D-glucosylation).[65]



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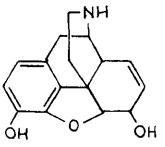

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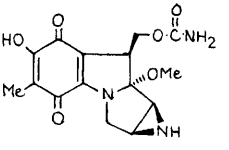

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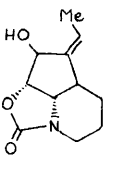


(29)

1.3 O-Glycosides Isolated from Natural Products.- Four flavan-3-ol β-D-allopyranosides and three proanthocyanidin allopyranosides have been isolated from a fern,[66] and the 6-benzoate (30) and the glucoside (31) have been obtained from a protea[67] and from strawberries,[68] respectively. In the latter case a mixture of diastereomers was found and the mixture was also produced by

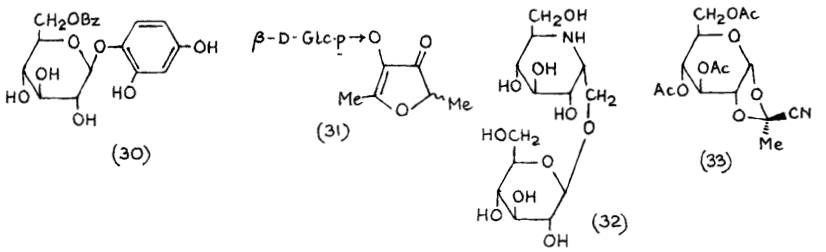
synthesis. 2-O-β-L-Arabinopyranosyl-myo-inositol is a main, and tasteless, constituent of tea.[69]

1.4 Synthesis of Disaccharides and their Derivatives.- In the area of non-reducing disaccharides bis-4,6-O-benzylidene-α,α-trehalose has been used to give, by way of the dibutylstannylene intermediate, the 2,2'-di-O-benzyl and 2,2'-di-O-allyl ethers; from the latter the 3,3'-di-O-benzyl compound was derived.[70] Bis-2-acetamido-2-deoxytrehalose compounds having long chain fatty acid esters at O-6,6' and peptide substituents at O-3, O-3' have been reported.[71] A newly isolated fructosyl transferase from Bacillus subtilis has exceptionally high propensity to form a range of α-1→2 linked disaccharides; by its use "xylosucrose", "galactosucrose" and 6-deoxysucrose have been prepared.[72] The 5-amino-5-deoxy-D-glucose derivative (32), which has structural similarities to non-reducing disaccharides, and which acts as an α-glucosidase inhibitor, has been reported.[73]

The synthesis, n.m.r. studies and conformational analysis of several 1,3- and 1,4-linked disaccharide methyl glycosides and related trisaccharide methyl glycosides have been undertaken.[74]

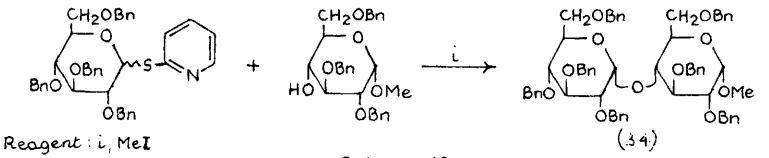
Reducing disaccharides are now treated according to their non-reducing moieties. β-D-Glucopyranosyl disaccharides can be synthesised in high yield by use of tetra-O-benzyl-α-D-glucopyranosyl fluoride together with Cp_2HFCl_2 - $AgClO_4$ in the proportions 1:2;[75] further studies of disaccharide synthesis using tetra-O-benzyl-α-D-glucopyranosyl chloride have been reported.[76]

Reaction of the cyanoethylidene reagent (33) with methyl



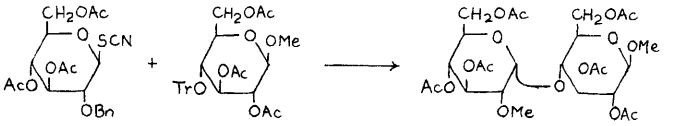
2,4,6-tri-O-acetyl-3-O-trityl-β-D-glucopyranoside under the catalytic effect of trityl perchlorate at high pressure gave a 95:5 ratio of β:α-3-linked disaccharides.[77]

In the area of 4-linked glucobioses the α-compound (34) was prepared in 82% yield as indicated in Scheme 13;[78] an analogous



Scheme 13

synthesis is depicted in Scheme 14, starting from the more novel glycosyl thiocyanate as glycosylating agent.[79] Several perfluoroalkyl maltosides have been reported to have abilities to stabilise emulsions.[80]

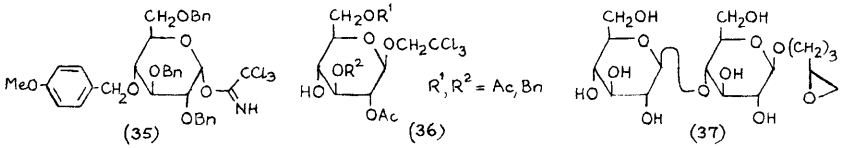


Scheme 14

Reaction of the glycosyl imidate (35) with the receptors (36) led to the correspond β-(1→4)-linked disaccharide when the protecting group at O-3 was benzyl whereas, unexpectedly, the α-linked analogue was the main product when the acetyl group was present.[81]

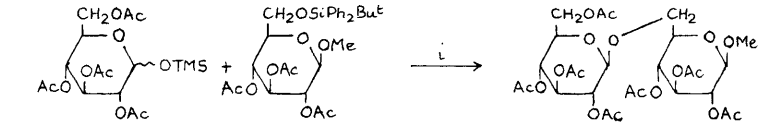
Tetra-O-benzyl-α-D-glucopyranosyl (diphenyl)phosphate and methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside, condensed in the presence of trimethylsilyl triflate, afforded the substituted cellobioside in high yield and with an α:β ratio of 7:93. This is an unusual use of phosphate esters and is of particular interest since the glycosyl phosphate used is claimed to have appreciable shelf life.[82]

Compound (37) is an active-site directed inhibitor of



cellulase of Schizophyllum commune;[83] tritiation at C-1′ aided the isolation of a complex of the inhibitor and the inactivated cellulase.[84]

A new method of synthesising 1,6-linked compounds affords products with ca. 70% efficiency (Scheme 15).[85] The mutagenicity and lethal toxicity of chemically synthesised lipid A analogues having 2,3-acyloxyacylglucosamine 4-phosphate with

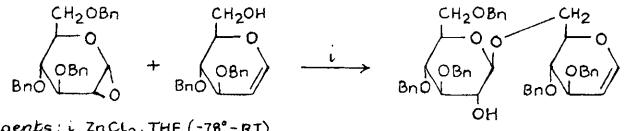


Reagent: i, TMSOTf

Scheme 15

tetraacetylhexose substituents bonded at O-6 vary according to the hexose.[86] The bromoacetate group can be used, by selective primary substitution, as a route to sets of 1,6-linked oligosaccharides.[87]

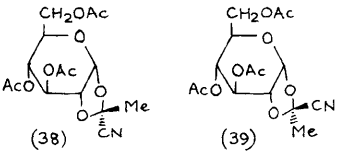
Epoxidation of tri-O-benzyl-D-glucal with dimethyldioxirane gave the 1,2-anhydro-D-gluco-sugar in good yield and with 20:1 stereoselectivity. (Other glycal derivatives afforded the 2,3-trans-adducts with similar selectivity). Use, in glycoside synthesis, of the glucal adduct, is illustrated in Scheme 16.[88]



Reagents: i, $ZnCl_2$, THF (-78°-RT)

Scheme 16

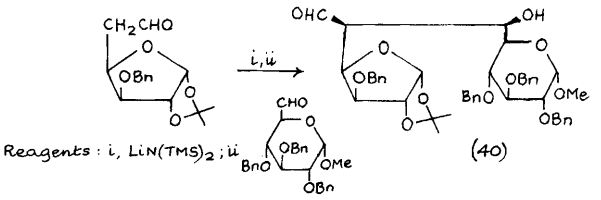
The endo-isomer (**38**) is more reactive than the exo- (**39**)



towards tritylated sugars in the presence of trityl perchlorate. Both have been used to make 6-β-linked glucosylgalactose. A related set of disaccharides was made in the course of this study.[89] Other hetero-glucosyl-disaccharides to have been reported are 6-O-β-D-glucopyranosyl-D-fructose (leucrose) (and the α-linked isomer),[90] 2-O-α-D-glucopyranosyl-L-rhamnose[91] and various derivatives of methyl α-D-galactopyranoside having O-3 or O-4 (or both) substituted by a glucopyranosyl group in either anomeric configuration.[92]

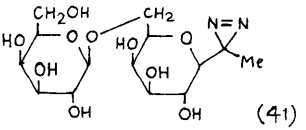
The unusual C-linked disaccharide analogue (**40**) has been made as illustrated in Scheme 17.[93]

In the series of galactobiosides the 6-O-α- and β-linked compounds have been made as their methyl glycosides by the orthodox Koenigs-Knorr approach,[94] and the analogous photolabile C-glycoside (**41**), which was used in immunological studies related to

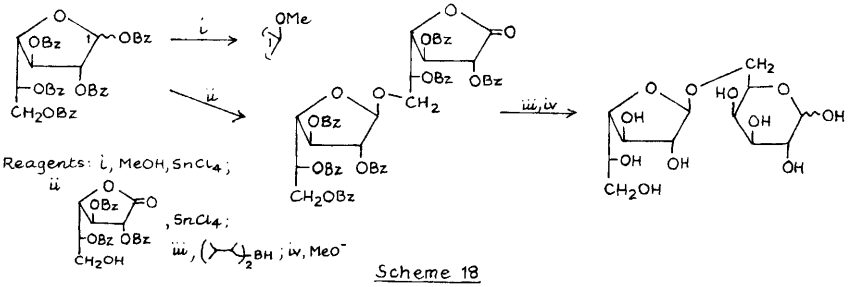


Scheme 17

IgAx24, has been made by chemical and enzymatic methods.[95] Glycosylation of 3- and 6-trityl ethers of methyl β-D-


(41)

galactopyranoside with 1,2-O-cyanoalkylidene derivatives of galactopyranose afforded routes to 1,3- and 1,6-linked galactobiosides.[96] Syntheses have been reported of the 3′-O-methyl, 4′-deoxy-4′-fluoro and 4′-epi-derivatives of methyl 4-O-β-D-galactopyranosyl-β-D-galactopyranoside as well as the 2′-, 3′-, 4′-, 6′-deoxy and 6′-deoxy-6′-fluoro-analogues. Calculations by molecular mechanics showed only small deviations for the conformations of these compounds from that of the parent disaccharide glycoside.[97] The procedure illustrated in Scheme 18



Scheme 18

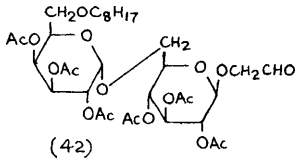
provides a convenient method for preparing β-D-galactofuranosides and D-galactofuranosyl disaccharides.[98]

1-O-β-D-Lactosyl-(R,S)-glycerol and 1,3-di-O-β-D-lactosyl-glycerol have been prepared to study their binding to the asialoglycoprotein receptor site of mammalian liver;[99] an extension of the work has afforded the α-linked monosubstituted compound and the 1-α, 3-β-linked disubstituted derivative.[100] A lactose ether

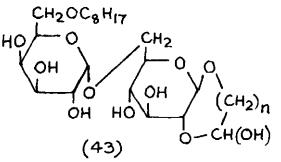
substituted at all positions except O-4' has been prepared as an acceptor in the synthesis of glycolipids, and various 2-azido-2-deoxylactosyl trichloroacetimidates have been made as glycosyl donors in the course of related work.[101]

Various 6'-octylmelibiose-based aldehydes (e.g. **42**) and related hemiacetals (e.g. **43**) have been made by reductive ozonolysis of corresponding alkenyl glycosides for reductive coupling to amino-acid derivatives.[102]

A 2'-deoxylactose derivative has been obtained as outlined in Scheme 19.[103]

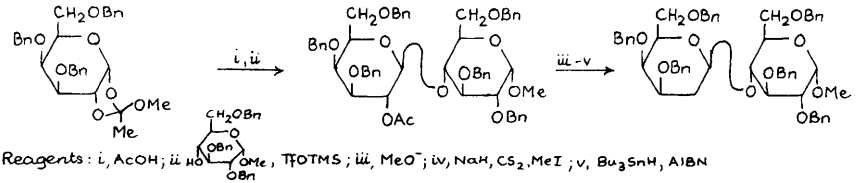


(42)



(43)

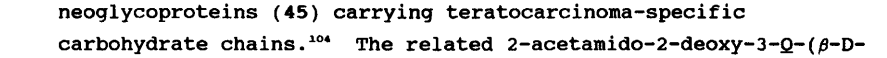
The 2-amino-2-deoxy-D-galactose-containing disaccharide glycoside (**44**) was coupled with various proteins to give



Reagents: i, AcOH; ii, TMSOTf; iii, MeO⁻; iv, NaH, CS_2, MeI; v, Bu_3SnH, AIBN

Scheme 19

neoglycoproteins (**45**) carrying teratocarcinoma-specific carbohydrate chains.[104] The related 2-acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-D-galactose was prepared enzymically from

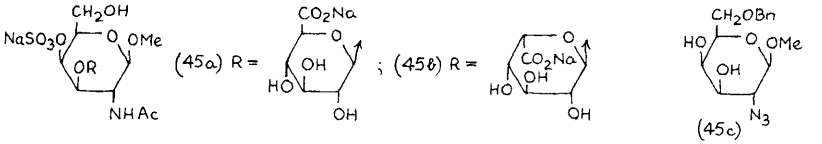


(44) R = $COCF_3$; (45) R = CO–(CH2)4–COR', R' = serum albumin or cytochrome C

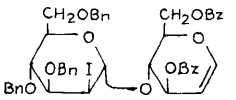
lactose and 2-acetamido-2-deoxy-D-galactose.[105] Other work has described similar preparation of the ethyl β-glycosides of this compound as well as the α,α- and β,α-linked isomers.[106]

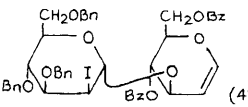
Tetra-O-benzyl-α-D-mannopyranosyl fluoride, used together with bis(cyclopentadienyl)zirconium chloride and silver tetrafluoroborate, affords an effective means of preparing α-linked mannopyranosyl disaccharides,[107] and β-linked analogues can be made by way of 2-O-imidazolsulphonates of β-D-glucose linked compounds as can 2-amino-2-deoxy-β-D-mannopyranosyl compounds.[103] The synthesis of the dermatan sulphate disaccharides (**45a**) and (**45b**)

has been reported; the paper also describes a new route to the azido-compound (**45c**).[108a]



Interest continues in the synthesis of deoxydisaccharides. A simple route to 2'-deoxy-D-arabino-hexosyl compounds proceeds from 1,2-di-O-acetyl-3,4,6-tri-O-benzyl-β-D-glucose, the glycosylation being catalysed by trimethylsilyl triflate and the deoxygenation at C-2' effected by radical induced reduction of derived xanthate esters.[109] Compounds (**46**) and (**47**), obtainable

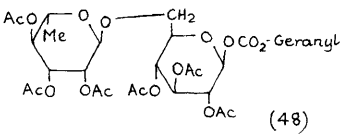

(46)

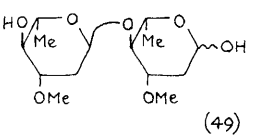

(47)

from glycal derivatives, can be used for 2,2'-dideoxy disaccharide production or in the production of related tri- and higher saccharide analogues and hence 2-deoxyhexose oligomers.[110]

Several fucosyl derivatives of methyl α-D-glucopyranoside, having the substituent sugar at O-3 or O-4 or O-3,4 and in both anomeric configurations, have been prepared and subjected to in-depth conformational analysis.[92] In an attempt to synthesise the geranyl glycoside of rutinose (6-O-α-L-rhamnopyranosyl-D-glucose) by use of the acetylated α-glycosyl chloride in pyridine with silver carbonate, the corresponding carbonate (**48**) was obtained instead.[111]

Ozonolysis of a silylated avermectin B_1 derivative gave improved access to oleandrosyloleandrose (**49**),[112] and the compound

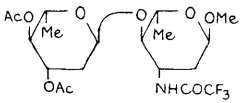

(48)


(49)

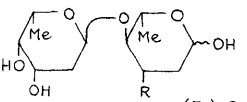
has been synthesised in good yield by use of the 2-pyridylthio-glycoside method.[113] The related α-1→4 linked 2,6-dideoxy-L-lyxo-hexose disaccharide, related to anthracycline components, has been made using the glycal, N-iodosuccinimide procedure.[114] The 3-O-α-paratosyl, abequosyl and tyvelosyl α-D-mannopyranoses have been

prepared as their alkyl and 2-acrylamidoethyl glycosides for conversion into artificial antigens related to those of the Salmonella.[115] Several selectively substituted derivatives of the β-(1→3)linked dimer of 2,6-dideoxy-D-xylo-hexose have been made by specific removal of benzyl, benzoyl and tosyl groups in turn.[116] Additions to glycal derivatives were used to obtain the pentadeoxyamino compounds (50)[117] and (51).[118]

3-O-(3,6-Dideoxy-α-D-xylo-hexopyranosyl)-L-rhamnopyranose was prepared as its α- and β-2-acrylamidoethyl glycosides for



(50)

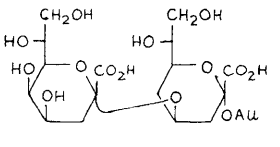


(51) R = NMe_2, $NHCOCF_3$

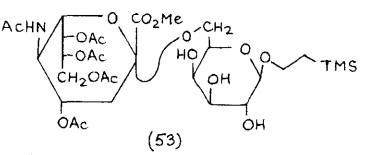
development of polyacrylamide copolymers with Salmonella antigen specificity.[119]

Use of a specific, immobilised hydrolase which cleaves α-1→4 bonds of sodium pectate gave access to the correspondingly linked di-D-galactosiduronic acid.[120]

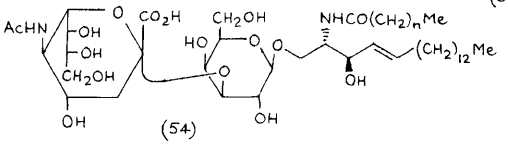
The 5-deoxy derivative (52) of a KDO disaccharide has been synthesised,[121] and a review has appeared on various glycosylating reagents derived from N-acetylneuraminic acid.[122] Specifically, in this area, compounds (53) and (54, n = 12 or 16) have been



(52)



(53)



(54)

prepared synthetically.[123,124]

In the area of disaccharides having 2-acetamido-2-deoxy-β-D-glucopyranose glycosidically bonded to other sugars, the 1→6 linked methyl β-D-galactopyranoside and the methyl α-D-mannopyranoside compounds have been made by use of glycosidases.[106] Chemical procedures have been applied to obtain the disaccharides having the amino-sugar 1→4 and 1→6 linked to methyl α-D-glucopyranoside,[125] methyl β-D-glucopyranoside and methyl α-D-mannopyranoside.[126] Similarly it has been coupled 1→6 to 2-amino-

2-deoxy-D-glucose,[127] 1→4 linked to N-acetylmuramic acid,[128] 1→4 and 1→6 linked to N-acetylmuramoyl-L-alanyl-D-isoglutamine[129] and 1→4 linked to N-acetylnormuramoyl-L-α-aminobutanoyl-D-isoglutamine.[130] Chitobiose octa-acetate has been obtained in improved yields by acetolysis of chitin (12-16% yield) and following microbial degradation of the polymer (31%); derived glycosides were reported.[131]

In the pentose series methyl 4-O-β-D-xylopyranosyl β-D-xylopyranoside has been synthesised by glycosylation of a methyl 4-O-trityl-β-D-xylopyranoside derivative.[132,133] Detailed ^{13}C n.m.r. studies of the methyl β-D-xylopyranosyl-β-D-xylopyranosides have been reported.[134]

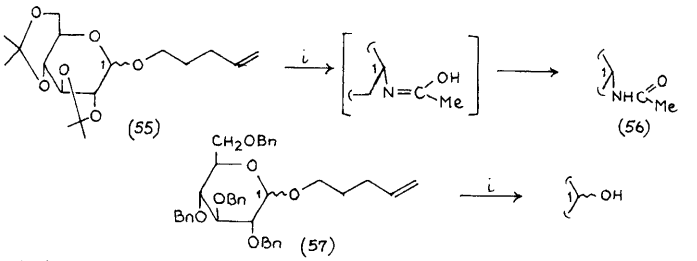
1.5 Hydrolysis and Other Reactions and Features.- *Ab initio* calculations on the protonation of dimethoxymethane have confirmed that a *syn*-periplanar alignment of a lone pair with a leaving group is on the pathway to the transition state and is energetically favoured relative to an *anti*-periplanar arrangement. These results were correlated with the optimal stereochemical requirements for glycoside hydrolysis.[135]

2-Methoxyethyl glycosides bearing such protecting groups as acetyl, benzyl and allyl may be cleaved by treatment with $TiCl_4$ in dichloromethane followed by hydrolysis on a column of silica gel.[136]

In a study of the relative rates of hydrolysis of conformationally restrained α- and β-4-pentenyl glucosides under neutral conditions, it was concluded that the Deslongchamps theory for glycoside hydrolysis (the *anti*-periplanar lone pair hypothesis) was not consistent with the results obtained.[137] In work on variously substituted 4-pentenyl glycosides compound (**55**, either anomer) gave the amide (**56**) on treatment with N-bromosuccinimide in aqueous acetonitrile, whereas the benzylated analogue (**57**) underwent hydrolysis in these conditions (Scheme 20). The first result was attributed to the strain imposed by the ring fusions on the pyranose system.[138]

Reductive cleavage of the acetal groups in some methyl 4,6-O-benzylidene-α-D-hexopyranosides with sodium cyanoborohydride has been shown to depend upon subtle structural features as illustrated in Scheme 21. In the first two examples, the products shown were the only ones isolated.[139]

Liberation of the sensitive aglycone ptaquilosin (**58**) from its glucoside has been achieved as illustrated in Scheme 22, the key step being the opening of the pyranosyl ring triggered by

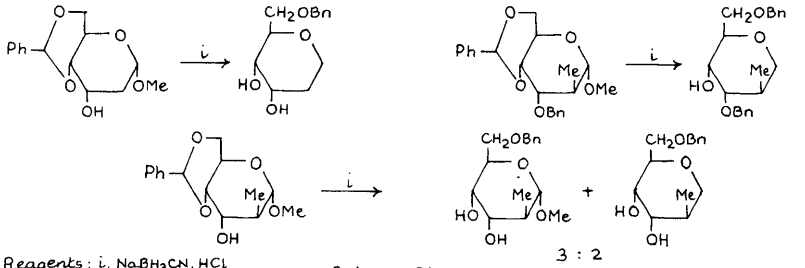


Reagents: i, NBS, MeCN, H_2O

Scheme 20

attack at the C-6 iodo-group with zinc.[140]

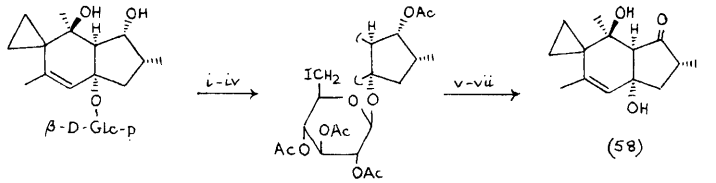
The configuration of the glycerol moiety of glycosylglycerols can be determined by perbenzylation followed by



Reagents: i, $NaBH_3CN$, HCl

Scheme 21

hydrolysis and ORD/CD examination of the dibenzylglycerols produced.[141]



Reagents: i, Bu_2SnO; ii, TsCl; iii, Ac_2O, Py; iv, KI, DMF; v, Zn, NH_4Cl, EtOH; vi, K_2CO_3, MeOH; vii, PCC

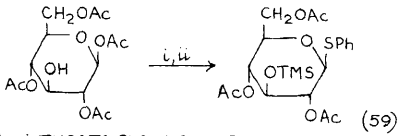
Scheme 22

A ^{13}C n.m.r. spin-lattice relaxation study of solvent effects on the rotational dynamics of methyl α- and β-glycosides has been reported. Rotation rates for both anomers follow the order MeOH~DMF~D_2O<pyridine<DMSO which appears to reflect both the viscosities and molecular weights of the solvents.[142]

2 S-Glycosides

Further applications of sugar peracetates to the synthesis of

ethyl and phenyl 1-thio-1,2-trans-D-glycopyranosides have used iron(III) chloride as catalyst and have led to 2-amino-2-deoxy-β-D-gluco- and α-D-manno-compounds.[143] A related report described p-nitrophenyl 1-thioglycosides made from 1,2-trans-related glycosyl fluorides, the products having the β-D-Xylf, β-D-Glcp, β-D-Galp, α-L-Rhap and α-L-Arap structures.[144] Compound (59), readily made according to Scheme 23, has clear value for the synthesis of oligosaccharides.[145]



(59)

Reagents: i, TMSOTf, PhS·TMS; ii, Py

Scheme 23

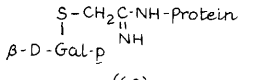
When penta-O-acetyl-β-D-glucopyranose was treated with ethanethiol and zirconium tetrachloride at 0°C in dichloromethane, the β-thioglycoside was obtained in 74% yield; at higher temperatures α,β mixtures were formed as the kinetically controlled product equilibrated with its anomer. Related studies were carried out in the D-xylo-, D-galacto- and D-manno-series.[146] Various 1-thio-α-D-gluco-compounds having long chain aglycons were prepared directly from the penta-acetate by use of boron trifluoride as catalyst and were studied as liquid crystals.[147]

Compound (60) was prepared as a carrier for introducing anti-hepatitis drugs, so that they concentrate on the hepatocytes, by reaction of bovine serum albumin with compound (61),[148] and fluorescent diastereomeric 1-isoindolyl 1-thio-β-D-glucoside derivatives (62) were made from amino acids and o-phthalaldehyde in the presence of 1-thio-β-D-glucose for the HPLC resolution of enantiomeric amino acids.[149]

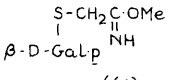
1-Thioglycosides remain of importance in the synthesis of O-glycosides and O-disaccharides. Dimethyl(methylthio)sulphonium triflate acts as a potent activator for such purposes; glycoside esters with participating groups at O-2 give 1,2-trans-related products, those with non-participating groups usually afford 1,2-cis-anomers. The latter selectively can be enhanced by addition of tetra-alkylammonium bromide.[150] Specifically, compound (63) has been used to glycosylate suitably protected 16-membered macrolides in the synthesis of 3-O-α-cladinosides,[151] and the ganglioside GM_4 thioanalogues (64, n = 12 or 16) have been prepared.[152]

3 C-Glycosides

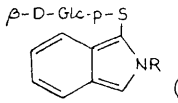
3.1 Pyranoid Compounds.- Giese has published two important reviews on the use of glycosyl radicals in the synthesis of C-glycosides and C-disaccharides.[153,154] Methods for the determination of C-glycoside stereochemistry, based on $^{1}J_{C-1,H-1}$ values, have been reported.[155]



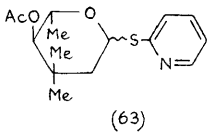
(60)



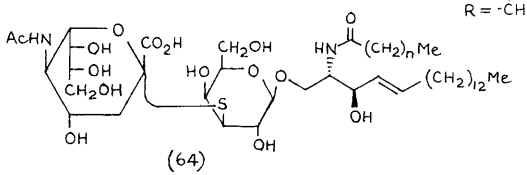
(61)



(62) R = -CH(R')CO2H

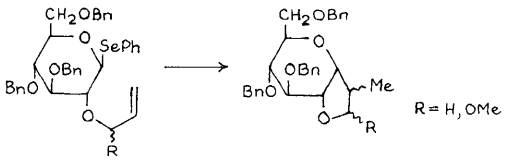


(63)



(64)

A further report of the addition of glycosyl radicals to acrylonitrile has appeared,[156] and a set of intramolecular addition reactions, illustrated in Scheme 24, have been reported.[157,158]

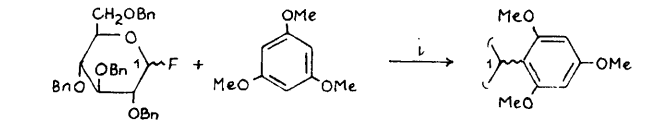


Reagents: i, Bu_3SnH, AIBN

Scheme 24

Several syntheses of aryl C-glycosides have appeared, and the use of metal phenolates for the production of compounds of this series has been reviewed.[159] Features of the use of acylated glycosyl halides with aryl Grignard reagents have been described, α,β ratios increasing with the leaving properties of the halide and when the reagent is less nucleophilic and more sterically hindered.[160] The use of a glycosyl fluoride is illustrated in Scheme 25, anomeric ratios of the products being controlled by the selection of reaction conditions.[161] A related reaction leading to the preparation of the C-aryl part of the vineomycins is shown in Scheme 26.[162] The FAB - mass spectra of α- and β-D-glucopyranosylbenzene and their methyl ethers are referred to in Chapter 22.

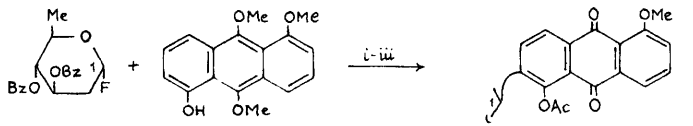
Tetra-O-benzyl-α-D-glucopyranosyl trifluoroacetate reacts



Reagents: i, Cp_2ZrCl_2, $AgClO_4$

Scheme 25

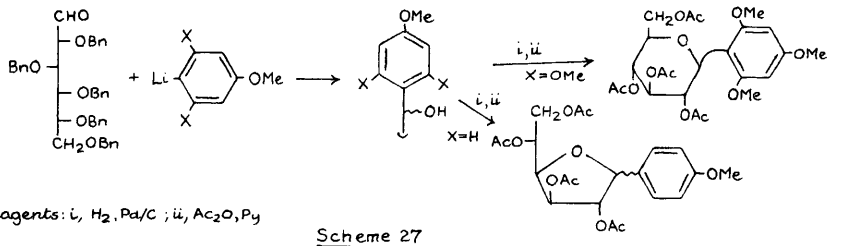
with electron rich benzene derivatives in the presence of boron trifluoride to give mainly β-linked aryl glycosides,[163] and similar



Reagents: i, $CpHFCl_2$, $AgClO_4$; ii, Ac_2O, Py; iii, CAN, MeCN

Scheme 26

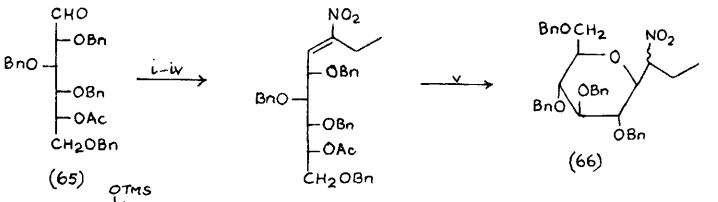
compounds may be made by the less orthodox route shown in Scheme 27. This method was then extended to the synthesis of 5,7,4'-tri-



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

Scheme 27

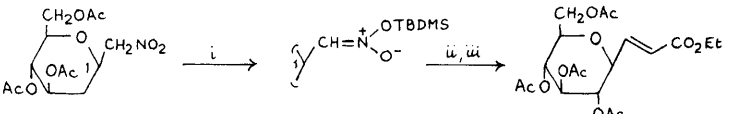
O-methylvitexin.[164] A similar acyclic starting material (65) was converted into the nitropropyl glycoside (66) as indicated in Scheme 28,[165] and related methodology was applied to obtain the



Reagents: i, ; ii, Bu_4NF; iii, H_2O; iv, Ac_2O, DMAP; v, NEt_3

Scheme 28

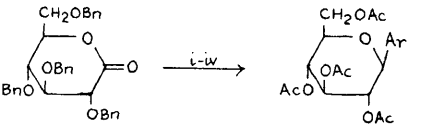
alkenoic acid glycoside (67) (Scheme 29).[166] Free radical addition reactions which lead to further, related C-glycosides and chain extended aldonic acid derivatives are referred to in Chapter 16.



Reagents: i, TBDMSCl, DBU ; ii, O_3 ; iii, $Ph_3PCH_2CO_2Et$ (67)

Scheme 29

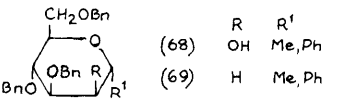
A further novel approach to aryl C-glycosides starts with aldonolactone derivatives (Scheme 30),[167] and another provided



Reagents: i, ArLi; ii, Et_3SiH, BF_3 ; iii, Pd/C ; iv, Ac_2O, Py

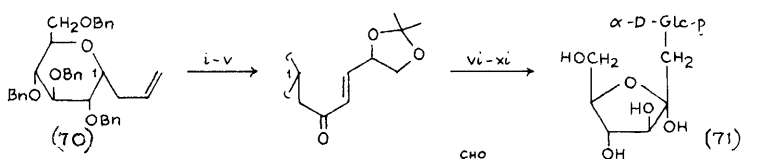
Scheme 30

access to β-linked alkyl and aryl tetra-O-acetyl-D-C-glucosides by treatment of Brigl's anhydride with organocuprates. 1,2-Anhydro-3,4,6-tri-O-benzyl-β-D-mannose similarly gave the 2-hydroxy α-mannoside (**68**) from which the 2-deoxy compound (**69**) was prepared.[168]



	R	R^1
(68)	OH	Me, Ph
(69)	H	Me, Ph

The allyl glycoside (**70**) has been used for the elaboration of the interesting C-linked sucrose derivative (**71**) which exists as a mixture of furanoid and pyranoid forms (Scheme 31).[169]

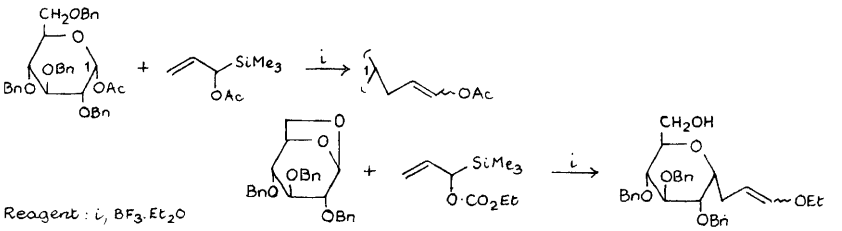


Reagents: i, $Hg(OAc)_2$, H_2O ; ii, I_2 ; iii, PCC ; iv, PPh_3, Et_3N ; v, ; vi, OsO_4 ; vii, Ac_2O, Py ; viii, $FeCl_3$, SiO_2 ; ix, Florisil ; x, K_2CO_3, EtOH ; xi, H_2, Pd/C

Scheme 31

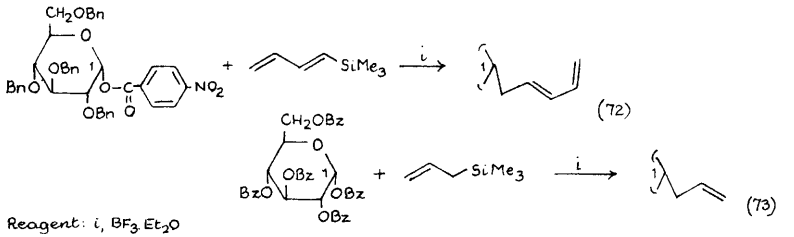
An alternative method for making 3'-oxygenated C-alkyl ethers is illustrated in Scheme 32; the α,β-anomeric ratio was ca. 8:1.[170]

The very stable (E)-isomer (**72**) and the allyl compounds (**73**) were obtained as shown in Scheme 33. While the former product



Scheme 32

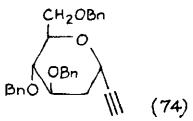
underwent Diels-Alder reaction with maleic anhydride, the latter (and the analogue activated by having a p-toluenesulphonyl



Scheme 33

substituent on the terminal alkene carbon atom) failed to react with dienes.[171]

The ethynyl C-glycoside (**74**) was prepared from the

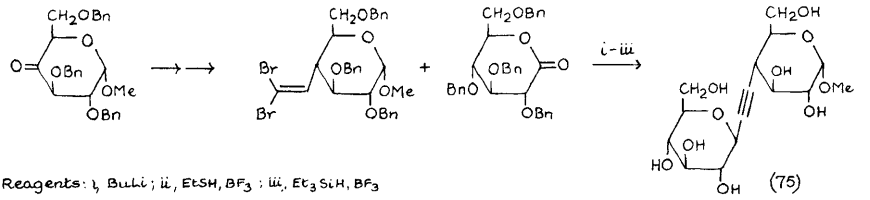


(74)

corresponding 2,4-dimethoxybenzoyl ester by use of ethynylmagnesium bromide in the presence of zinc chloride,[172] and the "linear" glycosyl, glycosid-4-yl alkyne (**75**) has been synthesised as shown in Scheme 34.[173]

A useful brief survey of methods for making C-glycosides is contained in a paper describing the reaction of 2,3,4,6-tetra-O-benzyl-D-glucose with silyl enol ethers in the presence of acid catalysts. The products bear a carbonyl group at C-2 of the aglycone and, in base, epimerise very efficiently to mixtures having α,β ratios of ca. 4:96 (Scheme 35).[174]

The Horner-Wittig products (glycosyl-CH_2CO_2Et) derived from 2,3,4,6-tetra-O-benzyl-D-glucose and D-mannose had the following

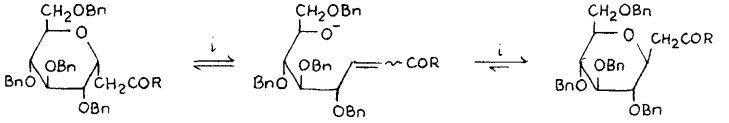


Reagents: i, BuLi; ii, EtSH, BF_3; iii, Et_3SiH, BF_3 (75)

Scheme 34

configurations:

	α-gluco	β-gluco	α-manno	β-manno
From the D-glucose ether:	13.2	5.6	2.3	1
From the D-mannose ether:	2.3	1	21	9



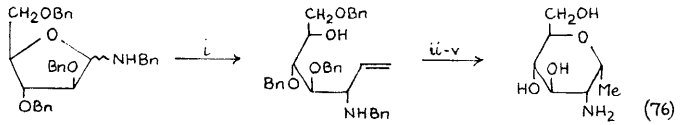
Reagent: i, base

Scheme 35

R = Me, CH_2OMe, Ph, OMe

In each case 86% yields were obtained overall. The Wittig reaction proceeded much less satisfactorily.[175]

Discussion of the use of the Tebbe reagent for the synthesis of methylene sugars from which C-linked disaccharides can be prepared is contained in a review of some Du Pont research.[176] In related work, the C-methyl α-D-glucosamine derivative (76) was obtained, together with minor proportions of the β-anomer, by use of vinylmagnesium bromide (Scheme 36),[177] but

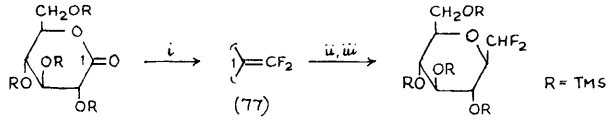


Reagents: i, ≈MgBr; ii, $Hg(OCOCF_3)_2$; iii, KCl; iv, $NaBH_4$; v, H_2, Pd/C (76)

Scheme 36

the β-anomer predominated on hydrogenation of the difluoromethylene compound (77) (Scheme 37).[178]

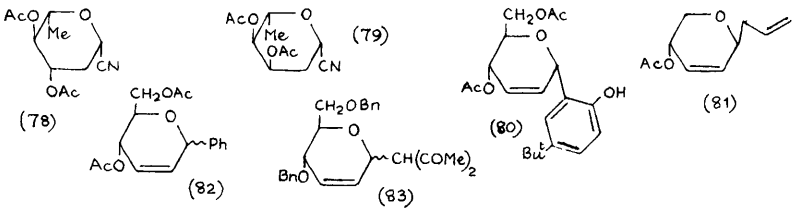
Michael addition of hydrogen cyanide to a glycal-3-ulose, followed by reduction with $CeCl_3$-$NaBH_4$ and acetylation, gave compounds (78) and (79) in 64 and 15% yield, respectively. The ratio of products was reversed when L-Selectride was used for the reduction, and the work was repeated with the D-erythro-ulose starting material.[179] 1,2-Unsaturated glycosyl cyanides are referred to in Chapter 13.



Reagents: i, $(Et\ N)_3P$ - CBr_2F_2, Zn ; ii, H_2, Pd/C ; iii, TMSCl, Py

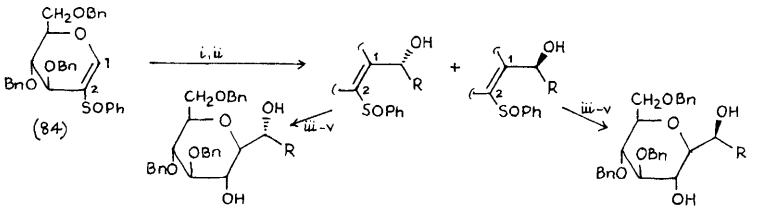
Scheme 37

The acylated glycal to 2,3-unsaturated C-glycoside rearrangement reaction continues to be used. Thus, tri-O-acetyl-D-glucal was converted in good yield into compound (**80**) and several related products by use of the bromomagnesium phenolates. Alternatively, tri-isopropoxytitanium and diethylaluminium phenolates gave exclusively the corresponding O-linked aryl glycosides.[180] The C-allyl compound (**81**) was obtained with high selectivity from di-O-acetyl-D-xylal, which contrasts with the preference found for the α-anomer when tri-O-acetyl-D-glucal was treated with allyltrimethylsilane in the presence of titanium tetrachloride. Compound (**81**) was used to prepare a conformationally restricted analogue of LTD_4.[181] The related (**82**) and (**83**) were the products formed when the analogous glycosyl



phenylsulphone and the phenyl glycoside were treated respectively with bromobenzene in the presence of butyllithium, zinc bromide and magnesium bromide,[182] and with pentane-2,4-dione in the presence of tetrakis(triphenylphosphine)palladium. In the latter case different active methylene compounds and phosphorus ligands were examined. Phenyl 2,3-unsaturated β-linked glycosides reacted with retention of configuration, whereas the α-anomers gave mixed products.[183]

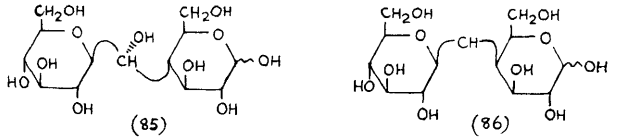
Further, with unsaturated sugar derivatives, the 2-phenylsulphinyl-D-glucal (**84**) was used as indicated in Scheme 38 to prepare 1'-hydroxyalkyl C-glycosides,[184] and this approach was developed to synthesise (via 4-deoxy-4-C-formyl-D-glucose and D-galactose derivatives) the C-linked cellobiose analogue (**85**) and the 1,4-β-linked glucosylgalactose isomer (**86**).[185]



Reagents: i, LDA; ii, RCHO; iii, Raney Ni; iv, $Me_2S.BH_3$; v, NaOH, H_2O_2

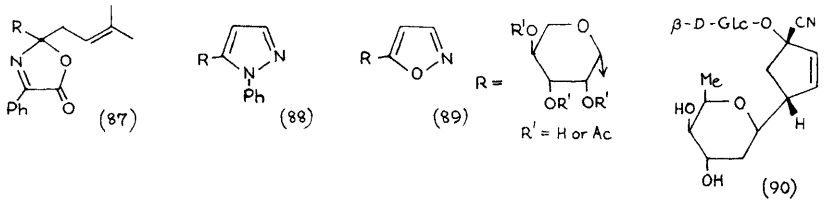
Scheme 38

A range of C-glycosides, e.g. (87)-(89), have been prepared from the corresponding glycosyl carboxylic acid,[186] and compound



(41) with a photolabile C-1 substituent has been mentioned previously.[95]

The cyanogenic C-glycoside (90) containing the rare 2,6-

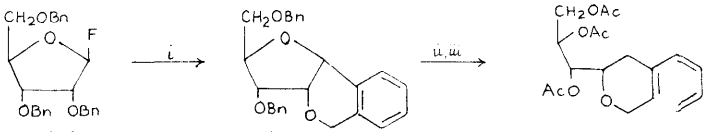


dideoxy-D-xylo-hexopyranose has been isolated from Passiflora capsularis.[187]

Further references to pyranoid C-glycosides are contained in Chapter 24.

3.2 Furanoid Compounds.- Treatment of the benzylated glycosyl fluoride (91) with boron trifluoride gave the product (92) of intramolecular C-glycosylation (cf. Carbohydr. Res., 1987, 171, 211). The 2,3-di-O-benzyl-5-O-methyl fluoride afforded the analogous C-glycoside, but the 5-O-benzyl-2,3-di-O-methyl triether did not react, establishing that in compound (92) the aglycone was derived from the ether group at O-2 of the starting material. Sugar ring opening of the tricyclic (92) was effected as indicated in Scheme 39.[188]

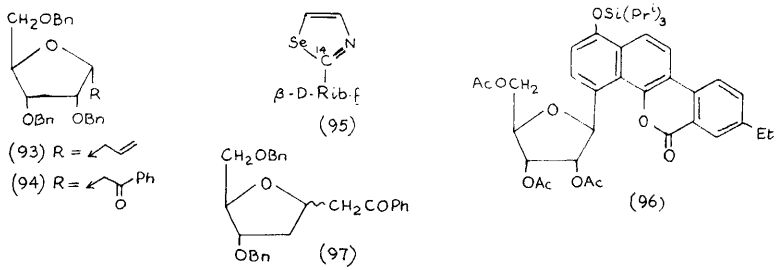
2,3,5-Tri-O-benzyl-β-D-ribofuranosyl acetate with allyltrimethylsilane and the trimethylsilyl enol ether of acetophenone, together with tin(IV) tetrachloride, tin(II) triflate and lithium perchlorate, gave only the α-C-glycosides (**93**) and (**94**), respectively,[5] and the radioactively labelled selenazolecarboxylate (**95**) has been elaborated from 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl acetate by way of the labelled glycosyl



Reagents: i, BF_3 Et_2O, ii, Pd/C, HCO_2H, MeOH; iii Ac_2O, Py

Scheme 39

nitrile.[189] The aryl C-glycoside (**96**) (in 1:1 mixture with the α-anomer) was prepared by direct substitution using tetra-O-acetyl-D-ribose,[190] and compounds (**97**) (α,β 82:18) were synthesised by use

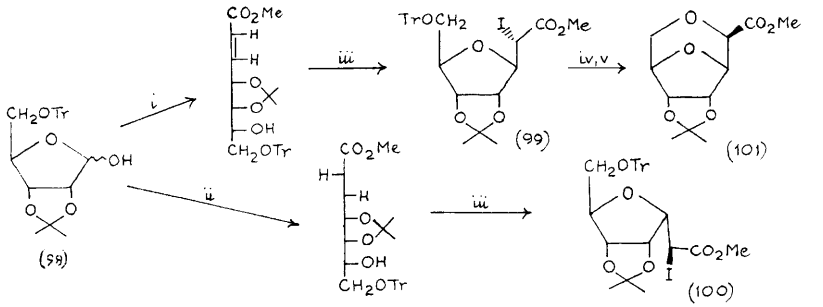


of the glycosyl acetate and the acetophenone enol silyl ether.[191]

Two methods based on the use of aldonolactones, mentioned in the above section on pyranoid C-glycosides, can be used to obtain furanoid aryl C-glycosides[167] and difluoromethyl analogues.[178]

The D-ribose derivative (**98**) was converted into the C-glycosides (**99**) and (**100**) via the 2- and E-alkenes as indicated in Scheme 40, the former product being used to prepare the 2,7-anhydride (**101**).[192] In a related study the effects of different groups and electrophiles on the electrophilic ring closure of compound (**102**) and related substances to α- and β-furanoid and pyranoid products were examined.[193]

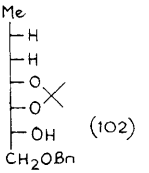
The furanoid glycal (**103**), treated with p-anisylmercury acetate in acetonitrile in the presence of palladium(II) acetate, gave the C-glycoside (**104**), whereas reaction in chloroform led to the unusual ring opening and silyl migration reaction shown in



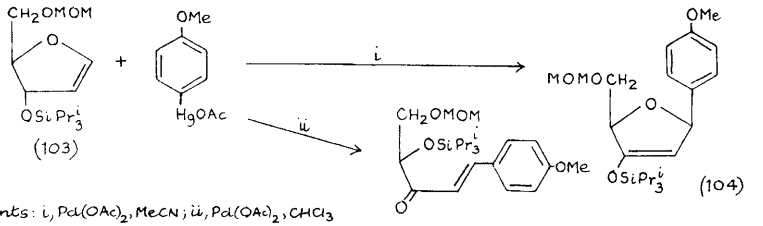
Reagents: i, $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; ii, $Ph_3P{=}CHCO_2Me$, hexane; iii, I_2, $NaHCO_3$ (aq); iv, H_3O^+; v, AgO_2CCF_3

Scheme 40

Scheme 41.[194]



The pyrrole and carbazole compounds (**105**) and (**106**) were prepared from the dihydrofuran derivative (**107**) as indicated in

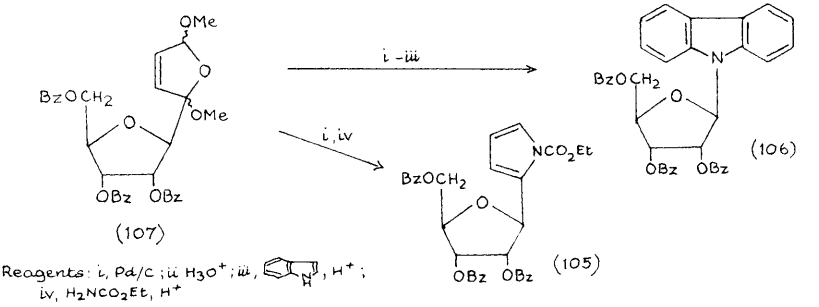


Reagents: i, $Pd(OAc)_2$, MeCN; ii, $Pd(OAc)_2$, $CHCl_3$

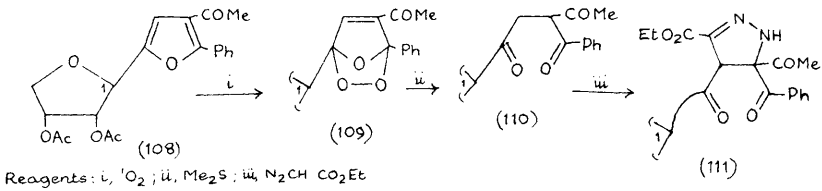
Scheme 41

Scheme 42.[195] Singlet oxygen addition to the furan (**108**) afforded the peroxide (**109**) which could be reduced to the diketone (**110**) and hence, with ethyl diazoacetate, converted into the pyrazolines (**111**) (Scheme 43).[196]

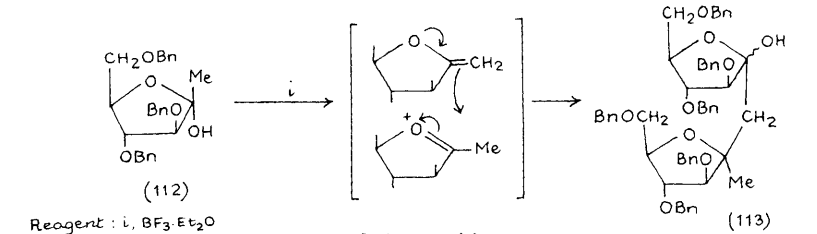
Reaction with boron trifluoride of the 1-deoxy-D-fructofuranose (**112**), available from the lactone by reaction with methyllithium, gave the isomeric C-disaccharides (**113**) in 93% yield. An indication of the possible mechanism of reaction is given in Scheme 44.[197]



Scheme 42



Scheme 43



Scheme 44

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4
Oligosaccharides

1 General

As before, this Chapter deals with specific tri- and higher oligosaccharides; most references relate to their syntheses by specific chemical methods. It does not deal with compounds made by the oligomerisation of monosaccharide derivatives, nor does it cover the cyclodextrins. The synthesis of, e.g. pentasaccharides is dealt with under that heading, and the required preparations of constituent parts are assumed and are not covered in their respective sections. Frequently, specific derivatives of the basic compounds are involved and this fact is often not recorded in the structural formulae used.

Examples of modified oligosaccharides, which include for example non-carbohydrate spacer units between the sugars, are included for the first time in this section.

A review containing 32 references has been published on sequencing methods applicable in the structural analysis of oligosaccharides.[1] A further review by Whitesides and coworkers has dealt with the enzymic in vitro synthesis of mono-, oligo- and poly-saccharides,[2] and the effects of several parameters on the yields and selectivities of glycosidase-catalysed formation of oligosaccharide glycosides have been discussed.[3]

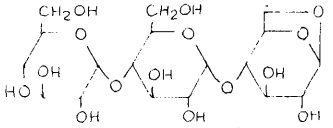
The synthesis of structural components of glycopeptides with emphasis on the use of selective protecting groups has been published (in German),[4] and a further review, also in German, has dealt with the synthesis of "neoglycoproteins" - artificial analogues in which mono- and oligo-saccharides are chemically bound to proteins. The strategies for coupling the sugars to proteins and the applications of the products as drug carriers, antigens and receptor probes are covered.[5]

Methods available for the synthesis of deoxyoligosaccharides found as parts of antibiotics and cytostatics have been described and illustrated for four different trisaccharides of aureolic acids.[6]

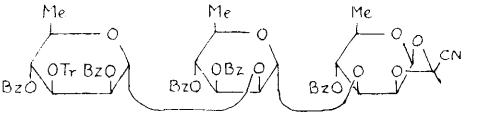
2 Trisaccharides

2.1 Linear Homotrisaccharides.- 1,6-Anhydro-β-maltotriose (**1**) has been prepared in 33% overall yield from the polysaccharide pullulan by enzymic degradation followed by conversion to pentachlorophenyl deca-O-acetyl-β-maltotrioside. A range of derivatives was then described.[7]

Chemical synthesis of the antigen of Pseudomonas aerogenosa was achieved by polycondensation of the D-rhamnose trimer derivative (**2**),[8] and in related work the 6-aminohexyl glycoside of α-L-Rhap-(1→3)-O-α-L-Rhap-(1→2)-α-L-Rhap was produced.[9]

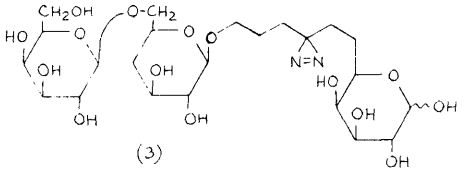


(1)

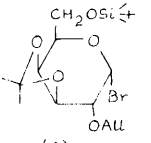


(2)

The spacer-inserted D-galactose trisaccharide (**3**) was made for affinity labelling of the "antigalactan" 2gA x 24[10] and the similarly β-(1→6), β-(1→6) linked simple trisaccharide was prepared by use of the glycosylating agent (**4**) generated in situ from the corresponding β-pent-4-enyl glycoside.[11]



(3)



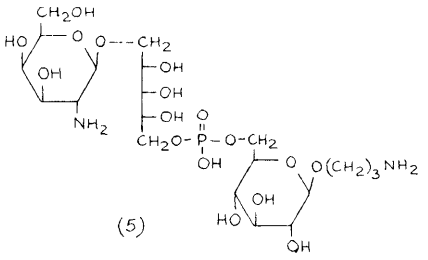
(4)

Isomeric O-α-D-KDOp-(2→4)-O-α-D-KDOp-2(2→4)-O-α-D-KDOp-All and O-α-D-KDOp-(2→4)-O-β-D-KDOp-(2→4)-O-α-D-KDOp-All have been prepared and copolymerised with acrylamide to afford artificial antigens.[12]

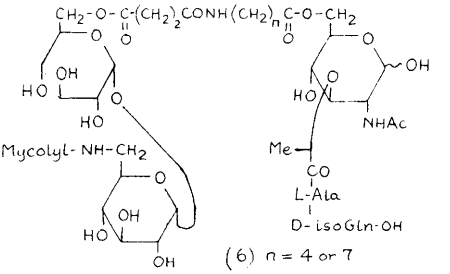
2.2 Linear Heterotrisaccharides.- The passage of D-galactose and sucrose through a column carrying immobilised β-D-galactosidase gave access to raffinose - O-β-D-Galp-(1→6)-O-α-D-Glcp-(1→2)-β-D-Fruf - in 17% yield. Similarly, immobilised α-D-galactosidase gave the α,α-linked isoraffinose in 10% yield.[13] O-α-D-NeupNAc-(2→3)-O-β-D-Galp-(1→4)-β-O-D-Glcp-OCH(N$_3$)CH(OBz)CH=CH(CH$_2$)$_{12}$Me has been converted into gangliosides GM$_3$ with three different fatty acids on

the ceramide moiety.[14] O-β-D-GalpNAc-(1→4)-O-β-D-Galp-NAc-(1→2)-O-α-D-Glcp-$(CH_2)_8CO_2Me$, carrying a sulphate substituent at O-3", has been prepared as a ^1H nmr standard to demonstrate the absence of 3"-sulphated D-Galp-NAc groups in bovine lutropin.[15] The spacer phosphate - containing trisaccharide derivative (**5**), a fragment of polysaccharide C of Streptococcus pneumoniae, has been synthesised using 1,6:2,3-dianhydro-β-D-talose.[16] The capsular polysaccharides of types 6A and 6B are potentially available using O-α-D-Galp-(1→3)-O-α-D-Glcp-(1→3)-O-α-L-Rhap which has been prepared for the purpose.[17]

The D-glucosamine-containing sialyl glycopeptide O-α-D-NeupNAc-(2→6)-O-β-D-Galp-(1→4)-O-β-D-GlcpNAc-(1→4)-L-Asp has been made by successive specific glycosylations from the glucosaminyl amino acid.[18] A more complex but related compound (**6**)



(5)

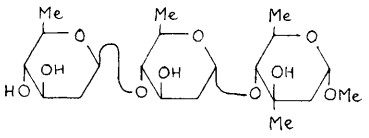


(6) n = 4 or 7

was synthesised by the condensation of 6-deoxy-6-mycolylamino-α,α-trehalose and an N-acetylmuramyl dipeptide; the product exhibited the biological properties of both its component parts.[19]

O-α-D-GlcpNAc-(1→2)-O-L-α-D-Hepp-(1→3)-O-L-α-D-Hepp-$O(CH_2)_3NH_2$, containing two units of L-glycero-D-manno-heptose and related to the core region of Neisseria meningitides polysaccharide, was made using chain extension with $PhSiMe_2$-CH_2MgCl applied to a D-manno dialdose derivative. The oxidative unmasking of the hydroxymethyl groups was carried out at the trisaccharide stage.[20]

2-Deoxyhexosyl-containing oligosaccharides can be made from benzylated glycals by the use of phenylselenyl chloride and sugar alcohols followed by radical reduction of the carbon-selenium bonds. A derivative of compound (**7**) was made in this manner.[21]



(7)

2.3 Branched Homotrisaccharides.- Oligosaccharide fragments of Salmonella kentucky O-antigenic polysaccharides in the form of β-methyl glycosides having D-galactosyl units at O-2 and O-3 have been synthesised.[22] Likewise, the trisaccharide branching point (6-O-α-D-glucopyranosylmaltose) of starch and glycogen (Vol. 18, p. 24, ref. 21) has been made as the (4-carboxy-2-nitro)benzyl glycoside for linking to polymers or for photorelease.[23] The trisaccharide of the inner core region of Citrobacter PCM 187 lipopolysaccharide consists of a (3,7-di-O-heptosyl)heptose with L-glycero-D-manno-heptose as the sugar; its synthesis by the method referred to in reference 20 has been reported.[24]

2.4 Branched Heterotrisaccharides.- Transglycosylation of lactose by use of the β-galactosidase of Aspergillus oryzae gave O-β-D-Galp-(1→4)-O-[β-D-Galp-(1→6)]-D-Glc.[25] O-α-D-Galp-(1→3)-O-[β-D-GlcpUA-(1→2)]-D-Man[26] and eight trisaccharides of methyl α-D-galactopyranoside having O-3 and O-4 substituted with either L-fucose or D-galactose or D-glucose units[27] have been prepared. In the latter work detailed nmr and theoretical conformational analyses (HSEA and GESA methods) were reported.

O-β-D-Galp-(1→4)-O-[β-D-GlcpUA-(1→3)]-L-Rha[28] and O-α-D-Galp-NAc-(1→3)-O-[β-D-GlcpUA-(1→4)]-L-Fuc having methyl ether groups at O-3 and O-4 of the two substituent sugars, respectively, have been synthesised.[29]

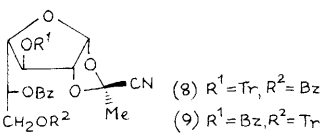
With aminosugars at the reducing termini O-β-D-Galp-(1→3)-O-[α-D-Neu5Ac-(2→6)]-O-α-D-GalNAc-(1→3)Ser[30] and O-β-D-Galp-(and O-α-L-Fucp)-(1→3)-O-[β-D-GlcpNAc-(1→6)]-D-GalpNAc[31] have been prepared as has the trisaccharide of the inner core region of lipopolysaccharides: O-L-α-D-Hepp-(1→5)-[α-D-KDOp-(2→4)]-D-KDO where the heptose is L-glycero-D-manno-heptose.[32]

3 Tetrasaccharides

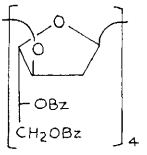
As with the trisaccharides, the following tetrasaccharides are classified according to whether they have linear or branched

structures, and then by the nature of the sugars at the reducing termini.

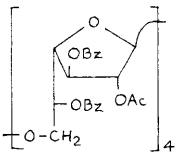
3.1 Linear Homotetrasaccharides.- Cyclo-oligomerisation of the isomeric (**8**) and (**9**) under Helferich conditions gave the unbranched tetramers (**10**) and (**11**), respectively, as well as the dimer and trimer from the latter trityl ether.[33]



(8) R^1=Tr, R^2=Bz
(9) R^1=Bz, R^2=Tr



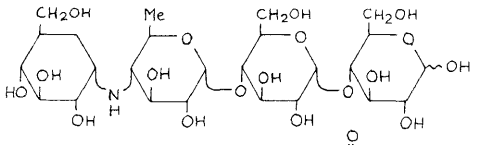
(10)



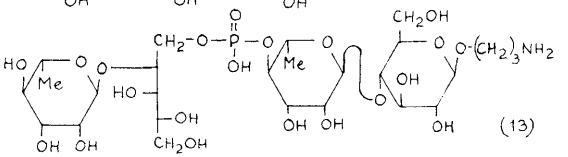
(11)

3.2 Linear Heterotetrasaccharides.- Compounds of this category having D-glucose as the reducing terminal sugar are as follows: O-β-D-GlcpNAc-(1→2)-O-α-D-Manp-(1→6)-O-β-D-Glcp-(1→4)-O-β-D-Glcp-All,[34] O-α-D-Galp-(1→3)-O-β-D-ManpNAc(1→4)-O-β-D-Glcp-(1→4)-O-α-D-Glcp-$(CH_2)_8CO_2Me$,[35] O-β-D-Galp-(1→3)-O-β-D-GalpNAc-(1→4)-O-β-D-Galp-(1→4)-O-β-D-GlcpCH$_2$CH$_2$TMS,[36] O-α-L-Fucp-(1→3)-O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→3)-O-β-D-GlcpCH$_2$CH$_2$C$_6$H$_4$NHCOCF$_3$,[37] O-α-D-NeupNAc-(2→8)-O-α-D-NeupNAc-(2→3)-O-β-D-Galp-(1→4)-O-β-D-Glcp-ceramide,[38] and O-β-D-Galp-(1→4)-O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→4)-O-β-D-Glcp-ceramide.[39]

Analogues containing a pseudo-sugar (i.e. the tetramer dihydroacarbose) and a phosphate spacer group have been synthesised and are illustrated in (**12**)[40] and (**13**),[41] respectively.

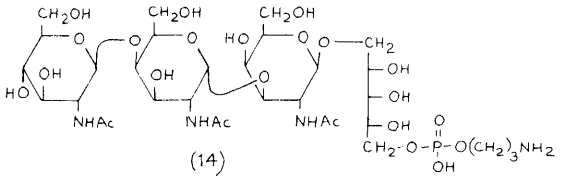


(12)



(13)

The ribitol-containing analogue (**14**) has also been prepared.[42] Other tetramers to have been synthesised



(14)

are: O-α-D-KDO-(2→4)-O-α-D-KDO-(2→6)-O-β-D-GlcpNH$_2$-(1-6)-D-GlcpNH$_2$[43] and O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→4)-O-β-D-GlcpNAc-(1→3)-D-Gal,[44] the latter being sulphated at O-6 of all the sugars other than that of the reducing moiety. The following 6-deoxyhexose tetramer was isolated from the tuber of Merremia mammosa and also synthesised: O-α-L-Rhap-(1→4)-O-α-L-Rhap-(1→4)-O-α-L-Rhap-(1→2)-β-D-Fucp.[45]

3.3 Branched Heterotetrasaccharides.- Syntheses of the following compounds have been reported: O-β-D-Galp-(1→4)-O-[α-L-Fucp-(1→3)]-O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-C$_6$H$_4$NHCOCF$_3$,[46] O-β-D-Galp-(1→4)-O-β-D-GlcpNAc-O-[β-D-GlcpNAc-(1→3)]-O-α-D-Galp-Ser,[47] O-β-D-Xylp-(1→2)-O-[α-D-Manp-(1→3)]-O-[α-D-Manp-(1→6)]-O-β-D-ManpMe,[48] O-L-Fucp-(1→2)-O-D-Galp-(1→4)-O-[L-Fucp-(1→3)]-D-GlcNH$_2$,[49] and O-α-D-NeupNAc-(2→3)-O-β-D-Galp-(1→3)-O-[α-D-NeupNAc-(2→6)]-α-D-GalpNAc-Ser.[50]

The branched tetrasaccharide lactones calonyctin A$_1$ (15) and A$_2$ (16) have been reported, their structures having been established by 2D ^{1}H and ^{13}C n.m.r. methods and by FAB mass spectrometry.[51] A related 6-deoxyhexose tetrasaccharide lactone is noted in Chapter 7.

4 Pentasaccharides

4.1 Linear Pentasaccharides.- The total synthesis of the Forssman glycolipid, O-α-D-GalpNAc-(1→3)-O-β-D-GalpNAc-(1→3)-O-α-D-Galp-(1→4)-O-β-D-Galp-(1→4)-O-β-D-Glcp-ceramide,[52] and the Para-Forssman isomer, which has the same structure but with the non-reducing terminal unit β-linked,[53] have been reported. Similarly, the pentasaccharide sialyl lactotetraosyl ceramide, O-α-D-NeuNAc-(2→3)-O-β-D-Galp-(1→3)-O-β-D-GlcpNAc-(1→3)-O-β-D-Galp-(1→4)-O-β-D-Glcp-ceramide,[54] and the isomeric sialyl neolactotetraosyl ceramide, which has a 1→4 linkage between the D-galactose and the N-acetylglucosamine units,[55] have been synthesised.

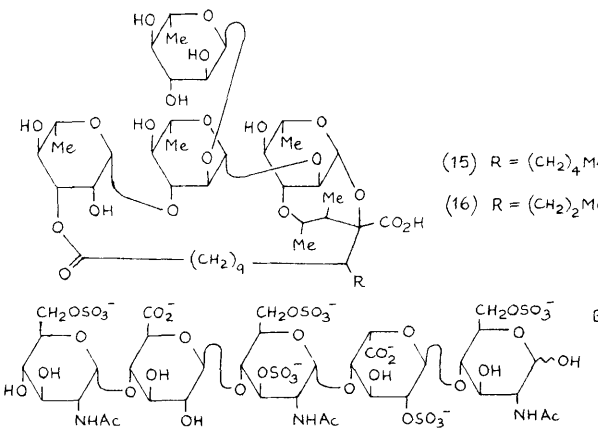
A pentasaccharide comprising five α-(1→2) linked 4-deoxy-4-formamido-D-rhamnose units has been prepared as a potential antigenic determinant of the Brucella A polysaccharide,[56] and

likewise isomers composed of the same α-D sugar (1→3), (1→2), (1→2), (1→2) and (1→2), (1→2), (1→2), (1→3) linked have been made for similar purposes related to the Brucella M polysaccharide.[57]

Synthesis of the N-acetylated heparin pentasaccharide (**17**) has been completed, the compound having 600 times less anticoagulant activity than does the N-sulphated analogue,[58] and several sulphated and non-sulphated pentasaccharides corresponding to units of E. coli K5 glycosaminoglycan have been synthesised.[59]

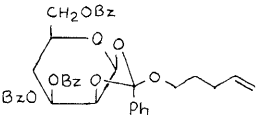
Compound (**18**), a highly reactive glycosylating agent, was used to prepare the pentasaccharide analogue which is the core oligosaccharide of the surface glycoprotein of Trypanosoma brucei i.e. O-α-D-Manp-(1→2)-O-α-D-Manp-(1→6)-O-α-D-Manp-(1→4)-O-α-D-Glcp-NH_2-1-myo-inositol.[60]

4.2 Branched Pentasaccharides.- O-β-D-Galp-(1→4)-O-β-D-GlcpNAc-(1→6)-O-[β-D-Galp-(1→3)]-O-β-D-Galp-(1→4)-D-Glc has been isolated from horse colostrum,[61] and α-D-Neup-NAc-(2→3)-O-β-D-Galp-(1→3)-O-



(15) R = $(CH_2)_4Me$

(16) R = $(CH_2)_2Me$



(18)

(17)

[α-D-Fucp-(1→4)]-O-β-D-Glcp-NAc-(1→X)-β-D-Galp-oR, where X = 3 or 6 and R = $O(CH_2)_8CO_2Me$, have been made by consequential use of porcine (2→3)-α-sialyltransferase and human milk α-L-fucosyltransferase on chemically prepared trisaccharides.[62]

A branched pentasaccharide containing a macrocyclic lactone ring related to that in compounds (**15**) and (**16**) is mentioned in Chapter 7.

5 Hexasaccharides

This section does not aim to cover the cyclodextrins comprehensively; the following however, are some references observed: a monograph has been published on the compounds covering their structures, derivatives, inclusion compounds and methods of preparation[63] and a collection of invited papers dealing mainly with inclusion complexes has appeared.[64] Cyclodextrin glucosyltransferase applied to 6'-O-methyl-α-maltosyl fluoride yielded 6^{A},6^{C},6^{E}-tri-O-methylcyclomaltohexaose.[65] Chemical approaches to the cyclodextrins have been reviewed,[66] and a synthesis of cyclomannohexaose has been reported.[67,68]

The linear hexasaccharide O-α-L-Rhap-(1→2)-O-α-L-Rhap-(1→3)-O-α-L-Rhap-(1→3)-O-β-D-GlcpNAc-(1→2)-O-α-L-Rhap-(1→2)-O-α-L-RhapPr, the hapten of Shigella flexneri variant Y polysaccharide, has been characterised by 2D NMR and synthesised.

In the series of branched hexasaccharides the ganglioside O-β-D-Galp-(1→3)-O-β-D-GalpNAc-(1→4)-O-[α-NeuNAc-(2→8)-O-α-NeuNAc-(2→3)]-O-β-D-Galp-(1→4)-O-β-D-Glcp-ceramide has been synthesised as a dilactone.[70] Several complex hexasaccharides have been isolated as triterpene glycosides from the bulbs of Muscari armeniacum[71] and others as diosgenin glycosides from a Liliaceae member.[72]

6 Higher Oligosaccharides

Compound (**19**) has been isolated from human milk[73] and compound (**20**), a core glycoheptaose of "bisected" complex glycans of a glycoprotein, has been synthesised.[74]

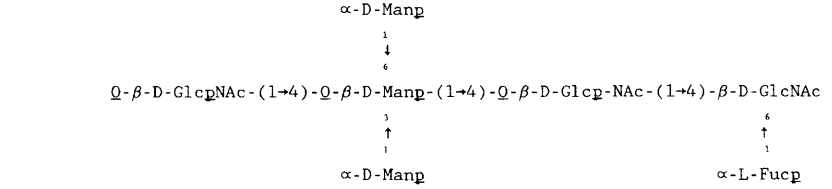
Octasaccharides comprising a β-cyclodextrin having 1-thio-α- and β-D-glucopyranose bonded to C-6 have been made via the 6-deoxy-6-iodo analogue,[75] and γ-cyclodextrins substituted at O-2 and O-6 with arylsulphonate esters, when cleaved with Taka-amylase A, gave a set of acyclic monosubstituted oligosaccharides which led to proposals regarding the binding of various hydroxyl groups to the enzyme.[76]

A nonasaccharide corresponding to compound (**19**) with α-L-fucopyranosyl units bonded to O-2 of the terminal β-D-galactosyl moiety and to O-3 of the neighbouring unit has been isolated from human milk,[77] and the tumour-associated compound (**21**) has been synthesised.[78]

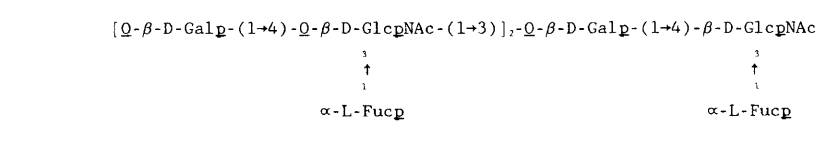
T. Ogawa and Nakahara have made the propyl glycoside of α-(1→4)-linked decagalacturonic acid, an endogenous phytoalexin

elicitor substance, by a process involving C-6 oxidation of the decagalactose analogue[79] and these workers have also described the synthesis of the analogous dodecamer.[80] Phytochemical studies have also led to the synthesis of $3^2,3^4,3^6$-tri-O-β-D-glucopyranosylgentioheptaose by block synthetic strategy.[81]

(19)



(20)



(21)

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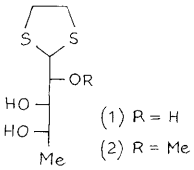
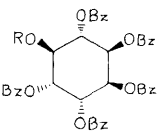
5
Ethers and Anhydro-sugars

1 Ethers

Methyl Ethers. - A short synthesis from L-arabinose of 2,6-dideoxy-3-O-methyl-L-arabino-hexose, suitable for large scale work, features the selective methylation (CH_2N_2,$SnCl_2$,DME) of the 5-deoxy-arabinose derivative (1) giving a 94% yield of the 2-O-methyl ether (2).[1] Acyl migration was observed during methylation (Ag_2O, MeI, $CHCl_3$) of 2,5-di-O-benzoyl-L-rhamnono-1,4-lactone so that 3,5-di-O-benzoyl-2-O-methyl-L-rhamnono-1,4-lactone was the product obtained. This was converted into 2-O-methyl-L-rhamnose.[2] A five step synthesis of methyl 2,6-di-O-methyl-α-D-glucofuranoside from 1,2-O-isopropylidene-α-D-glucofuranose has been described.[3] Methyl ethers of methyl α-L-arabinofuranoside have been synthesised in a partial methylation study which employed standard reagents.[4] The methyl ether (3) has



(1) R = H
(2) R = Me



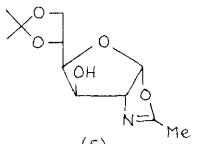
(3) R = Me
(4) R = H

been selectively deprotected to the parent alcohol (4) by use of $BF_3.OEt_2$ and Bu_4NI.[5] Some O-methyl derivatives of methyl β-D-galactobioside have been prepared,[6,7] and the synthesis of a tri-O-methyl-cyclomaltohexaose is discussed in Chapter 4.

Other Alkyl and Aryl Ethers. - The reagent system of allyl ethyl carbonate and a Pd(0) catalyst, applied to carbohydrate alcohols, has been utilised for making allyl ethers under neutral conditions.[8] The synthesis of benzyl ethers from the parent alcohols under non-basic conditions has been achieved using phenyldiazomethane and HBF_4.[9] Dibutylstannylene compounds derived from benzyl β-D-lactoside and its derivatives have been regioselectively benzylated.[10] Similarly, 2,2'-di-O-alkyl-4,6:4'6'-di-O-benzylidene-α,α-trehaloses have been prepared by regioselective alkylation of a dibutylstannylene derivative.[11] Phase transfer catalysed benzylation

of benzyl 4,6-O-benzylidene-β-D-galactopyranoside afforded predominantly the corresponding 3-benzyl ether.[12]

Alkylation and subsequent hydrolysis of oxazoline (5) has given access to 2-acetamido-3-O-alkyl-2-deoxy-D-glucose derivatives such as the corresponding 3-benzyl ether and N-acetylmuramic acid.[13] A D-glucose ether of a hydroporphyrin has been synthesised and shown to have improved in vivo activity as a tumour photosensitiser.[14] Some 6-O-(2-alkoxycarbonylallyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoses have been synthesized and co-polymerised with maleic anhydride to yield poly(vinylsaccharides) after removal of the acetonide protecting groups by hydrolysis.[15]



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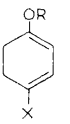
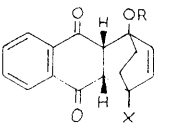


(6)



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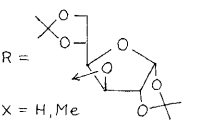
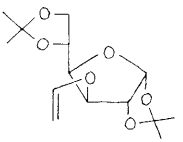


The alkoxy dienes (6) containing a chiral carbohydrate auxiliary each undergo a highly stereoselective Diels-Alder reaction with naphthoquinone affording adducts (7).[16] The vinyl ether (8), on treatment with tosyl isocyanate, stereoselectively produced the β-lactam derivative (9).[17]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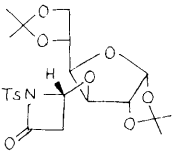
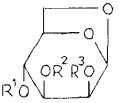


(9)

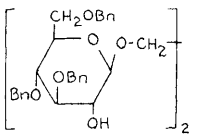


(10) $R^1 = R^2 = R^3 = Bn$
(11) $R^1 = R^3 = Bn$, $R^2 = Me$
(12) $R^1 = R^2 = Bn$, $R^3 = H$
(13) $R^1 = Bn$, $R^2 = Me$, $R^3 = H$
(14) $R^1 = R^2 = Bn$, $R^3 = Me$
(15) $R^1 = Bn$, $R^2 = H$, $R^3 = Me$

Some benzyl ether derivatives of 1,6-anhydro-β-D-mannopyranose have been selectively debenzylated using stannic chloride. Thus, both the tribenzyl ether (10) and the 3-O-methyl derivative (11) afforded selectively the 2-mono-ols (12) and (13) respectively, whereas the 2-methyl ether (14), under the same conditions, generated the 3-mono-ol (15).[18] Some sugar 3,4-dimethoxybenzyl ethers and and 4,8-dimethoxynaphthylmethyl ethers have been selectively cleaved to generate the sugar alcohols in moderate to good yield by a photochemical single-electron transfer reaction, using dicyanonaphthalene and anthraquinone as electron acceptors.[19]

Macrocycles (16) and (17) have been prepared from diol (18), and their binding with ammonium salts and use as catalysts in asymmetric Michael additions has been studied.[20] Treatment of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside with ethanolamine gave a product that was converted into the mono-

aza crown ether (19).[21]



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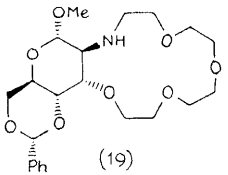

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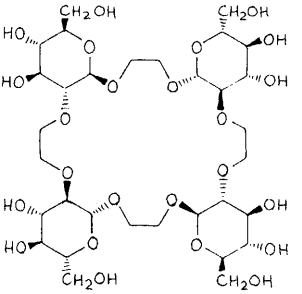
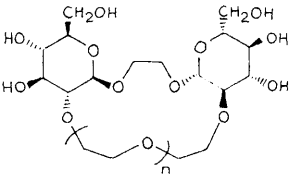


(16)

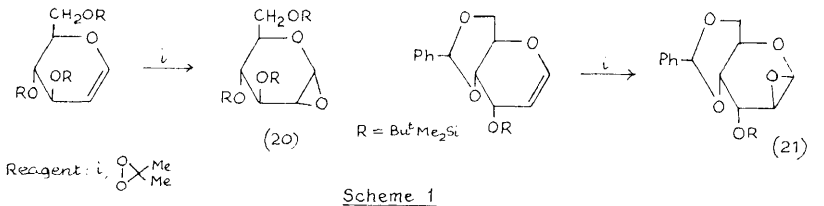


(17)

Silyl Ethers; Attempted preparation of trimethylsilylmethyl ethers of sugar alcohols by their treatment with Me_3SiCH_2I and sodium hydride has led only to mixtures of trimethylsilyl ethers and methyl ethers.[22] A series of papers reporting the synthesis and hydrolytic stability of a number of 3',5'-O-(dialkylsilanediyl) derivatives of uridine, adenosine and thymidine is discussed in Chapter 20.

2 Intramolecular Ethers (Anhydro-Sugars)

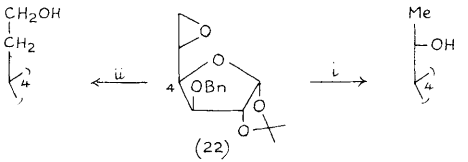
Oxirans. - Glycal derivatives have been treated with dimethyl-dioxirane affording 1,2-anhydro-sugars with the stereo-chemistry determined by the orientation of the substituent at C-3. 3,4,6-Tri-O-tert-butyldimethylsilyl-D-glucal afforded the 1,2-anhydride (20) as the only product, and 4,6-O-benzylidene-3-O-tert-



Scheme 1

butyldimethylsilyl-D-allal gave only (21) (Scheme 1).[23] Glycosylation reactions of these epoxides and the reaction of some analogous 1,2-epoxides with organocuprates are covered in Chapter 3. Separate syntheses affording unambiguously 1,2-anhydro-3,4:5,6 di-O-isopropylidene-D-glucitol, and -D-mannitol from D-glucono-1,5-lactone have been carried out.[24] Phase-transfer conditions have been utilised for the mono-tosylation of a 1,2-diol and then the in situ formation of an epoxide.[25] An unexplained reversal in the ratio of secondary to primary alcohol product, from 15:1

using LiI, to 1:5 using MgI_2, was observed in the one-pot reductive cleavage of

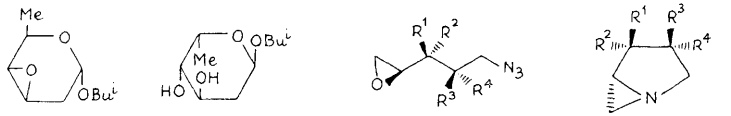


Reagents : i, LiI, Bu_3SnH, AIBN ; ii, MgI_2, Bu_3SnH, AIBN

Scheme 2

epoxide (22) (Scheme 2), which is presumed to proceed via initial opening of the epoxide with halide.[26] The formation of some anhydro derivatives in low yield during the treatment of sucrose under Mitsunobu chlorinating conditions (DIAD, PPh_3, $ZnCl_2(Py)_2$) has been noted.[27]

Enzymic hydrolysis of racemic epoxide (23) with microsomal epoxide hydrolase gave, with 50% conversion, the L-sugar (24) and recovered D-epoxide (25) in >96% ee.[28]



(23) D,L (25) D (24) (26) (27)

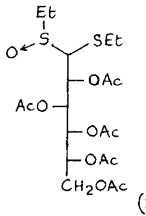
The treatment of some azidoepoxides, e.g. (26) (R^1=OBn, R^2=H, R^3=H, R^4=Me; or R^1=H, R^2=OBn, R^3=Me, R^4=H; or R^1=OBn, R^2=H, R^3=OBn, R^4=H) with triphenylphosphine under aprotic conditions affords 1-azabicyclo[3.1.0]hexanes, e.g. (27).[29] The conversion of a 3,4-anhydro-fructose derivative into 4-deoxy-fructose is covered in Chapter 12.

A total synthesis of the α-glucosidase inhibitor acarbose, featuring a non-regioselective opening of a 3",4"-anhydro-1,6-anhydro-maltotriose derivative is outlined in Chapter 18, while the Sharpless epoxidation of an octose nucleoside allylic alcohol is discussed in Chapter 20. The selectivity of some carbon nucleophiles in opening some 1,6:2,3- and 1,6:3,4- dianhydro-hexose derivatives is mentioned in Chapter 14 as is the opening of an epoxide by a reagent bearing an electrophilic carbon atom.

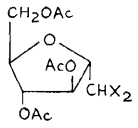
Other Anhydrides.- Procedures for the large scale synthesis of 1,6-anhydrohexopyranoses have been outlined whereby the free sugars are selectively tosylated at O-6 and the products are treated with base.[30,31] The heating of starch or other (1→4)-glucans in a conventional microwave oven yields 1,6-anhydro-β-D-

glucopyranose within a few minutes.[32] Some partially protected 1,6-anhydrosugars have been prepared as synthons for oligosaccharide synthesis by acid catalysed anhydride formation of the respective 6-hydroxy methyl glycosides.[33] 1,6-anhydro-β-maltotriose has been synthesized in 33% overall yield from the polysaccharide pullulan by way of enzymic degradation followed by chemical manipulation via pentachlorophenyl deca-O-acetyl-β-maltotrioside.[34] Calculations on the chair-boat equilibrium for 1,6-anhydro-β-D-glucopyranose have been described.[35]

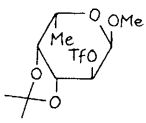
Controlled oxidation of penta-O-acetyl-D-glucose diethyldithioacetal gave the mono-sulphoxide (28) which, on treatment with sodium methoxide in methanol gave, after acetylation, the 2,5-anhydro-D-mannose derivative (29) which was converted into the diethyl acetal (30).[36] Attempted nucleophilic displacements applied to the α-L-fucopyranoside triflate (31) and its β-anomer with a variety of nucleophiles



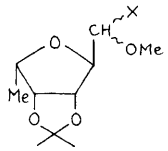
(28)



(29) X = SOEt, SEt
(30) X = OEt

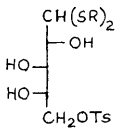


(31)

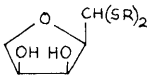


(32) X = F, OMe, OBz, N_3, H

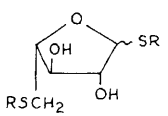
under mild conditions led to the 2,5-anhydro-sugar compounds (32), the nucleophiles having attacked the anomeric carbon and the sulphonyloxy group having been displaced by the C-1-O-5 bond. The same type of ring contraction occurred with methyl 4-O-benzyl-3-O-(4-methoxybenzyl)-2-O-trifluoromethanesulphonyl-α-L-fucopyranoside and with methyl 4,6-dideoxy-3-O-(4-methoxybenzyl)-2-O-trifluoromethanesulphonyl-α-L-xylo-hexopyranoside.[37] In an attempt to prepare 2,5-anhydro-sugar derivatives, 5-O-p-toluenesulphonyl dialkyl dithioacetals (33) of L-arabinose were heated under basic conditions. Moderate yields of the desired compounds (34) were formed together with the thioglycosides (35) produced following participation of sulphur in the displacement processes.[38] Tosylation of



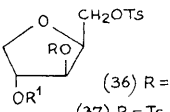
(33)



(34)



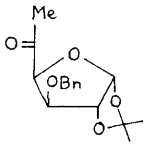
(35)



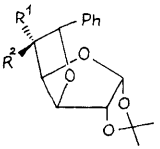
(36) R = R¹ = H
(37) R = Ts, R¹ = H
(38) R = R¹ = Ts

pyridine solutions of xylitol has given selectively either the mono-(36), di-(37), or tri-tosylate (38) 2,5-anhydro-D,L-xylitol derivatives depending on the quantities of toluenesulphonyl chloride and the temperatures used.[39]

Photolysis of the benzyl ether (39) produced a 5:1 ratio of the cyclised



(39)



(40) R^1 = OH, R^2 = Me
(41) R^1 = Me, R^2 = OH

products (40) and (41).[40] While conventional partial esterification of 1,4:3,6-dianhydro-D-glucitol is directed towards the 5-endo position, the 2-exo position has been regioselectively esterified by forming the dialkoxide and subsequent treatment with pivaloyl chloride.[41] Standard tritylation of the above starting material has also afforded 1,4:3,6-dianhydro-2,5-di-O-trityl-D-glucitol.[42] A periodate oxidation/reduction sequence applied to (6S)-(6-^{2}H)-1,6-anhydro-β-D-galactopyranose has been used to prepare (1S)-(1-^{2}H)-sn-glycerol.[43]

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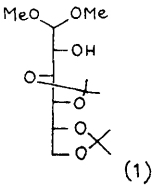
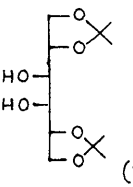
6
Acetals

1 Isopropylidene Acetals

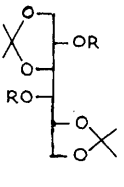
An improved procedure for the direct synthesis of 1,2-O-isopropylidene-α-D-glucofuranose has been published; treatment of D-glucose monohydrate with acetone in the presence of sulphuric acid gave, after filtration of unreacted starting material and neutralisation with NaOH, a product mixture consisting to 83% of the 1,2-acetonide. The contaminants, mainly α- and β-D-glucopyranose, were readily removed by fractional crystallisation.[1] D-Glucose has been converted to the synthetically useful diacetonide dimethyl acetal (1) by exposure to 2,2-dimethoxypropane and sulphuric acid in methanol.[2] The transformation of compound (1) to 2-azido-2-deoxy-D-mannose and hence to neuraminic acid is covered in Chapter 16.



(1)



(2)



(3) R = H

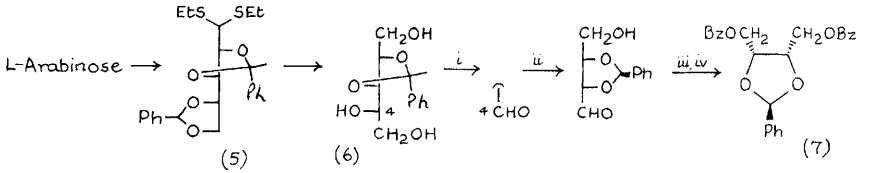
(4) R,R = >CMe$_2$

From the reaction of D-galactitol with 2,2-dimethoxypropane in dimethyl sulphoxide catalysed by pyridinium p-toluenesulphonate the diacetonides (2) and (3) have been isolated. From the latter, the 1,3 : 2,4 : 5,6-tri-O-isopropylidene derivative (4) was obtained on treatment with fresh reagents. The structures of these new acetals were established spectrometrically and their possible role in the conventional isopropylidenation of D-galactitol has been assessed.[3]

The isopropylidenation of maltitol with 2,2-dimethoxypropane and p-toluenesulphonic acid in N,N-dimethylformamide at ambient temperature for 15 h gave the 1,2 : 5,6 : 4',6' and 2,3 : 5,6 : 4'6'-triacetals and the 1,2 : 5,6- and 1,3 : 5,6-diacetals in 14, 40, 4 and 12% yield, respectively. Use of excess of reagent and prolonged reaction times led to 1,2 → 2,3 acetal migration.[4]

2 Benzylidene Acetals

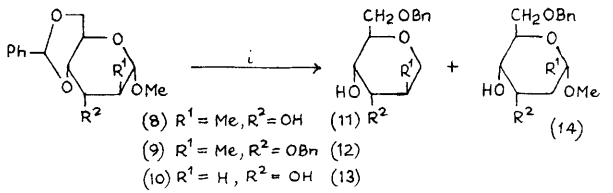
The effect of ultrasound on the conventional Freudenberg benzylidenation ($ZnCl_2$-benzaldehyde) of some alkyl D-glucopyranosides (e.g. methyl α- and β-D-glucopyranoside) has been described. Considerable enhancement in the rate of formation of the 4,5-O-acetals was observed and pure products were obtained in good yields (67-70%) after reaction times of ca 1 h.[5] The configuration at the acetal centre of 2,3-O-benzylidene-L-arabinitol (6), obtained from L-arabinose via the di-O-benzylidene dithioacetal (5) was deduced to be (R) following its conversion to the 1,4-di-O-benzoyl-2,3-O-benzylideneerthritol derivative (7) with trans-disposed benzyloxymethyl and phenyl groups, as indicated in Scheme 1.[6]



Reagents: i, $NaIO_4$; ii, OH^-; iii, $NaBH_4$; iv, BzCl, Py

Scheme 1

The reductive opening of the dioxane ring in the 4,6-O-benzylidene acetal (8) with sodium cyanoborohydride in the presence of hydrochloric acid was accompanied by deoxygenation at the anomeric centre giving the products (11) and (14) in 3:2 ratio as outlined in Scheme 2. In the case of benzylidene derivatives (9) and (10) the 1,6-anhydroalditols (12) and (13) respectively were the only products isolated.[7]



(8) R^1 = Me, R^2 = OH (11)
(9) R^1 = Me, R^2 = OBn (12)
(10) R^1 = H, R^2 = OH (13)

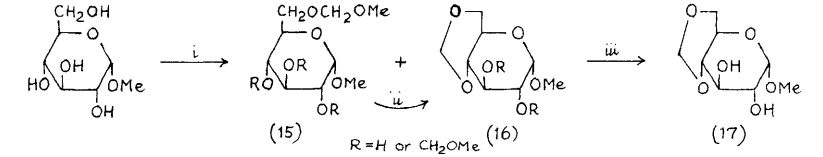
Reagents: i, $NaBH_3CN$, HCl

Scheme 2

3 Other Acetals

The use of a range of protecting groups which incorporate the n-pentenyl acetal moiety (e.g. the 4-pentenyloxymethyl group) is discussed in a review on novel carbohydrate transformations discovered en route to natural products.[8]

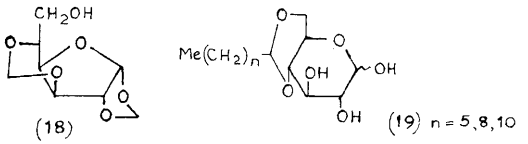
The 4,6-O-methylidene acetal (17) was obtained in ca. 30% yield from the reaction of methyl α-D-glucopyranoside with dimethoxymethane in the presence of p-toluenesulphonic acid and lithium bromide. As indicated in Scheme 3, a mixture of products (15) and (16) was initially formed. Treatment with acid resin and molecular sieves ensured complete conversion to the 4,6-acetals (16). Under similar conditions methyl β-D-glucopyranoside suffered partial anomerisation. Reaction of methyl α-D-glucopyranoside or D-glucose with formaldehyde and hydrochloric acid gave in 20% yield the furanose dimethylidene derivative (18).[9]



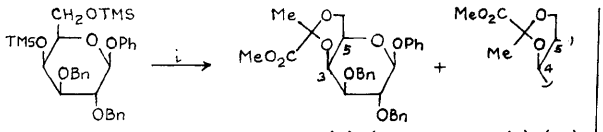
Reagents: i, $CH_2(OMe)_2$, TsOH, LiBr, MeOH; ii, Resin H^+, Å 4 sieves, CH_2Cl_2, iii, Resin-H^+, MeOH

Scheme 3

Ultrasound-accelerated Freudenberg acetalisation was used to prepare the amphiphilic 4,6-O-n-alkylidene-D-glucopyranose derivatives (19); only the n-heptylidene and n-octylidene acetals were sufficiently water-soluble to attain critical micelle concentrations.[10]

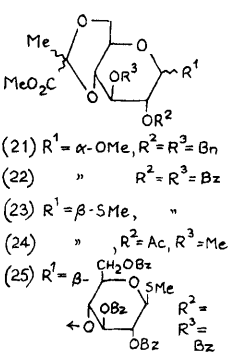


The 4,6-O-pyruvate acetals (20)-(25) have been synthesized from the corresponding bis-O-(trimethylsilyl)ethers in yields of 50-75% and with (R/S) ratios of 2:5-1:1. An example is given in Scheme 4. The configurations at the acetal centres were assigned with the help of ^{13}C-n.m.r. spectroscopy; axial methyl groups

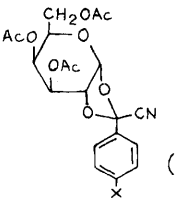


Reagents: i, $MeCOCO_2Me$, TMSOTf, CH_2Cl_2

Scheme 4

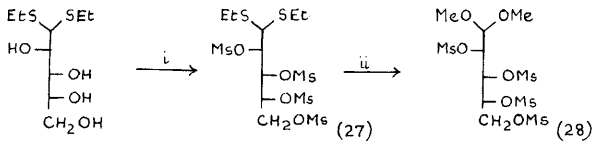


resonated at higher field then equatorial ones.[11] The preparation of 3,4,6-tri-O-acetyl-1,2-O-(α-cyanobenzylidene)-α-D-galactopyranoses (26) from the respective 2-O-benzoates of 3,4,6-tri-O-acetyl-α-D-galactopyranosyl bromides has been reported. The latter were derived from α-acetobromogalactose via α-D-galactopyranose 1,3,4,6-tetraacetate.[12]



(26) X = H, Br, OMe

Mild and rapid conversion of sugar dithioacetals into dimethyl acetals has been effected with N-bromosuccinimide in methanol. The unstable tetra-O-mesyl-D-arabino diethyl dithioacetal (27) of Scheme 5, for example, gave the dimethyl acetal (28) in high yield.[13]



Reagents : i, MsCl, Et_3N, CH_2Cl_2 ; ii, NBS, MeOH

Scheme 5

The use of an enantiomerically pure acetal protecting group to achieve asymmetric induction in the aldolysation of glycoladehyde is referred to in Chapters 2 and 18.

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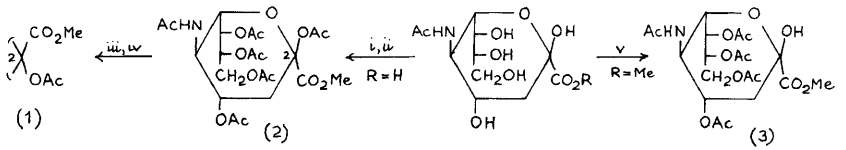
7
Esters

1 Carboxylic Esters

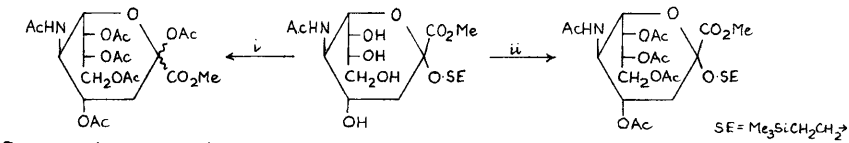
1.1 Synthesis and Reactions.- The α- and β-penta-O-acetates (1) and (2), respectively, and the β-tetra-O-acetate (3) of N-acetylneuraminic acid methyl ester have been prepared in good to excellent yields by use of the reagents indicated in Scheme 1. Direct acetylation of methyl N-acetylneuraminate with acetic anhydride-pyridine gave a 1:3 mixture of the anomeric peracetates (1) and (2).[1] The selective synthesis of mono- and di-O-acetates of an aryl glycoside of N-acetylneuraminic acid benzyl ester is covered in Chapter 16.



Reagents: i, Ac_2O, Py; ii, CH_2N_2; iii, AcCl, HCl; iv, CsOAc; v, Ac_2O, $HClO_4$

Scheme 1

Exposure of 2-(trimethylsilyl)ethyl glycosides to acetic anhydride and iron(III) chloride (substrate : $FeCl_3$ = 3:1, w/w) led to acetylation of all free hydroxy groups and concommitant acetolysis of the glycosidic function. With catalytic quantities of the iron salt (substrate : $FeCl_3$ = 20:1, w/w) acetylation of the free hydroxy groups proceeded with retention of the 2-(trimethylsilyl)ethyl group. Examples are given in Scheme 2. Benzyl ethers, but not p-methoxybenzyl or benzyloxymethyl ethers, were stable under both sets of conditions.[2] Treatment of methyl α-D-gluco- and α-D-galacto-pyranoside with acetic anhydride-$FeCl_3$ (substrate : $FeCl_3$ = 12.5:1, w/w) produced mixtures of peracetylated pyranoses, furanoses and acyclic sugars.[3]



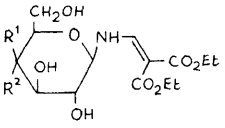
Reagents: i, Ac_2O, $FeCl_3$ (1:3, w/w); ii, Ac_2O, $FeCl_3$ (1:20, w/w).

Scheme 2

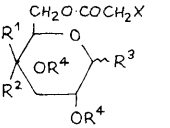
In a study of the regioselective benzoylation of N-2,2-(diethoxycarbonyl)vinyl-β-D-hexopyranosylamines with 2-3 mol equivalents of benzoyl chloride in pyridine, the gluco isomer (4) afforded the 2,6-di-, 3,6-di-, 2,3,6-tri-, and 2,3,4,6-tetra-O-benzoates in 19,19,27, and 5% yield, respectively. From the galacto analogue (5) the 3,6-diester was obtained as the main product in 54% yield, accompanied by minor amounts of the 2,3,6-tri- and 2,3,4,6-tetra-O-benzoates (11 and 6%, respectively).[4]

The six mono- and di-O-butyryl derivatives of 1,6-anhydro-β-D-glucopyranose and the six corresponding palmitic acid esters have been prepared from the tributyrate and tripalmitate respectively, by partial methanolysis and hydrazinolysis. The experimental findings regarding the regioselectivity of the deesterification reactions were related to polar and steric effects identified by quantum-chemical calculations (PCILO).[5]

Preferential hydrolysis at the anomeric centres of peracetylated α-D-gluco-, -galacto-, and -manno-, and β-D-gluco-, -galacto-, and -xylo-pyranose has been achieved with ammonium carbonate in DMF in yields of 63-95%, and the same base in THF-methanol was used for the preferential anomeric deacylation of α-D-glucose pentabenzoate (60% yield).[6]



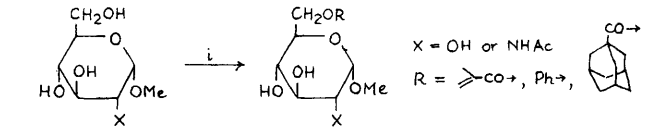
(4) $R^1 = H$, $R^2 = OH$
(5) $R^1 = OH$, $R^2 = H$



(6) X = Br, $R^4 = H$
(7) X = Cl, $R^4 = Bz$

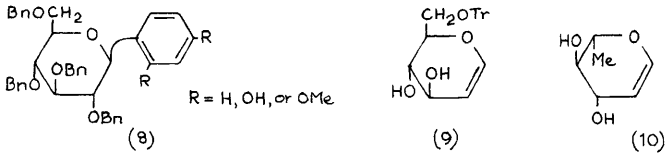
$R^1 = H$, $R^2 = OH$ or $R^1 = OH$, $R^2 = H$
$R^3 = \alpha$- or β-OMe

The 6-O-bromoacetates (6) obtained selectively by reaction of methyl α- or β-D-gluco- or -galacto-pyranoside with 1.3 mol equivalents of bromoacetyl bromide underwent halogen exchange during conventional benzoylation of the secondary hydroxy groups to give chloroacetyl derivatives (7). Removal of the chloroacetyl groups by use of thiourea proceeded without acyl migration in contrast to previous experiences with acetyl protection (see Vol. 19, Chapter 4, refs. 15 and 16).[7] The application of this procedure to the synthesis of (1→6)-linked disaccharides is referred to in Chapter 3. Selective primary protection has also been effected under Mitsunobu conditions as exemplified in Scheme 3.[8] The primary benzyl groups of perbenzylated β-C-glucosides (8) were selectively acetolysed on treatment with acetic anhydride in the presence of boron trifluoride etherate in ether. Phenolic hydroxy groups were acetylated in the process. Under identical reaction conditions, α-anomers were stable.[9]

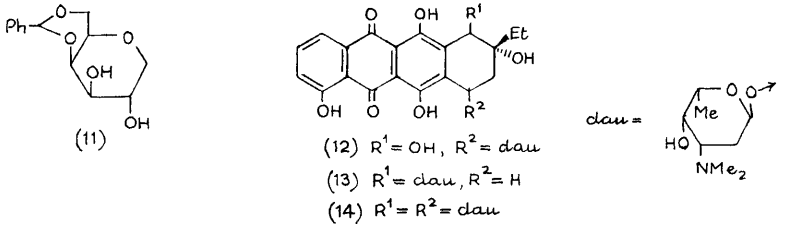


Scheme 3

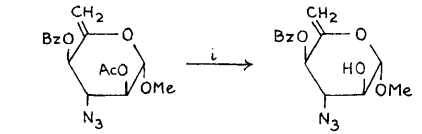
The glycal diols (9) and (10) were selectively acetylated at O-3 via their dibutylstannylene derivates,[10] and 1,5-anhydro-4,6-O-benzylidene-D-galactitol(11) reacted preferentially at O-3 with benzoyl or p-toluenesulphonyl chloride in pyridine at -15°C. Activation of this position by intramolecular hydrogen bonding is thought to be responsible.[11]



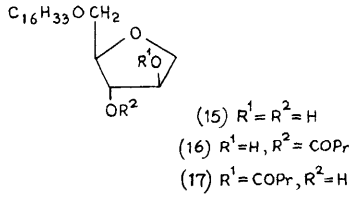
Rhodomycins I(12) and II(13), and iremycin(14) were esterified at the hydroxy groups of the sugar moiety (OH-4') only, on exposure to p-methoxybenzoyl chloride (1 mol. equiv. per daunosamine residue) and sodium hydrogen carbonate in a two-phase system ($CHCl_3$-H_2O).[12]



By use of DBU in benzene, acetates were cleaved in the presence of benzoates on a variety of substrates including three carbohydrate examples, one of which is shown in Scheme 4.[13] Benzoyl migration during the Purdie methylation (MeI, Ag_2O) of 2,5-di-O-benzoyl-L-rhamnono-1,4-lactone is referred to in Chapter 5.



Scheme 4



Further examples of selective acylations and deacylations by means of enzymes, especially lipases, have been reported. Acetylation at the primary centre of N-acetylneuraminic acid was performed by acyl transfer from 2,2,2-trichloroethyl acetate under catalysis by porcine pancreatic lipase in pyridine,[14] and use of an immobilised microbial lipase in a solvent-free process allowed selective 6-O-esterification of ethyl α-D-glucopyranoside with long-chain fatty acids. Under the same conditions methyl α-D-glucopyranoside and D-glucose reacted similarly but at much slower rates.[15]

Sucrose was acylated at O-1' preferentially by subtilisin-catalysed transesterification from the trifluoro- or trichloro- ethyl esters of acetic, propionic, octanoic, benzoic, and acrylic acid in DMF. Subsequent hydrolysis of the glycosidic bond with α-glucosidase gave D-fructose 1-esters.[16]

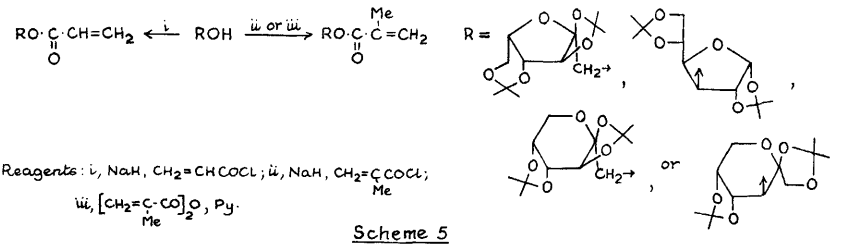
For the selective deacetylation of sucrose octaacetate various lipolytic enzymes have been employed. Purified wheat germ lipase, for example, liberated the free hydroxy groups at O-1', O-4' and O-6'; addition of calcium ions or cosolvents (e.g. di-n-butyl ether) had little effect on the activity or selectivity of the enzyme, but lowering of the reaction temperature or immobilisation on agarose decreased the activity drastically without improving the selectivity. With *candida cylindracea* lipase in aqueous phosphate buffer-toluene (9:1) deacetylation occurred selectively at O-4'; in the absence of toluene complete, non-selective hydrolysis was observed.[17]

The lipase-mediated selective hydrolysis of peracylated 1,6-anhydro-hexoses has been studied. Lipase from *candida cylindracea* deesterified 1,6-anhydro-2,3,4-tri-O-butyryl-β-D-glucopyranose at O-2 and O-4, whereas lipases from several other sources cleaved only the 4-ester.[18] For 1,6-anhydro-2,3,4-tri-O-acetyl- and -butyryl-β-D-galactopyranose the relative rates of hydrolysis by a number of soluble and immobilised lipases were in the order O-2> O-4> O-3. The 3-mono- and the 3,4-di-O-acyl derivatives could be isolated in moderate to excellent yields by choice of suitable conditions.[19]

Twenty enzymes were tested for selectivity in the butyrylation of the 1,5-anhydro-D-arabinitol derivative (15). Good results were obtained with lipases from *rhizopus japanicus* [ratio (16)/(17) = 86:14, combined yield 71%] and from *humicula lanuginosa* [ratio (16)/(17) = 3:97, combined yield 71%].[20] The enzymatic synthesis of acylated glucals is covered in Chapter 13.

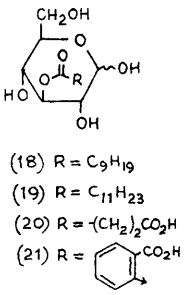
A convenient synthesis of 1-O-benzoyl-β-D- [^{14}C]- glucose esters uses acyl transfer from unlabelled 1-O-benzoyl-glucose esters to ^{14}C-labelled glucose by an acyl transferase from young oak leaves.[21]

The acrylates and methacrylates of several di-O-isopropylidene hexoses have been prepared, as shown in Scheme 5, in yields of 25-50% for use in the synthesis of hydrogels by radical-induced polymerisation.[22]

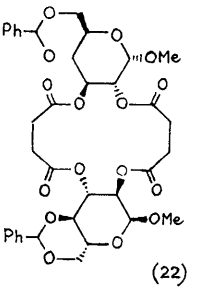


Scheme 5

In the course of a surface activity study the decanoate (18) and the laurate (19) were synthesised by treatment of diacetone glucose with the respective acyl chlorides under phase transfer conditions followed by removal of the acetal groups. The corresponding 6-esters were similarly obtained from 1,2-O-isopropylidene-α-D-glucofuranose.[23] Conventional acylation (acid anhydride-pyridine) and subsequent hydrolysis were used to prepare the succinate (20) and the phthalate (21) from diacetone glucose, and the 6-succinate and 6-phthalate of D-galactose from diacetone galactose.[24] Base-catalysed acylation with succinic and phthalic anhydride has also been applied to methyl α-D-glucopyranoside and to α,α'-trehalose. Primary esters were mainly formed, phthalylation being more regioselective than succinylation.[25] The conversion of these esters to potential herbicides is covered in Chapter 17.



(18) R = C_9H_{19}
(19) R = $C_{11}H_{23}$
(20) R = $-(CH_2)_2CO_2H$
(21) R = CO_2H



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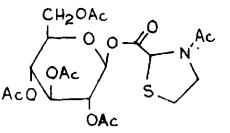
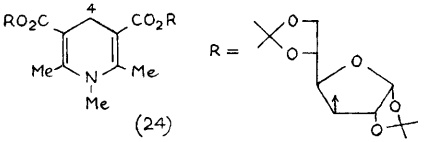


(23)

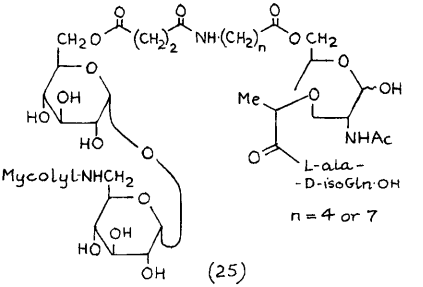
Condensation of methyl 4,6-O-benzylidene-2,3-O- butylstannylene α-D-glucopyranoside with succinyl chloride furnished the macrocyclic tetralactone (22) and its regioisomer, accompanied by small quantities of a hexa- and an octa-lactone.[26]

The synthesis of the 3-, 6-, and 6'-sucrose monoesters of arachidonic acid from sucrose and ethyl arachidonate has been reported.[27]

The 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl ester (23) and five other sugar esters of N-acetyl-thiazolidine-4-carboxylic acid were prepared by DCC coupling,[28] Koenigs-Knorr methodology was employed to synthesise three giberellin β-D-glucosyl esters,[29] and the antineoplastic disaccharide ester (+)-phyllanthostatin 3 was formed by use of the Mitsunobu reaction.[30] Three carboxylic acid antiinflammatory analgesics (asprin, diclofenac and ketoprofen) were esterified by reaction with acetobromoglucose under phase-transfer conditions. The tetra-O-acetyl-β-D-glucopyranose esters thus obtained had comparable antiinflammatory but lower ulcerogenic activity than the parent acids.[31] The Hantzsch ester (24) was prepared to serve as an NADH model in the asymmetric reduction of prochiral ketones.[32] A Hantzsch ester with a sugar residue attached to C-4 of the dihydropyridine ring is referred to in Chapter 10.



(24)



(25)

Reaction of the 6-tosylates of L-glucose, 2-deoxy-D-glucose, 2-amino-2-deoxy-D-glucose, and 2-amino-1,5-anhydro-2-deoxy-D-glucitol with the potassium salt of mycolic acid gave monosaccharide esters related to the biologically active glycolipid trehalose 6,6'-dimycolate.[33] Novel synthetic immunomodulators (25) have been constructed by linking of N-acetyl-6-O-(aminoacyl)muramyl dipeptides to the free primary hydroxy group of 6-deoxy-6-mycolylamino-α,α-trehalose via a succinic acid bridge. The conjugates (25) displayed biological properties of both moieties.[34]

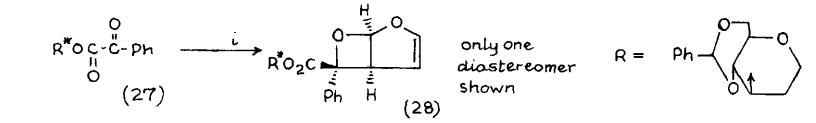
Activated esters of peptides reacted directly with D-glucose or 2-amino-2-deoxy-D-glucose in the presence of imidazole to give 6-O-peptidyl derivatives such as compound (26) as well as β-1-O-analogues.[35,36]

(26) 6-O-(Boc-Phe-Leu)-D-Glc

Flavonoid glycosides esterified in the sugar moiety with malonic acid have been observed to lose CO_2, furnishing the corresponding acetates, under conditions

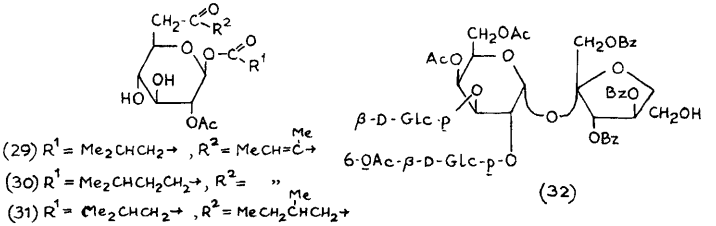
often used to determine their n.m.r. spectra (DMSO-d_6, 80-100°C). In the presence of exchangeable deuterium (e.g. D_2O) trideuteroacetyl derivatives can form by exchange at the malonyl methylene group prior to and during decarboxylation.[37]

Carbohydrates have been used with considerable success as chiral auxiliaries in the asymmetric Paterno-Büchi reaction. Diastereomeric excess of 80% was achieved, for example, in the formation of oxetans (28) from furan and the sugar phenylglyoxalate (27) (Scheme 6).[38]

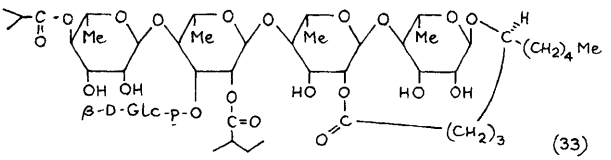


Scheme 6

1.2 Isolation from Natural Sources.- The three new tri-O-acyl-β-D-glucopyranoses (29)-(31) have been isolated from the Mexican desert plant *Bahia schaffneri*,[39] and amarelloside, a very bitter constituent of *Polygala amarella*, has been identified as the tri-O-acetyl-tri-O-benzoyl-tetrasaccharide (32).[40] The caffeic esters verbascoside and plantamoside have been found in several *Plantago* species from widely different locations indicating that they are valuable as taxonomic markers,[41] and the investigation of a cell culture from *Ruta chalepensis* yielded rutarensin, a new biscoumarine β-D-glucoside esterified at O-6 with 3-hydroxy-3-methyl glucaric acid.[42]



The ionophoretic properties of eight new resin glycoside esters such as merremoside h_1 (33), isolated from the tuber of the Indonesian medicinal plant *Merremia mammosa*, and all containing a lactone macrocycle, have been studied by



use of erythrocyte membranes and artificial membranes. Opening of the lactone ring destroyed the ion (Na^+, K^+, Ca^{2+}) transporting activities completely.[43,44]

From the leaves of *Cornus officinalis* a novel gallotannin, 1,7-di-O-galloyl-D-sedoheptulose, has been isolated.[45] 1,2,3,4,6-Penta- and 1,2,3,4-tetra-O-galloyl-β-D-glucose have been shown to be inhibitors of human placenta aldose reductase and of a mitochondrial oxidoreductase, respectively,[46,47] and the ability of penta-O-galloyl-β-D-glucose and twenty-four related, more complex, natural, hydrolysable tannins to scavenge radicals (e.g., superoxide radicals) has been demonstrated.[48]

"3-O-Digalloyl-1,2,6-trigalloyl glucose", a tannin isolated several years ago from a fresh water green alga (see Nishizawa et al., Phytochem., 1985, 24, 2411) is a specific, irreversible α-glucosidase inhibitor and has antibiotic activity,[49] whereas oenothein B, a hydrolysable tannin with a macrocyclic structure, has antiviral properties.[50] The latter compound is also referred to in Chapter 19.

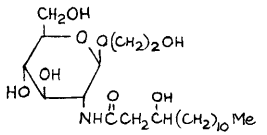
2 Phosphates and Related Esters

Reviews have been published on the synthesis of carbohydrate phosphodiesters and trinucleoside monophosphates[51] and on phosphodiester-bridged saccharide structures comprising both anomerically and non-anomerically linked compounds.[52]

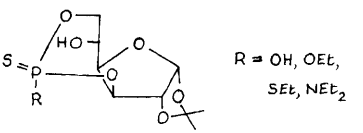
A number of deoxy-, dideoxy-monofluoro-, and dideoxy-difluoro-α-D-glucopyranosyl phosphates have been prepared for a comparative study of their acid hydrolysis rates. As in the hydrolysis of alkyl glycosides, deoxy derivatives reacted faster and fluorinated analogues much slower than the parent 1-phosphates, and it was concluded that the transition states for the hydrolysis of glycosides and glycosyl phosphates are essentially identical.[53]

In an effort to prove that phosphate migration takes place under conditions of acid hydrolysis (4N HCl, 4 h at 100°C) used in the determination of the structure of Lipid A, the 4- and 6-phosphates of 2-amino- and 2-acetamido-2-deoxy-D-glucose as well as the Lipid A model (34) were synthesised. Migration of the phosphate from O-4 to O-6 was observed under the above conditions. Deacylation conditions were then found (1N HCl, 1 h at 100°C) which did not cause phosphate migration.[54]

A rapid, high yield synthesis of ^{13}C-enriched intermediates of the pentose-phosphate pathway has been developed based on a combination of chemical and enzymic reactions. [1-^{13}C]Ribose and [1-^{13}C]arbinose 5-phosphates, available by the classical Kiliani method, were converted to a variety of specifically labelled 5-, 6-, 7-, and 8-carbon sugar phosphates (e.g., D-erythro-pentulose 5-phosphate, sedoheptulose mono- and di-phosphates) with the help of aldolase, transaldolase, and transketolase.[55]

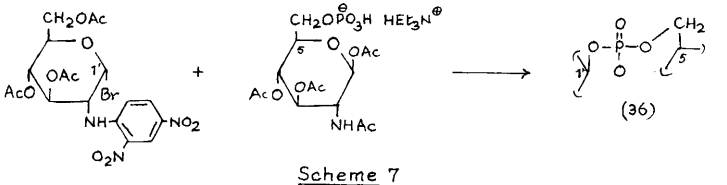


(34)



(35)

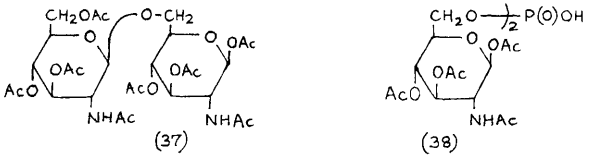
3,6-Cyclic thiophosphates (35) of 1,2-O-isopropylidene-α-D-glucofuranose have been obtained from the corresponding 3,5,6-bicyclic thiophosphate by treatment with various nucleophiles.[56] 6-Deoxy-6-sulphono-α-D glucopyranosyl phosphate has been prepared as shown in Chapter 11, Scheme 5; the synthesis of individual enantiomers and racemates of myo-inositol mono-, di-, and tri-phosphates is covered in Chapter 18, and the use of glycopyranosyl phosphates as glycosyl donors is referred to in Chapter 3.



(36)

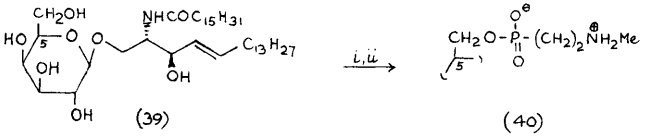
Scheme 7

Synthesis of the phosphate-bridged disaccharide (36) was achieved by the method outlined in Scheme 7. Attempts to make compound (36) from the pyridinium salt of a 1-phosphate as the donor and 2-acetamido-1,3,4-tri-O-acetyl-2-deoxy-β-D-glucopyranose as the acceptor gave the disaccharide (37) and the di-sugar diphosphate (38) instead.[57]



(37) (38)

The 2-N-methylaminoethyl group of the phosphonosphingolipid (40) was introduced by selective phosphonylation at the primary hydroxy group of the precursor (39) with an unprotected galactose moiety, by a procedure using DCC and ultrasound, as indicated in Scheme 8.[58] Further details regarding the synthesis of

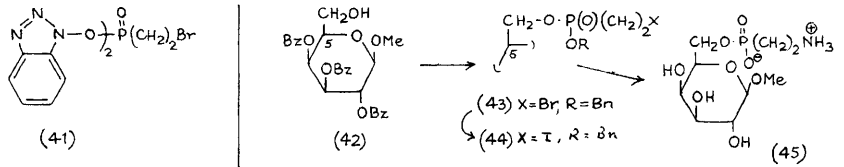


(39) (40)

Reagents: i, $(HO)_2P(O)(CH_2)_2NMeCO_2CCl_3$, DCC, DMAP, Py (cccc); ii, Zn-HOAc, H_2O

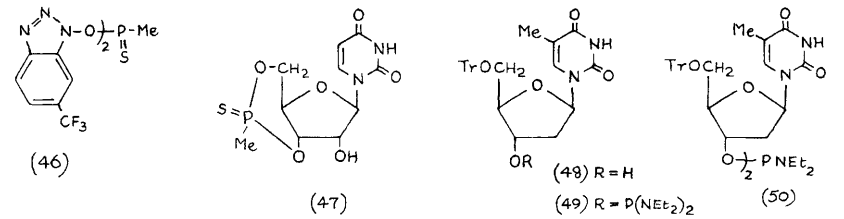
Scheme 8

compound (40) are given in Chapters 3 and 24. For the preparation of the 2-N-aminoethyl phosphonate (45) from the methyl galactoside (42) the bifunctional reagent bis(benzotriazolyl)-2-bromoethyl phosphonate (41) was employed. The transformation of the bromo-intermediate (43) via the iodide (44) to the target (45) is shown in Scheme 9.[59] Another benzotriazole-derived reagent, the thiophosphonate (46) was very effective in the synthesis of uridine 3',5'-cyclic methyl thiophosphonate (47).[60]

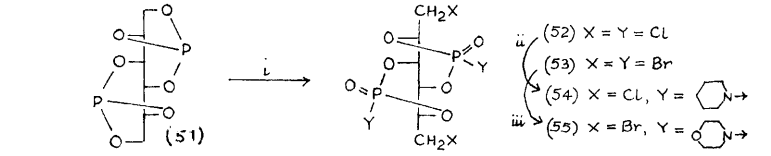


Scheme 9

Phosphitylation of the nucleoside (48) to give the bisamidite (50) without contamination by the monoamidite (49) was possible with tris(diethylamino)-phosphine and tetrazole in the presence of diisopropylamine. The usefulness of bisamidites such as compound (50) in oligodeoxyribonucleotide synthesis has been demonstrated.[61]



1,6-Dichloro-1,6-dideoxy-2,4:3,5-bis-O-(piperidinophosphoryl)-D-mannitol (54) and its 1,6-dibromo-bis-O-(morpholinophosphoryl) analogue (55) were obtained from D-mannitol bisphosphite (51) via bis-O-(halophosphoryl) intermediates (52) and (53), respectively on treatment with halogen and cyclic amine (Scheme 10).[62,63]



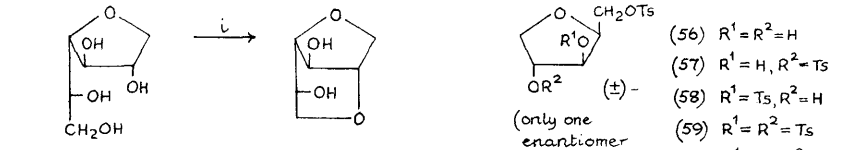
Reagents: i, Cl_2 or Br_2; ii, ; iii,

Scheme 10

3 Sulphonates

A protocol has been developed for the one-pot microsynthesis of dianhydrohexitols from monoanhydrohexitols which involves primary tosylation followed by base-promoted intramolecular displacement of the tosyloxy group. An example is given in Scheme 11. The products were identified, after acetylation, by g.c.-m.s. As by-products mono-(and traces of di-) chlorides were detected, formed by substitution of the tosyloxy group by chloride ions liberated during sulphonylation. Dianhydrohexitols uncontaminated by such chloro compounds were obtained after post-tosylation treatment with methoxide.[64]

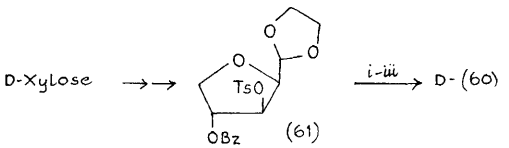
Treatment of xylitol with two molar equivalents of toluene-p-sulphonyl chloride in pyridine gave the racemic anhydrotosylate (56) in 56% yield. With three



Reagents: i, TsCl, Py

Scheme 11

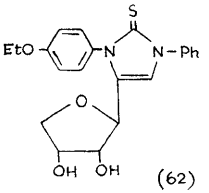
equivalents of reagent the ditosylates (57) and (58) were produced each in ca. 30% yield and, in addition, small quantities of the tritosylate (59). This last compound was the only product obtained when five equivalents of tosyl chloride were used. The ditosylate (58), on benzoylation, furnished the triester DL-(60), an important intermediate in the planned synthesis of biotin analogues. Enantiomerically pure triester D-(60) was available in eight steps from D-xylose via the known 2,5-anhydro-D-xylose derivative (61) (Scheme 12).[65] Further papers describing cyclisations under tosylating conditions are referred to in Chapters 5, 11 and 18, and the synthesis of 3,4-di-O-acetyl-6-O-tosyl-D-glucal from D-glucose is covered in Chapter 13.



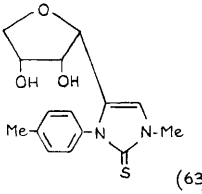
Reagents: i, HCl, CCl_3CO_2H ; ii, $Me_2NH{\cdot}BH_3$; iii, TsCl, Py

Scheme 12

A comparative study of the mono- and di-tosylation of the imidazole-2-thiones (62) and (63) by the standard procedure (toluene-p-sulphonyl chloride - pyridine), under phase transfer catalysis, and via organotin intermediates has been published. Both 2-O- and 3-O-tosylates were prepared.[66]

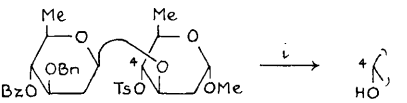


(62)



(63)

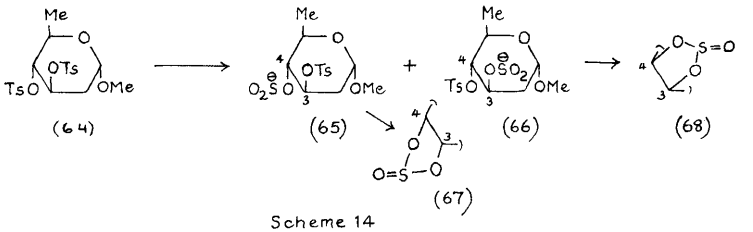
Tosyl groups can be photoremoved in the presence of carboxylic esters and benzylethers by use of tertiary amines as electron donors. Tosyl protection can thus become valuable in the preparation of selectively substituted products, as exemplified in Scheme 13.[67] Photolysis of tosylates in the gas phase is initiated by



Reagents: i, Et_3N, MeOH, hν

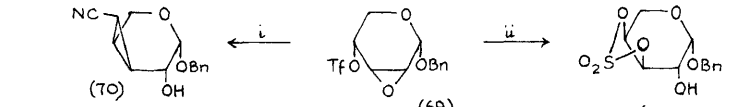
Scheme 13

electron capture and then proceeds with homolytic C-S cleavage in marked contrast to solution chemistry. A study using negative ion mass spectrometry showed that from the vicinal ditosylate (64) the sulphite ions (65) and (66) are produced which then undergo internal nucleophilic displacement to give the cyclic sulphites (67) and (68) respectively as outlined in Scheme 14.[68]



Scheme 14

Carbon - oxygen bond cleavage in a secondary tosylate during reduction with lithium aluminium hydride due to intramolecular hydride transfer from an alkoxyaluminium hydride intermediate is referred to in Chapters 12 and 13.

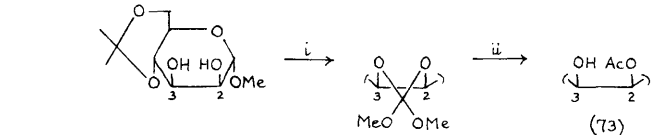


Scheme 15

Scheme 15 shows two reactions undergone by benzyl 2,3-anhydro-4-O-triflyl-D-ribopyranoside (69). With $LiCH_2CN$ in the presence of LDA, nucleophilic substitution accompanied by epoxide-opening afforded the 3,4-cyclopropanated product (70). The lyxo analogue of epoxide (69) reacted similarly. Thus, epoxy-triflates with favourable relative configuration offer an entry into annulated sugars. With Bu_4NHSO_4, compound (69) reacted to give the cyclic sulphate (71).[69]

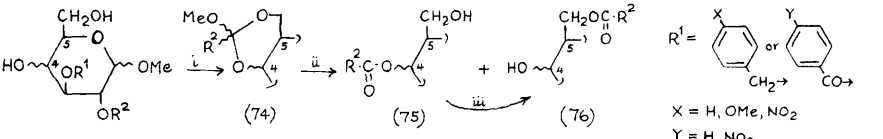
4 Other Esters

A symposium paper on new methods of orthoesterification under kinetic control has been published. In particular, the use of ketene dimethylacetal for the preparation of methoxyethylidene derivatives, e.g., compound (72) of Scheme 16, is described. Orthoesters are hydrolysed by very mild acid to give α-hydroxyesters [e.g., compound (73)] or β-hydroxyesters, as for example in the acid opening of the 4,6-O-



Scheme 16

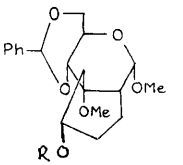
orthoesters (74) of methyl α- and β-D-gluco- and -galactopyranosides shown in Scheme 17. In the latter case, mixtures of 4-O- and 6-O-acyl products (75) and (76), respectively, were formed in ratios varying from 1:2 to 2:1 depending on the protecting groups at C-2 and C-3 rather than on the configurations at C-1 and C-4. Exposure of the mixed products (75)/(76) obtained from orthoacetates (74, R=Me) to base caused acetyl migration from O-4 to O-6 allowing isolation of 6-acetates in high yields. The 4-benzoates (75, R = C_6H_5) were stable towards base.[71]



Scheme 17

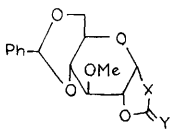
Reaction of a number of methyl 2,3-di-O-benzyl aldohexopyranosides with phenylchlorosulphate - sodium hydride gave, depending on the conditions used, primary phenylsulphates or 4,6-cyclic sulphates.[72] The formation of cyclic sulphates from epoxy triflates and of cyclic sulphites from vicinal ditosylates are referred to in Section 3 of this Chapter.

The ^{1}H- and ^{13}C-n.m.r. spectra of methyl 4,6-O-benzylidene-α-D-glucopyranoside 3-nitrate and of methyl 4,6-O-benzylidene α- and β-D-glucopyranoside 2,3-dinitrate have been examined and compared with the spectra of methyl 4,6-O-benzylidene-α-D-glucopyranoside.[73] The fact that alkoxy radicals are generated from nitrates on heating with tributyltin hydride in the presence of a radical initiator in benzene has been exploited to regenerate the alcohol (77) from the sugar nitrate (78).[74]

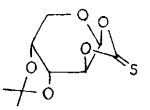


(77) R = H
(78) R = NO_2

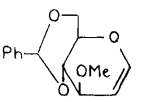
Some cyclic thiocarbonates derived from carbohydrate 1,2-diols undergo O → S isomerisation when exposed to methyl iodide and proton sponge. The gluco derivative (79), for example, was converted to the rearranged product (80). Others, e.g., the arabino compound (81), were stable under identical conditions. Attempts to reduce the thiocarbonate (79) by treatment with tributyltin radicals furnished instead the glycal (82).[75]



(79) X = O, Y = S
(80) X = S, Y = O

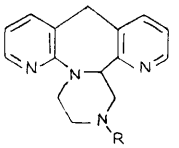


(81)



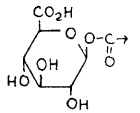
(82)

The novel carbamate glucuronide (83) has been identified as a metabolite of the tetracyclic compound (84). The key step in its synthesis was the condensation of benzyl 2,3,4-tri-O-benzyl-D-glucuronate with the reactive 1,2,4-triazole derivative (85).[76]

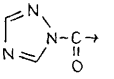


(84) R = H

(83) R =



(85) R =



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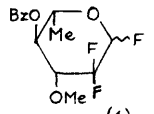
8
Halogeno-sugars

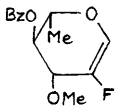
1 Fluoro-sugars

A number of reviews on the chemical synthesis of fluorinated carbohydrates have been published,[1-4] as well as others covering the chemoenzymic synthesis of fluorosugars,[5] the preparation and reactions of glycosyl fluorides,[6] and the preparation of ^{18}F-deoxyfluorohexoses.[7]

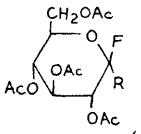
Glycosyl fluorides have been prepared under neutral conditions from the corresponding free sugars using 1-dimethylamino-1-fluoro-2-methylprop-1-ene. The reaction conditions are compatible with the presence of ester, acetal, benzyl and silyl ether protecting groups.[8] An efficient synthesis of the 2,6-dideoxy- 2,2-difluoro-L-arabinopyranosyl fluorides (1) by treatment of the fluorinated glycal (2) with XeF_2 has been described.[9] The effects on the H-F and C-F coupling constants in



(1)

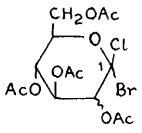


(2)



(3)

the n.m.r. spectra of a series of C-1 dihalosugars (3) on varying the anomeric configuration and the substitution (R = Br, Cl, F) have been studied.[10] Further examination of the free-radical bromination of peracetylated D-gluco- and D-manno-pyranosyl halides has given rise to a variety of either 1,1- or 1,5-dihalogenated derivatives. The 1,1- bromochloro- derivatives (4) were converted to the chlorofluoro- compounds (5) or the difluorides



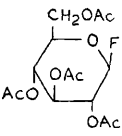
(4)

(5)

(6)

(6).[11] It was incorrectly stated (Vol 21, p.77) that the β-fluoride (7) affords the

corresponding 1,1-dihalocompound on photo-bromination whereas in fact the C-5 bromo-glycosyl fluorides (8) are the major products from either the α- or β-fluoride.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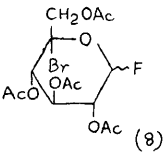
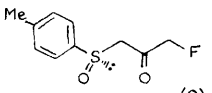

(8)

Methyl 4'-deoxy-4'-fluoro- and 6'-deoxy-6'-fluoro-β-D-galactobioside have been synthesized[12] and some related work on derivatives of methyl β-D-galactobioside is discussed in Chapter 14. Deoxyfluoro derivatives of the tetrasaccharide Lewis b human blood group determinant modified in the galactose residue have been prepared.[13] Attempted displacements with Bu_4NF in a variety of solvents on benzyl 3-O-benzyl- 4,6-O-benzylidene -2-O-trifluoromethanesulphonyl-α-D-mannopyranoside gave only the corresponding 2,3-olefin.[14] The α-fluoro-ketone (9), bearing a chiral sulphoxide group, has been alkylated (LDA, then allyl bromide) to give adduct (10) and its stereoisomer which were transformed into the 2,3-dideoxy-3-fluoro-pentoses (11) and (12) respectively.[15]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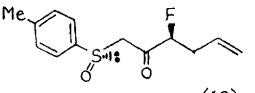
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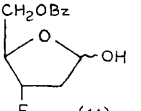
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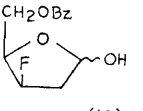
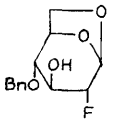

(12)

2,3,4-Trideoxy-2,3,4-trifluoro-D-glucose and -D-galactose derivatives have been prepared. The known 1,6-anhydro compound (13), treated with DAST, gave the product (14) with retention of configuration, whereas the alcohols (15) and (16), on treatment with DAST, gave the products (17) and (18) resulting from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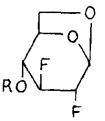
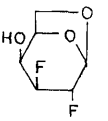

(14) R = Bn
(15) R = H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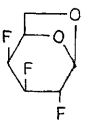
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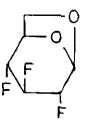

(18)

displacement with inversion of configuration. These trifluorinated compounds were acetolysed to give 1,6-di-O-acetyl- 2,3,4-trideoxy- 2,3,4-trifluoro-D-galacto- and glucopyranose respectively.[16] 3-Deoxy-3-fluoro-derivatives of N-acetylneuraminic acid have been prepared as potential inhibiters of CMP-sialate synthase.[17] Syntheses from D-glucose of methyl 3-O-benzyl-6-O-benzoyl- 2,5-dideoxy- 2-fluoro-D-ribo-hexofuranoside and 1,2-di-O-acetyl-6-O-benzoyl- 3,5-dideoxy-3-fluoro-D-xylo-

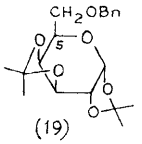
hexofuranose have been reported.[18]

Some 4',5'-unsaturated-5'-fluoroadenosine nucleosides are described in Chapter 20 as well as some purine nucleosides containing the 2'-deoxy-2'-fluoro-β-D-arabinofuransoyl moiety. A number of dideoxymonofluoro- and dideoxydifluoro-α-D-glucopyranosyl phosphates have been prepared in order to study their relative rates of acid hydrolysis.[19] The synthesis of a fluorinated 3-deoxy-D-glyceric acid phosphonate is discussed in Chapter 17 and the conversion of a 1,3-anhydro-2-deoxy- 2,2-difluoro-D-hexose derivative into a hydrolytically stable thromboxane A_2 mimic is covered in Chapter 24.

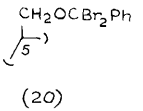
The rate of reaction of ^{18}F anion with some hexose triflate and cyclic sulphate derivatives showed no apparent difference between Et_4N^+ and the aminopolyether kryptofix -2,2,2 as cation.[20] 2-Deoxy-2-[^{18}F]-D-galactose was synthesized from a taloside 2-triflate derivative.[21] The automated production of 2-deoxy-2-[^{18}F]-D-glucose using $Bu_4N^{18}F$ as the fluoride source has been achieved using a modified literature procedure,[22] and another automated process for the production of radiochemicals has been programmed such that 2-deoxy-2-[^{18}F]-D-glucose is prepared in 55% yield in < 1 hour.[23]

2 Chloro-, Bromo-, and Iodo-sugars

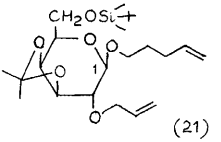
The photobromination of methyl 4,6-O-benzylidene-α-D-glucopyranoside to give methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside has been published as an Org. Synth. procedure.[24] The bromination of carbohydrate benzyl ethers, e.g. (19), using $BrCCl_3$ and u.v. light gives α,α-dibromides, e.g. (20), whereas benzyl glycosides afford the corresponding glycosyl bromides.[25] Glycosyl halides have been prepared from free sugars under neutral conditions using $Me_2C{=}C(X)NMe_2$ (X = F, Cl, Br, I). The reaction conditions are compatible with the presence of ester, acetal, benzyl and silyl ether protecting groups.[8]



(19)



(20)



(21)

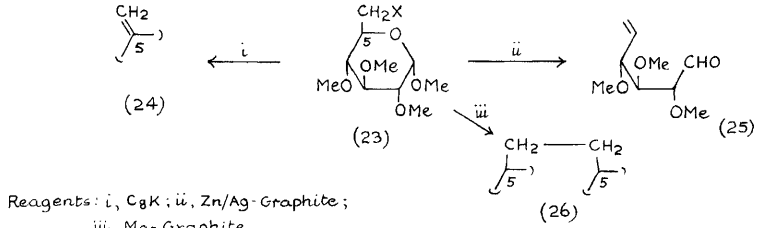
(22)

The treatment of pent-4-enyl glycosides with bromine has allowed an exceptionally mild new synthesis of glycosyl bromides, e.g., galactoside (21) affords bromide (22). The yields are high and the reactions are generally sufficiently specific for the products to be used in situ for saccharide coupling.[26]

2,3-O-Isopropylidene-L-sorbofuranose has been selectively chlorinated (Ph_3P,CCl_4,Py) to give, after hydrolysis, 6-chloro-6-deoxy-L-sorbose. The above starting material was also treated with MsCl in DMF and then subsequent hydrolysis gave 1,6-dichloro-1,6-dideoxy-L-sorbose.[27]

The conversion of some protected deoxyiodo derivatives of neuraminic acid into 7-, 8-, and 9-deoxy- and 4,7-dideoxy- neuraminic acids is covered in Chapter 12. Another example of an NIS - promoted coupling of a glycal with a sugar alcohol has afforded methyl 4-O-(2,6-dideoxy-2-iodo-α-L-mannopyranosyl)α-L-acosaminide,[28] and the same procedure has been used to prepare 2'-iodo analogues of β-rhodomycins.[29]

Some highly selective metal-graphite reductions of deoxyhalosugars have been elucidated. For example, halides (23) (X = I, Br, Cl) (Scheme 1) with K-graphite laminate (C_8K) afforded olefin (24), whereas with Zn/Ag-graphite the enal (25) was



Scheme 1

produced. Iodide (23) (X=I) with Mg-graphite gave the product (26) of Wurtz-like coupling.[30] Liberation of the sensitive aglycone ptaquilosin from its naturally occurring glucoside by zinc reduction of the 6-deoxy-6-iodo-glucosyl derivative is mentioned in Chapter 3. The treatment of benzyl 4,6-O-benzylidene-3-O-benzyl-2-O-trifluoromethanesulphonyl-α-D-mannopyranoside with halide nucleophiles in solvents of varying polarity has given moderate to low yields of products of displacement of triflate along with considerable amounts of the corresponding 2,3-olefin resulting from elimination of TfOH.[14] The synthesis of some 2-bromo- and 2-chloro-2-deoxy-hexopyranosid-3-uloses is discussed in Chapter 15.

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9
Amino-sugars

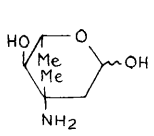
1 Natural Products

The branched-chain amino-sugar (1) has been identified as a component sugar in glycopeptide antibiotics (see also Chapter 19).[1]

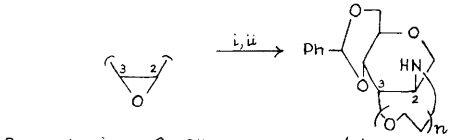
2 Synthesis

The synthesis and biological effects of immunostimulating analogues of MDP (muramyl dipeptide) have been reviewed, some details of previously patented reaction schemes being included.[2] A review (28 refs) has appeared on the halo-functionalisation of allyl and homoallyl alcohols for the preparation of amino-alkanediols, and the application of this method for preparation of aminodeoxysugars such as daunosamine and ristosamine.[3] Other syntheses covered in this section are grouped according to the method used for introducing the amino-functionality.

The Amadori rearrangement product 1-deoxy-1-[(4-quinazolon-3-yl)amino]-D-fructose was synthesised by condensation of D-glucose with 3-amino-4-quinazolone oxalate salt, in order to observe the effect of the sugar moiety on the central nervous system activity of quinazolones.[4]

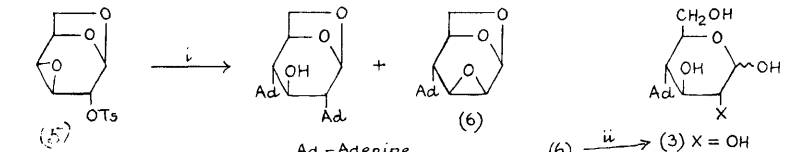


(1)



Scheme 1

Aminosugar-incorporating azacrown ethers have been synthesised, as exemplified by compound (2) in Scheme 1.[5] Non-glycosyl linked adenosine analogues (3) and (4), and the corresponding hexitol analogues (formed from

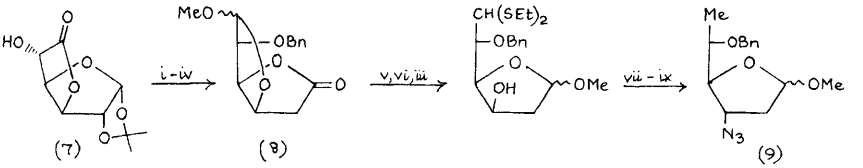


Scheme 2

them by reduction with $NaBH_4$), have been synthesised from the dianhydrosugar tosylate (5) via epoxide (6) (Scheme 2).[6]

Mono-(3-arylmethylamino-3-deoxy)-β-cyclodextrins have been synthesised from β-cyclodextrin 2-O-tosylate by formation and ring-opening of a manno-2,3-epoxide, while the corresponding mono-(6-arylmethylamino-6-deoxy)-derivatives were obtained by direct displacement reactions applied to cyclodextrin 6-O-tosylate. The greater ability of pyridyl-methylamino-β-cyclodextrins (relative to β-cyclodextrins) to catalyse the hydrolysis of nitrophenyl acetates was demonstrated.[7]

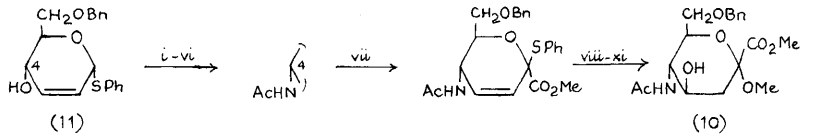
A new strategy for the synthesis of L-daunosamine, in which C-6 of D-glucurono-6,3-lactone becomes C-1 of the target, is shown in Scheme 3. The



Scheme 3

acetonide (7) was first deoxygenated at C-5, methanolysed and benzylated at O-2 to yield lactone (8). The required amino-function was introduced by mesylate displacement with azide. The 3-azido-2,6-dideoxy-derivative (9), a known precursor of L-daunosamine, was obtained in only 1.9% overall yield, the diisobutylaluminium hydride reduction (step vi) being low yielding.[8]

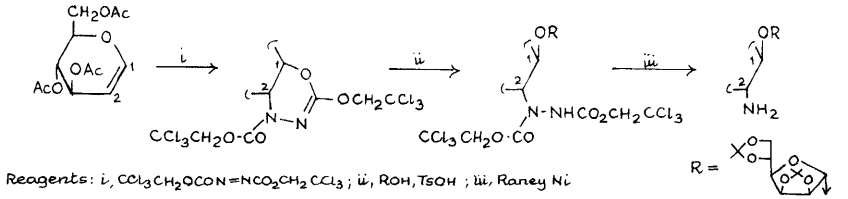
The lower homologue (10) of N-acetylneuraminic acid, with the same stereochemistry and substitution in the pyranose ring, has been synthesised



Scheme 4

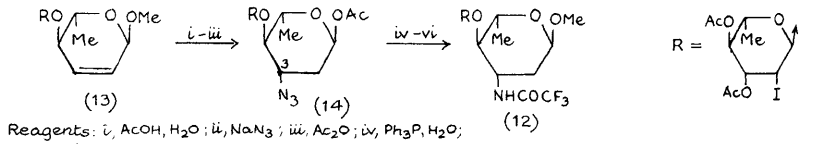
from D-glucal triacetate via the unsaturated thioglycoside (11) (Scheme 4). The amino-function was introduced by a double inversion sequence at C-4 involving Mitsunobu displacement with benzoate, followed by mesylate displacement with azide.[9]

Full details have been published on the [4+2]cyclo-addition of dibenzyl azodicarboxylate to O-silylated glycals, and the conversion of the adducts to 1,2-trans-related 2-amino-2-deoxy-glycosides by reaction with alcohol in the presence of an acid catalyst (cf. Vol.22, p.97).[10] By using bis(trichloroethyl) azodicarboxylate, this route has now been extended for use with acetylated



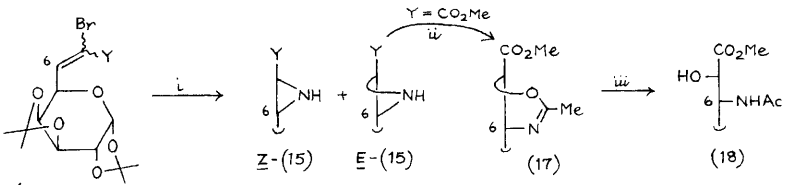
Scheme 5

glycals (Scheme 5).[11] The anomalously coupled nucleosides 2,3-dideoxy-3-(7-theophyllyl)-D-erythro- and -threo-pentopyranose were obtained by coupling theophylline with 2-deoxy-D-ribose (using P_2O_5-Bu_3N-H_2O in $CHCl_3$)[12], while the analogous coupling with phthalimide gave 2,3-dideoxy-3-phthalimido-D-arabino-hexopyranose and its D-ribo-hexofuranose isomer.[13] 1,5,6-Tri-O-acetyl-2,3-dideoxy-3-phthalimido-α-D-arabino-hexofuranose was obtained by reaction of (E)-4,6-di-O-acetyl-2,3-dideoxy-D-erythro-hex-2-enose with the DBU salt of phthalimide, followed by reacetylation.[13] Methyl 4-O-(2,6-dideoxy-2-iodo-α-L-mannopyranosyl)-α-L-acosaminide (12) and its dehalogenated analogue have been synthesised, the key step being 1,4-addition of hydrazoic acid to the enal formed on hydrolysis of the unsaturated disaccharide (13), which yielded azide (14) and its 3-epimer in a 2:1



Scheme 6

ratio (Scheme 6).[14] Aziridines (15), either as the E-isomer or as a mixture of E- and Z-isomers, were obtained from reaction of the bromoenoses (16) with ammonia (Scheme 7). The E-aziridine (16, Y=CO_2Me) rearranged to the

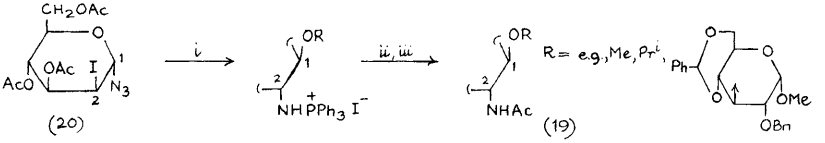


Reagents: i, NH_3, MeOH ; ii, AcBr, Et_3N ; iii, Na_2CO_3, H_2O

Scheme 7

oxazoline (17) with overall retention of stereo-chemistry at the 6,7-positions, and this then was hydrolysed to the 6-amino-6-deoxy-octuronate (18); the corresponding Z-aziridine led to the 7-epimer of uronate (18).[15]

β-Glycosides (19) of 2-acetamido-2-deoxy-D-glucose, including disaccharides, can be obtained via Staudinger-type reaction (Scheme 8) of the iodo-azide (20),

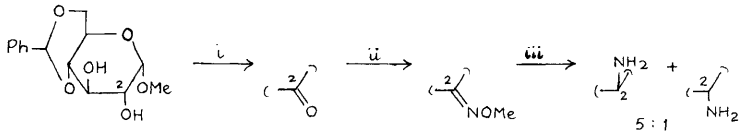


Reagents: i, Ph_3P, ROH, CH_2Cl_2 ; ii, NaOMe, MeOH ; iii, Ac_2O, Py

Scheme 8

available from addition of iodine azide to D-glucal triacetate (Vol.21, p.101). The isomer of (20) epimeric at C-1 and C-2 similarly gave α-glycosides of 2-acetamido-2-deoxy-D-mannose, albeit in somewhat lower yield, while iodoazides derived from D-galactal triacetate failed to react.[16]

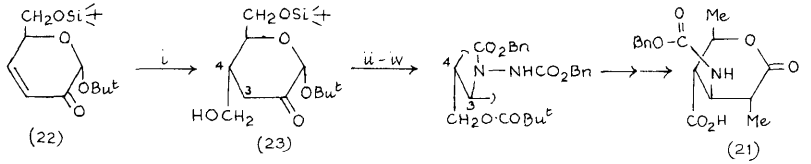
Tsuda and co-workers have coupled their regioselective secondary alcohol-ketone method (Vol.15, p.149) with an O-methyloxime formation and reduction sequence for the synthesis of glycosides of the following amino-sugars in satisfactory yields: 4-amino-4-deoxy-D-galactose and -L-arabinose, 3-amino-3-deoxy-D-allose, -D-glucose, -D-ribose and -D-xylose, 2-amino-2-deoxy-D-mannose (see Scheme 9), and 5-amino-5-deoxy-D-glucose (i.e., nojirimycin; c.f. Vol.22, p.97 for preliminary



Reagents: i, $(Bu_3Sn)_2O$, then Br_2 ; ii, $MeONH_2$; iii, AlH_3

Scheme 9

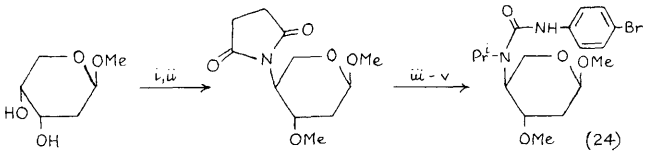
report). The stereoselectivity of reduction of the O-methyloxime intermediates by aluminium hydride or by hydrogen over a catalyst was studied.[17] Trehalose has been converted into analogues in which one of its glucosyl residues is replaced by a 3-amino-3-deoxy-allosyl, -glucosyl or -mannosyl residue by enzymatic oxidation to a 3-keto-derivative with the D-glucoside dehydrogenase from Flavobacterium saccharophilum, followed by reductive amination ($NaBH_3CN$ - NH_4OAc). The glucosyl residue of sucrose was similarly converted into a 3-amino-3-deoxy-allosyl or -glucosyl residue.[18] A key step in the synthesis of the branched chain lactone (21), an intermediate for construction of 1β-methylcarbapenams, from enone (22), was the electrophilic amination of the 3-deoxy-hexosid-2-ulose (23) (Scheme 10).[19]



Reagents: i, MeOH, Ph_2CO, hν; ii, Bu^tCOCl; iii, $KOBu^t$; iv, $BnO_2CN{=}NCO_2Bn$

Scheme 10

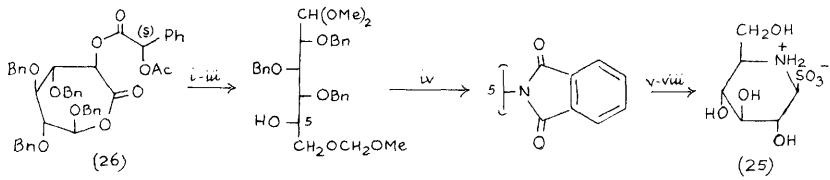
The Mitsunobu reaction has been employed for the synthesis of the 4-isopropylamino-sugar derivative (24) (Scheme 11) and its antipode; the α-L-threo-



Reagents: i, MeI, Ag_2O (36%); ii, , Ph_3P, DEAD; iii, N_2H_4; iv, $NaBH_3CN$, Me_2CO; v, 4-BrC_6H_4NCO, Py

Scheme 11

enantiomer shown was identical (by c.d.) to material obtained from the potent antitumor antibiotics esperamicin.[20] The Mitsunobu reaction also features in the synthesis of the hydrogen sulphite adduct (25) of nojirimicin from myo-inositol via

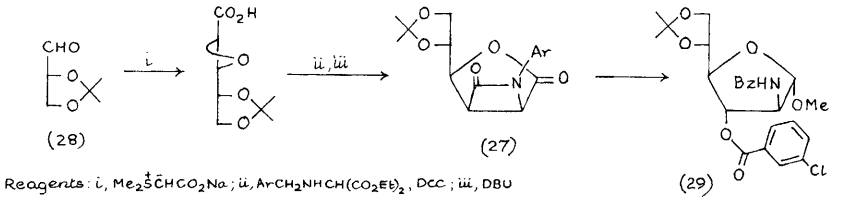


Reagents: i, $(MeO)_3CH$, TsOH, MeOH; ii, LAH; iii, $MeOCH_2Cl$, Et_2NPr^i; iv, PhthNH, Ph_3P, DEAD; v, N_2H_4; vi, $(Bu^tO_2C)_2O$, Et_3N; vii, H_2, $Pd(OH)_2$; viii, SO_2

Scheme 12

the optically active seven-membered ring lactone (26) (Vol.22, p.165) (Scheme 12). The enantiomer of adduct (25) was synthesised analogously from the enantiomer of lactone (26), and shown to be a potent inhibitor of β-glucosidase and α-mannosidase.[21] A purported synthesis[22] of nojirimycin from 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone has since been refuted.[23]

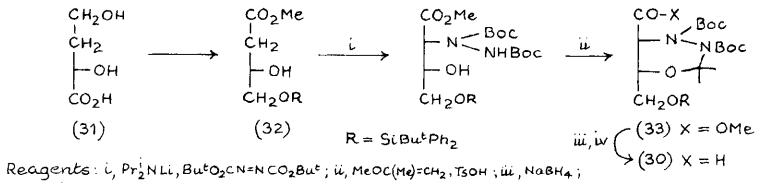
A number of syntheses of amino-sugars from chiral non-carbohydrate starting materials have been reported. Full details have been published on the synthesis of N-benzoyl-daunosamine (Vol.21, p.90) and 3-benzamido-2,3-dideoxy-pentoses (Vol.22, p.98) using chiral nitrones derived from 2,3-O-isopropylidene-L-glyceraldehyde and diethyl L-tartrate, respectively.[24,25] Branched-chain amino-sugars have been prepared and converted by oxidative cleavage to unbranched amino-sugars. 2-Amino-2-deoxy-3-C-branched-D-manno-hexose (27) was obtained from 2,3-O-isopropylidene-D-glyceraldehyde (28), epimerised at C-3 to its D-altro-analogue, and converted by oxidative decarboxylation to compounds such as (29)



Scheme 13

(Scheme 13).[26] Full details have been published on the synthesis of L-acosamine and L-daunosamine derivatives from ethyl (S)-3-hydroxybutyrate via a common branched-chain intermediate (Vol.21, p.88).[27]

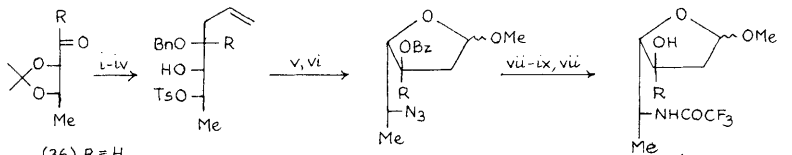
The 2-amino-2-deoxy-D-erythrose derivative (30) was synthesised from L-malic acid (31) via the known synthon (32) (Scheme 14). Its D-threose



Scheme 14

isomer was obtained by epimerisation (Bu^{t}OK-Bu^{t}OH) of the cis-fused intermediate (33). The corresponding 3-amino-3-deoxy-tetroses were obtained by reversing the oxidation levels at C-1 and C-4.[28] 2,5,6-Trideoxy-5-amino-D-lyxo-hexose derivative

(34) and its 3-C-methyl analogue (35) were obtained from the cis-fused aldehyde (36) and ketone (37) (Scheme 15), derived from the chiral adducts formed between



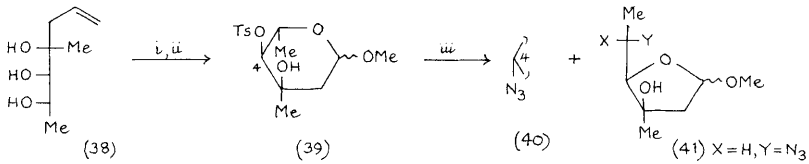
(36) R = H
(37) R = Me

(34) R = H
(35) R = Me

Reagents: i, $(\text{CH}_2=\text{CHCH}_2\text{Br})_2$Zn; ii, BnCl, NaH; iii, AcOH, MeOH; iv, TsCl, Py; v, O_3, MeOH, Me_2S; vi, NaN_3, DMF; vii, NaOMe, MeOH; viii, H_2, Pd/C; ix, $(CF_3CO)_2O$

Scheme 15

acetaldehyde and cinnamaldehyde or α-methylcinnamaldehyde, respectively, in the presence of baker's yeast (Vol.14, p.72; Vol.15, p.97). The D-ribo-isomer of compound (34) was similarly synthesised from the trans-fused C-2 epimer of compound (36) (Vol.15, p.96). The unprotected branched-chain intermediate (38), obtained from ketone (37), was converted to the tosylated (39) which gave the 4-azide (40) and the D-arabino-(41) and L-xylo-(42) 5-azides from nucleophilic attack of azide at C-5 with inversion, and C-4 with inversion and retention, in a 15:65:20 ratio, respectively (Scheme 16).[29]



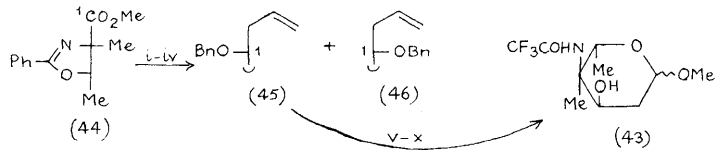
(38) (39) (40)

(41) X = H, Y = N_3
(42) X = N_3, Y = H

Reagents: i, O_3, MeOH, Me_2S; ii, TsCl, Py; iii, NaN_3, DMF

Scheme 16

Some amino-sugar syntheses have begun with chiral amino-acids. The four isomeric methyl 2,4,6-trideoxy-4-C-methyl-4-trifluoroacetamido-L-hexopyranosides have been synthesised from L-threonine. The L-ribo-isomer (43) was obtained from the known oxazoline derivative (44) by a ten step procedure (Scheme 17). Grignard

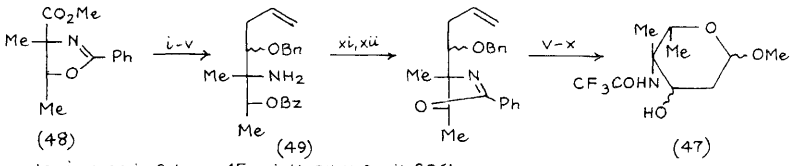


(44) (45) (46) (43)

Reagents: i, LAH; ii, $(COCl)_2$, DMSO, Et_3N; iii, $\text{CH}_2=\text{CHCH}_2$MgBr; iv, NaH, BnCl; v, H_2O, MeOH, HCl; vi, $(CF_3CO)_2O$, DMAP; vii, MeONa, MeOH; viii, O_3, Me_2S; ix, MeOH, HCl; x, H_2, Pd/C

Scheme 17

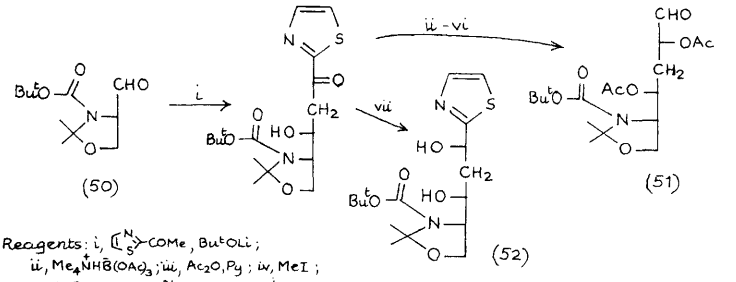
addition (step iii) gave a separable mixture of isomers (45) and (46) in a ratio of 98:2 at -90°C, but 55:45 at 20°C. The minor isomer was converted into the L-arabino-isomer of compound (43). The L-lyxo- and L-xylo-isomers (47) were separately prepared from the enantiomeric starting material (48) (also available from L-threonine) by a process involving separation of the isomeric adducts (49)



Reagents: i-x, as in Scheme 15 ; xi, NaOH, H_2O ; xii, $SOCl_2$

Scheme 18

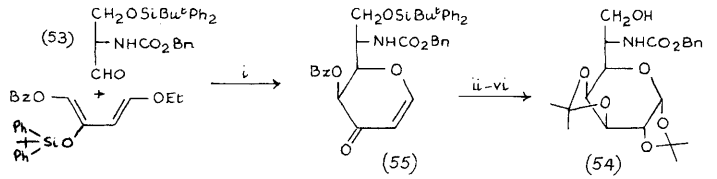
and inversion of configuration at position-5 (final product numbering) (Scheme 18).[30] The L-serinal derivative (50) has been elaborated into the 5-amino-3,5-dideoxy-L-arabino-hexose derivatives (51) and (52) (Scheme 19).[31] A different L-



Reagents: i, , Bu^tOLi ; ii, $Me_4\overset{+}{N}H\bar{B}(OAc)_3$; iii, Ac_2O, Py ; iv, MeI ; v, $NaBH_4$; vi, Hg^{2+}, H_2O ; vii, Bu^i_2AlH

Scheme 19

serinal derivative (53) has been converted by hetero-Diels-Alder methodology into the 6-amino-6-deoxy-L-glycero-D-galacto-heptose derivative (54) (Scheme 20), an

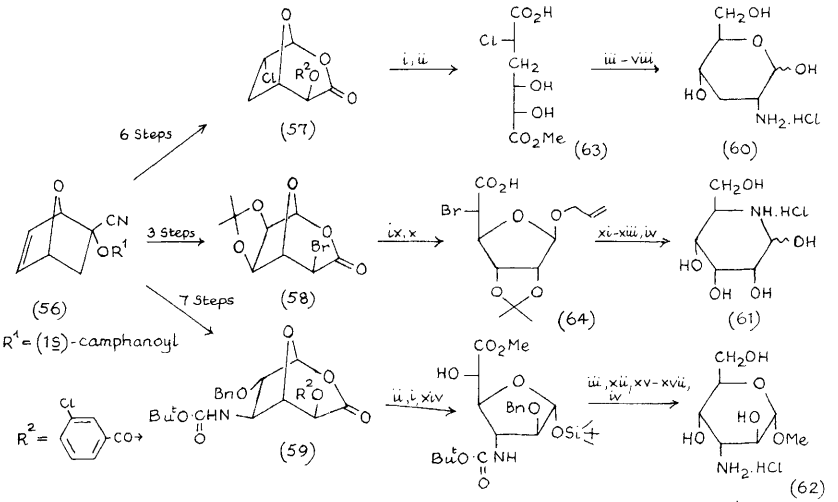


Reagents: i, $ZnBr_2$, then TFA ; ii, $NaBH_4$, $CeCl_3$; iii, K_2CO_3, MeOH ; iv, OsO_4, NMNO ; v, $(MeO)_2CMe_2$, H^+ ; vi, Bu_4NF

Scheme 20

intermediate previously used in the synthesis of destomic acid; the initial adduct (55) was the major component in an 87:8:4:1 mixture of diastereoisomers.[32]

Vogel and co-workers have synthesised a variety of aminodeoxy- and deoxy-sugars from the chiral Diels-Alder adducts of furan with cyanovinyl (1R)- or (1S)-camphanate. The adduct (56) has been converted to the lactones (57)-(59) by electrophilic functionalisation of the alkene and the masked α-keto-position, and Baeyer-Villiger oxidation, and thence into the hydrochlorides (60)-(62) of D-lividosamine,[33] allonojirimycin,[34] and the methyl α-glycoside of 3-amino-3-deoxy-D-

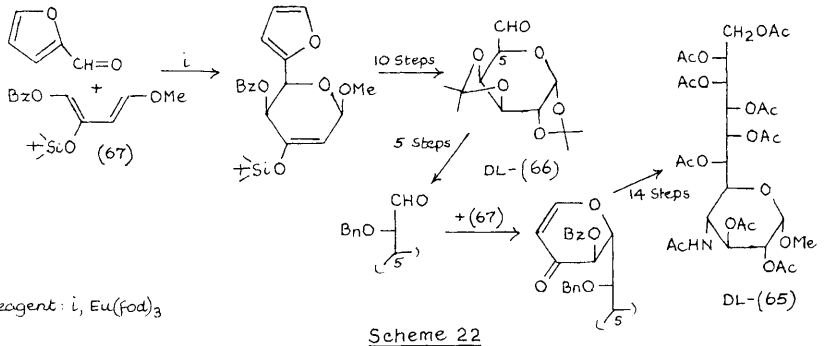


Reagents: i, K_2CO_3, MeOH; ii, MCPBA; iii, $LiBH_4$; iv, HCl, H_2O; v, $Me_2C(OMe)_2$, $SnCl_2$; vi, Bu_4NN_3; vii, Bu^i_2AlH; viii, H_2, Pd/C, HCl; ix,  , MSOH; x, EtOH, H_2O, $Rh(PPh_3)_3Cl$, DABCO; xi, NaN_3; xii, H_2, Pd/C; xiii, $BH_3.SMe_2$; xiv, $LiN(SiMe_3)_2$, Bu^tMe_2SiCl; xv, Bu^tMe_2SiOTf; xvi, Bu_4NF; xvii, Ac_2O

Scheme 21

altrose,[35] respectively (Scheme 21). The nitrogen-functionality in compounds (60) and (61) was introduced by displacement of halide with azide. While the chlorine in acid (63) was displaced from a lactone intermediate with inversion, the bromine in acid (64) was displaced from the corresponding potassium salt with retention due to participation of the carboxylate group.

Racemic methyl α-hikosaminide peracetate (65) has been synthesised via DL-galactodialdose derivative (66), by a process involving two hetero-Diels-Alder reactions with diene (67) (Scheme 22).[36] A similar approach to racemic N-acetyl-neuraminic acid has been reviewed.[37]

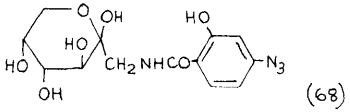


Scheme 22

Syntheses of polyoxamic acid from pyroglutamic acid and L-tartaric acid and of a 4-amino-2,3-dihydroxyhexanedioic acid from pyroglutamic acid are covered in Chapter 16. Synthesis of imino-alditols are covered in Chapter 18.

3 Reactions

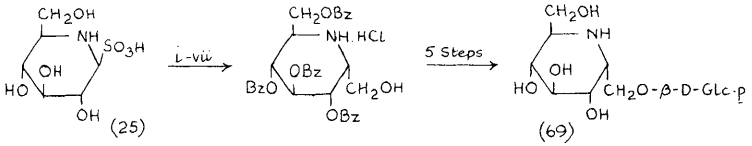
The 1-(4-azidobenzamido)-1-deoxy-D-fructose derivative (68) has been



(68)

synthesised from 1-azido-1-deoxy-2,3:4,5-di-O-isopropylidene-D-fructopyranose,[38] and the e.i.-mass spectra of fifteen N-(1-deoxy-D-fructopyranos-1-yl)aminoacids have been reported.[39]

The bisulphite adduct (25) of nojirimycin has been converted into the disaccharide mimic (69), which was shown to be an α-glucosidase inhibitor (Scheme

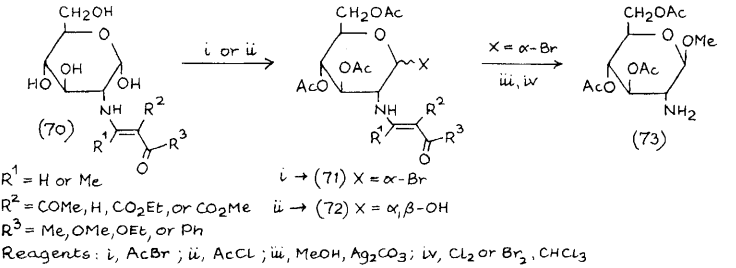


Scheme 23

23).[40] Syntheses of aminosugar O- and C-glycosides are covered in Chapter 3.

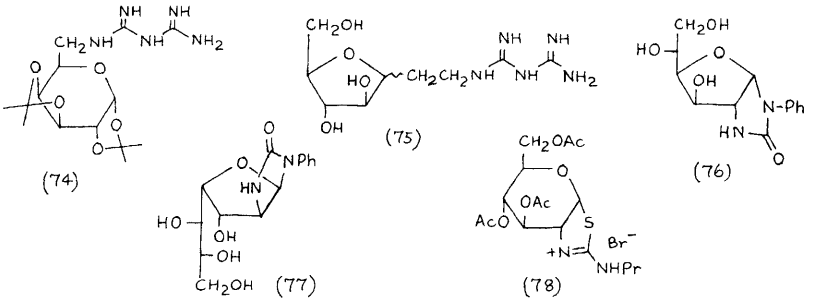
Three N-acylated 2-amino-2-deoxy-D-glucoses [bearing $HO(CH_2)_3CO$ →, $HO_2C(CH_2)_2CO$ →, or $HOCH_2CH{=}CHCO$ → as the acyl group] were synthesised via

per-O-acetylated 2-amino-2-deoxy-β-D-glucose and tested for biological activity as GBH (gamma-hydroxybutyric acid) analogues, but found to be inactive.[41] 2-N-Acylvinyl- and diacylvinyl-amino-2-deoxy-D-glucoses (70), prepared from 2-amino-2-deoxy-D-glucose and readily available materials, have been converted into the bromides (71) or the free sugar (72) by reaction with acetyl bromide or acetyl chloride, respectively (Scheme 24). The bromides (71) were used in Koenigs-Knorr



Scheme 24

glycosidations of methanol to give, after N-deprotection, the β-glycosides (73).[42] ^{14}C-Labelled methyl 2-acetamido-2-deoxy-3,6-di-O-pivaloyl-α- and β-D-glucopyranosides have been synthesised from 2-acetamido-2-deoxy-D-[1-^{14}C]glucopyranose by glycosidation and partial acylation, and examined as substrates for the esterase from rabbit serum. The 6-ester was rapidly and selectively hydrolysed from the α-anomer, but hydrolysis was slow and not as selective for the β-anomer.[43] Several carbohydrate biguanides have been synthesised as potential hypoglycemic agents. The galactos-6-yl derivative (74) was obtained from the corresponding 6-amino-6-deoxy-derivative [by reaction with $H_2NC(=NH)NHCN$]. Glucos-1- and 6-yl biguanido-analogues were obtained similarly, while the C-glycosidic analogue (75) was obtained from D-arabinose.[44] The synthesis and biological activity of Lipid A disaccharide analogues, and of 6-O-peptidyl-2-acetamido-2-deoxy-D-glucoses as glycoconjugates of opioid peptides, are covered in Chapters 3 and 7 respectively.



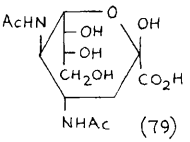
The synthesis and reactions of 1,2-dideoxy-hexopyrano[2,1-d]oxazolines and oxazolinium salts have been reviewed.[45] Acid-catalysed cyclisations of N-(glycos-2-yl)-urea and -thiourea derivatives have provided imidazolin-2-one[46] and 2-thiazoline[47] derivatives, e.g. (76)-(78).

Six naturally occurring sialic acids (Neu5Ac, Neu5,9-Ac_2, Neu5Ac9Lac, Neu5Gc, Neu9Ac5Gc, and the 2-acetoxyacetamido-derivative) have been synthesised in multigram quantities by using immobilised acylneuraminate pyruvate lyase to couple the corresponding mannosamine with pyruvate. Inexpensive routes to substrates avoiding the use of costly mannosamine were reported, and methylated derivatives (Neu5Ac7Me and Neu5Ac9Me, but not so well Neu5Ac8Me) were also synthesised.[48] A chemical synthesis of N-acetylmuramic acid from 2-acetamido-2-deoxy-D-glucose is covered in Chapter 5.

Amino-glycal and -nucleoside derivatives are referred to in Chapters 13 and 20, respectively.

4 Di-amino-Sugars

The 4-acetamido-4-deoxy-analogue (79) of N-acetylneuraminic acid has been



(79)

synthesised (see Chapter 16), and shown to be activated by CMP-sialate synthase.[49] Full details on the synthesis of the methyl di-N-acetyl-α-glycoside derivative of purpurosamine B (cf. Vol.22, p.105) have been published.[50]

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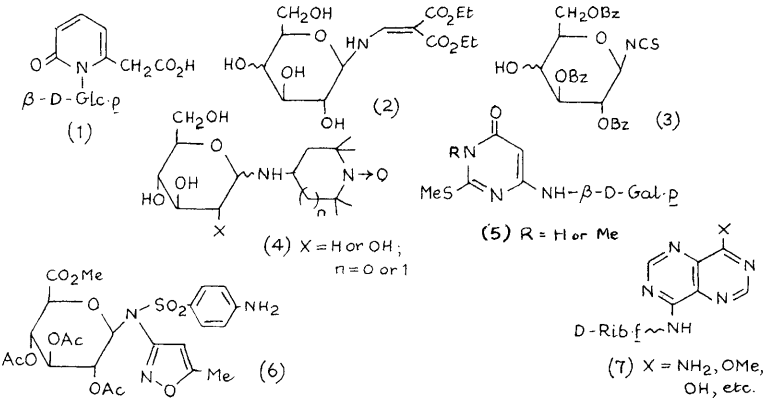
10
Miscellaneous Nitrogen Derivatives

1 Glycosylamines

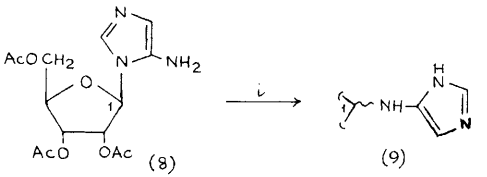
The novel pyridone N-glycoside (1) has been isolated from the Algerian newt as a strongly fluorescent pigment.[1]

2,3,6-Tri-O-benzoyl-β-D-galacto- and gluco-pyranosylamine hydrogen halide salts have been synthesised by partial benzoylation of the N-[2,2-di(ethoxycarbonyl)vinyl]-glycosylamines (2) followed by N-deprotection with chlorine or bromine, and have been converted to the corresponding isothiocyanates (3) on reaction with thiophosgene.[2] The water-soluble spin-labelled glycosylamines (4) were obtained as α,β-mixtures on reaction of the free sugars with the amines.[3] 4-(N-Galactopyranosylamino)pyrimidines (5) were likewise obtained by direct condensation.[4] The N^1-β-D-glucosides of the sulphonamide drugs sulfadimidine, sulfamerazine and sulfamethoxazole have been synthesised and shown by h.p.l.c. and m.s. analysis to be the minor urinary metabolites in humans.[5] The β-D-glucuronide derivative (6) of sulfamethoxazole was synthesised by reaction of the



corresponding uronosyl bromide with the drug under phase-transfer catalysis.[6] The α,β-D-ribosylamino-pyrimido[5,4-d]pyrimidines (7) have been synthesised by N-

heteroarylation of 2,3-O-isopropylidene-D-ribofuranosylamine p-toluenesulphonic acid salt.[7] The 5-aminoimidazole ribonucleoside (8) rearranged in aqueous buffer at pH 7 to the glycosylamine (9) (Scheme 1).[8] Fructosamine 1,6-diphosphate has been synthesised by transamination of amino-acids, e.g. L-alanine, with fructose 1,6-diphosphate in the presence of pyridoxal, which acts as the carrier of the amino-group from amino-acid to ketose. The 1-phosphate group catalysed the reaction.[9]

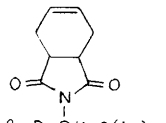


(8) (9)

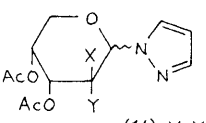
Reagent: i, H_2O - pH 7

Scheme 1

The N-ribosylated imide (10) and its dihydro-analogue have been synthesised in good yield by condensation ($SnCl_4$-catalysed) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose with the N-silylated carboxyimides, whereas the corresponding phthalimido-analogue was obtained only in low yield.[10] Catalysed fusion condensation of benzothiazole-2-thione with peracetylated aldoses led predominantly or exclusively to the 1,2-trans-N-glycosides. The products were tested as fungicides, but none displayed activity against Fusarium oxysporum in vitro.[11] The D-pentopyranosyl-pyrazoles (11) were synthesised from the corresponding 2-oxime derivatives (12) (Vol.22, p.108) by reduction of the released ketones.[12]

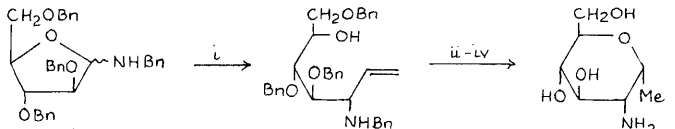


β-D-Rib·f(Ac)$_4$ (10)



(11) X, Y = H, OAc
(12) X, Y = :NOH

Reaction of the N-benzyl-arabinofuranosylamine (13) with vinylmagnesium bromide yielded the alkene (14), which was converted to the C-glycoside (15) by a mercuration-reduction sequence (Scheme 2).[13]



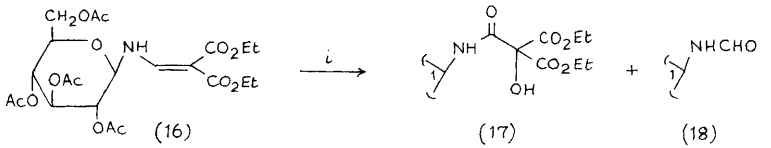
(13) (14) (15)

Reagents: i, ⌒MgBr ; ii, $Hg(OCOCF_3)_2$, then KCl ; iii, $NaBH_4$; iv, H_2, Pd/C

Scheme 2

Oligosaccharide N-acryloyl-glycosylamines, required for co-polymerization with acrylamide, have been synthesised in high yield from the corresponding free oligosaccharides (e.g., lactose, lacto-N-tetraose, and lacto-N-fucopentaose I and II) by amination [$(NH_4)_2CO_3$-H_2O] and acylation [CH_2=CHCOCl - $NaHCO_3$ - MeOH].[14]

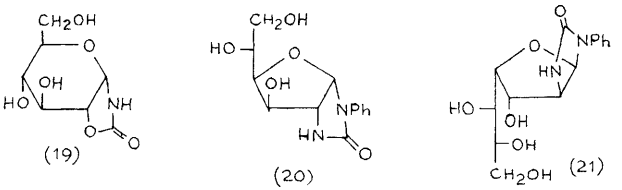
Oxidation of the N-vinylglucosylamine derivative (16) yielded the N-acylated and N-formylated derivatives (17) and (18) (Scheme 3); reactions of related



Reagents, i, $NaIO_4$, $KMnO_4$, H_2O, Me_2CO

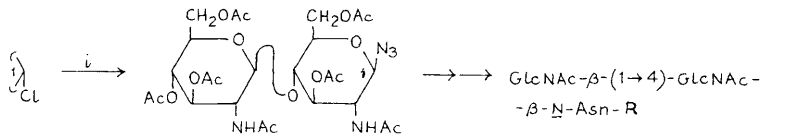
Scheme 3

derivatives, including examples with the enamine group bonded to C-2, were also studied.[15] The sulphuric acid-catalysed reaction of D-glucose with urea in phenol-water solution has been studied as part of an investigation into the chemistry of carbohydrate-based adhesives. N-β-D-Glucopyranosylurea, N,N'-di-β-D-glucopyranosylurea[16] and the cyclic carbamate (19)[17] were isolated from the resinous product. N-Glucosyl-biguanidine has been synthesised as a potential hypoglycemic



agent.[18] The imidazolin-2-ones (20) and (21) resulted from acid-catalysed cyclisation of the corresponding 2-deoxy-2-(N'-phenylureido)-aldoses.[19]

The N-chitobiosylasparagine peptides (22) have been synthesised as partial structures of N-glycopeptides, a new phase-transfer catalysis procedure being used

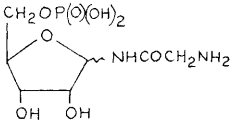


Reagents : i, NaN_3, $(C_8H_{17})_3\overset{+}{N}Me.Cl^-$, $CHCl_3$, H_2O

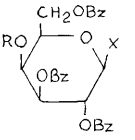
Scheme 4

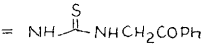
in the preparation of the azide (23) (Scheme 4).[20] The glycinamide ribonucleotide (24), which is N-formylated in the first step of purine biosynthesis, has been synthesized from 2,3,5-tri-O-benzoyl-β-D-ribosyl azide using conventional protecting group methodology.[21]

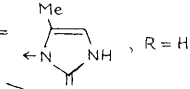
Routine syntheses of glycosyl isothiocyanates, involving reaction of the corresponding hexopyranosyl bromides with potassium thiocyanate, and their subsequent conversion to thiourea and thiosemicarbazide derivatives on reaction with amines and hydrazine, respectively, have been reported.[22] Partially protected β-D-galactopyranosylamine derivatives, e.g. (25) and (26), have been obtained by reaction of the corresponding galactosyl isothiocyanate with α-aminoaceto-phenones and α-aminoacetone, respectively. In acetic anhydride, the thiourea (25) cyclised to compound (27).[23]

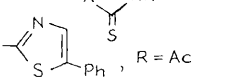


(24)

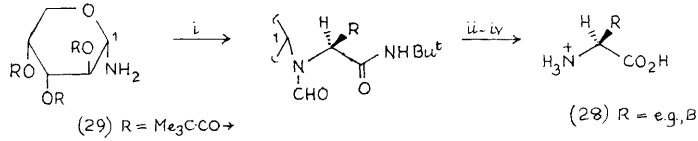


(25) X =  R = H

(26) X =  R = H

(27) X =  R = Ac

Kunz and co-workers continue to exploit per-O-pivaloylated hexopyranosylamines as chiral templates for the synthesis of amino-acids and



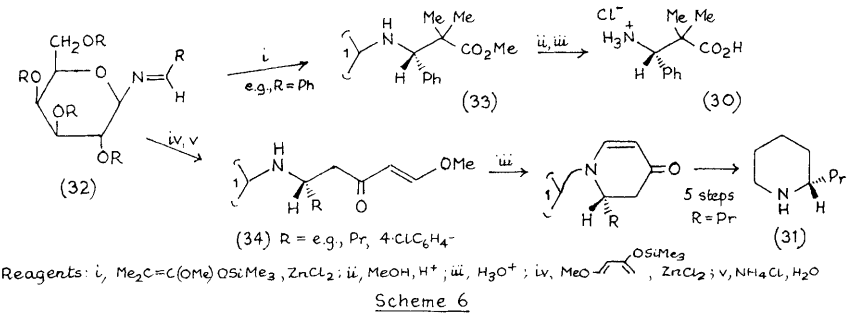
(29) R = $Me_3C{\cdot}CO\rightarrow$

(28) R = e.g., Bn, Bu^t

Reagents: i, RCHO, Bu^tNC, HCO_2H, $ZnCl_2$; ii, HCl, MeOH; iii, H_2O; iv, H_3O^+

Scheme 5

alkaloids. Optically active (S)-amino-acids (28) were obtained by diastereoselective Ugi reaction employing the D-arabinosylamine (29) (Scheme 5).[24] The corresponding (R)-amino-acids are available using a D-galactosylamine derivative, which is effectively enantiomeric with compound (29) (Vol.22, p.111). Chiral β-amino-acids (30) were constructed by hetero-aldol-type condensation,[25] and piperidine alkaloids, e.g. (+)-coniine (31), by tandem Mannich and Michael reactions[26] applied to the D-galactopyranosylimine derivative (32), respectively



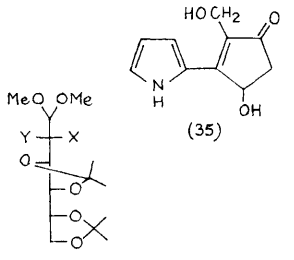
Scheme 6

(Scheme 6). The galactosylamine adducts (33) and (34) were the favoured diastereomers by ratios of between 5:1 and 250:1. In the case of compound (32) with R = 3-pyridyl, the opposite diastereoisomer of compound (34, R = 3-pyridyl) predominated, and this was used in the synthesis of (S)-anabasine.

The Maillard reaction between reducing sugars and amino-acids or proteins, as it occurs in foods during storage or on thermal treatment, has been reviewed (in German, with 41 refs.), and pathways leading to odour, taste and colour components were presented.[27] From the thermal degradation of fructose-valine products (themselves isolated from Maillard reaction of glucose and valine), 100 compounds have been separated and 70 of them identified by g.c.-m.s. with e.i. and positive ion c.i. detection. Nitrogen heterocyclic compounds made up ca. 40% of the reaction product. The mechanism of formation of the various categories of compounds was discussed.[28] The 3-(2'-pyrrolyl)-2-cyclopenten-1-one derivative (35) has been isolated from a xylose-lysine Maillard reaction,[29] and the (1'-pyrrolyl)-norleucine derivative (36) has been shown to be the major product from the glucose-bovine serum albumin Maillard reaction, and synthesized by reaction of glucose with N^{α}-acetyl-lysine.[30] In a study of the Maillard reaction of ovalbumin with disaccharides, it was observed that isomaltose and melibiose induced brown coloration and the formation of fluorescent compounds much more strongly than did maltose, cellobiose, and lactose, although all five disaccharides decreased the content of free amino-groups in the protein to <20% within one week at 50°. It was concluded that a 4-linked pyranoside unit on the reducing glucose moiety retarded the further degradation to aldehydic compounds of the initial Amadori rearrangement products.[31]

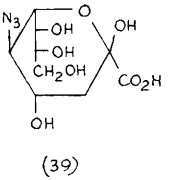
2 Azido-, Azi- and Diazo-Sugars

Several syntheses of azido-sugar derivatives have relied upon sulphonate displacement reactions. A cheap synthesis of 2-azido-2-deoxy-D-mannose utilised the crude mixture containing the 2-hydroxy-compound (37) formed directly from D-glucose [$Me_2C(OMe)_2$-MeOH-H_2SO_4]. The 2-azide (38) was thus obtained in 10% overall yield from D-glucose by formation and displacement of the 2-O-imidazolesulphonate derivative of compound (37), and was then hydrolysed to the free 2-azido-sugar. Further transformation to the N-acetylneuraminic acid analogue (39) was effected by sialate aldolase catalysed condensation with sodium pyruvate.[32] For the construction of 2-azido-2-deoxy-β-D-mannopyranosyl-(1→4)- and -(1→6)-D-glucose, the requisite gluco-disaccharide derivatives with a single free hydroxy-group were constructed, imidazole-sulphonylated, and subjected to displacement with azide.[33] Displacement reactions of 2-O-triflate (40) with a variety of nucleophiles as their tetrabutylammonium salts in various solvents have been investigated, the 2-azido-2-deoxy-D-glucoside (41) and its 2-phthalimido-analogue being obtained in

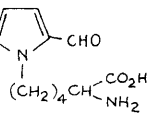


(35)

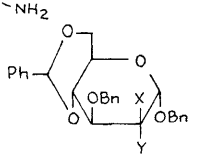
(37) X = OH, Y = H
(38) X = H, Y = N_3



(39)

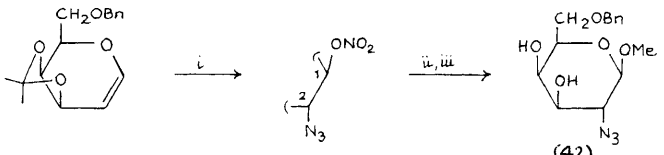


(36)



(40) X = OTf, Y = H
(41) X = H, Y = N_3

moderate yield.[34] A new route to the 2-azido-2-deoxy-D-galactoside (42) has been reported (Scheme 7),[35] the product being used in the synthesis of disaccharide fragments of dermatan sulphate (see Chapter 3). A synthesis of the 2-azido-2-

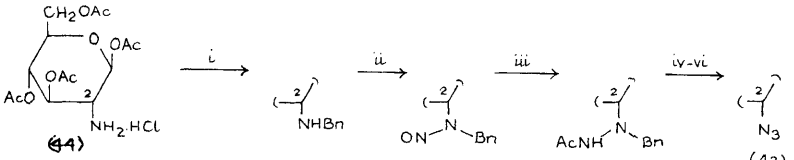


Reagents: i, $(NH_4)_2Ce(NO_3)_6$, NaN_3; ii, MeONa, MeOH; iii, HOAc, H_2O

(42)

Scheme 7

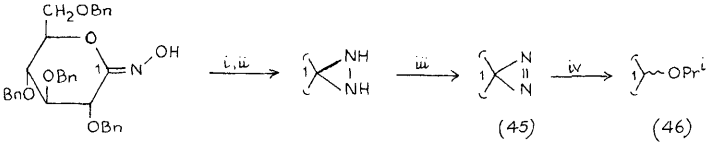
deoxy-D-glucose derivative (43) in ca. 50% overall yield from the 2-amino-2-deoxy-D-glucose tetraacetate (44) has also been reported (Scheme 8).[36]



Reagents: i, BnBr, K_2CO_3, DMF; ii, N_2O_4, CH_2Cl_2, NaOAc; iii, Zn, HOAc, Ac_2O; iv, H_2, Pt/C, TsOH; v, Py, Ac_2O; vi, isoamyl nitrite, THF, H_2O

Scheme 8

The D-gluco-diazirine derivative (45) and its D-manno- and D-galacto-analogues have been prepared from the corresponding hexono-1,5-lactone oximes, and shown to be stable at low temperatures (Scheme 9). They are precursors of

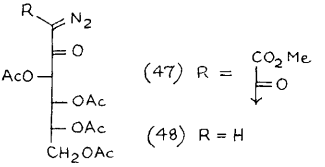


Reagents: i, MsCl, Et_3N; ii, NH_3, MeOH; iii, I_2, Et_3N, MeOH; iv, Pr^iOH

Scheme 9

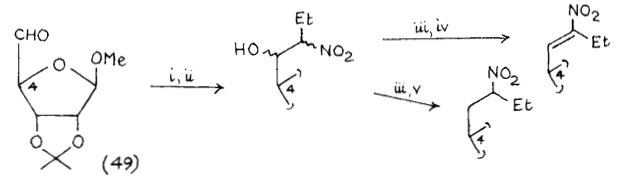
glycosylidene carbenes, and in a preliminary experiment diazirine (45) was converted into the glycosides (46).[37]

The 3-deoxy-3-diazo-D-arabino-oct-2,4-diulosonate derivative (47) has been synthesised by condensation of 1-diazo-D-fructose derivative (48) with methyl oxalyl chloride. In contrast to other carbohydrate diazoketones, compound (47) is relatively stable to acids, although it reverts to the precursor (48) on exposure to water.[38]



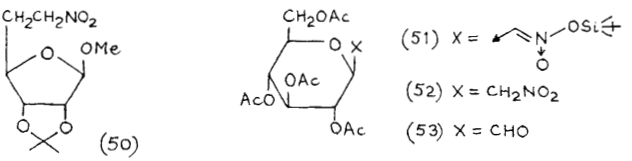
3 Nitro-Sugars

Aldehydro-sugar derivatives, e.g. (49), have been chain extended using Seebach's silyl nitronate methodology (Scheme 10).[39] Unhindered nitromethyl-sugar

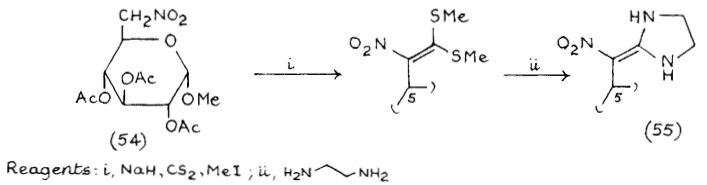


Scheme 10

derivatives such as (50) formed silyl nitronates that could be condensed with p-nitrobenzaldehyde, but silyl nitronates such as (51) from the C-glycoside (52)



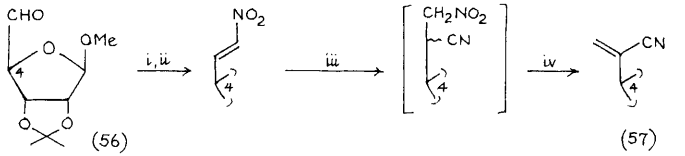
failed to react with aldehydes. Ozonolysis converted silyl nitronate (51) into aldehyde (53).[40] Chain extension of nitromethyl sugars such as (54) could also be effected as shown in Scheme 11, and one or both of the methylthio-groups in the products could be displaced by nitrogen nucleophiles, e.g. to give compound (55).[41]



Scheme 11

4 Nitriles, Isonitriles, Oximes and Hydroxylamines

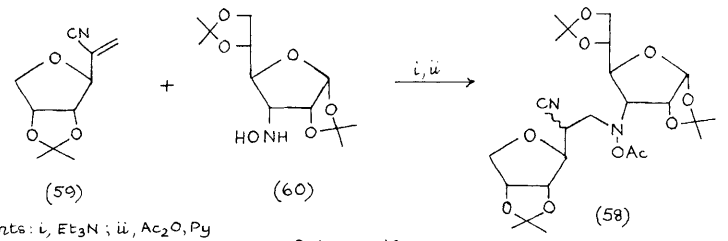
Eleven protected sugar derivatives bearing a terminal 1-cyanovinyl group have been prepared from sugar aldehydes, as shown for the conversion of the 5-aldehydo-riboside (56) into the product (57) (Scheme 12). These compounds were prepared



Reagents: i, $MeNO_2$, MeONa, MeOH; ii, Ac_2O, NaOAc; iii, KCN, Bu_4NBr, H_2O, PhMe; iv, Et_3N

Scheme 12

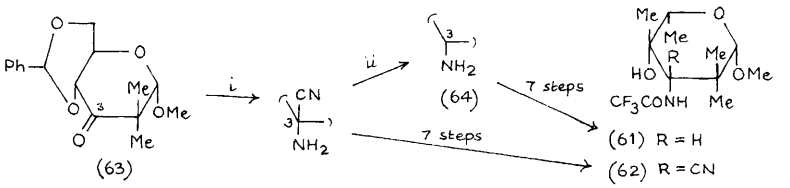
for use in a structure-activity study of cytotoxic, antiviral and antimicrobial properties. A disaccharide analogue (58) was obtained by condensation of



Reagents: i, Et_3N; ii, Ac_2O, Py

Scheme 13

cyanovinyl-derivative (59) with the hydroxylamine (60) (Scheme 13).[42] The extremely hindered analogues (61) and (62) of daunosamine have been synthesized

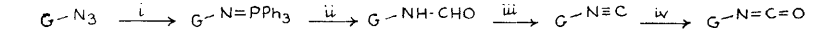


Reagents: i, KCN, NH_3, NH_4Cl, MeOH; ii, $LiAlH_4$

Scheme 14

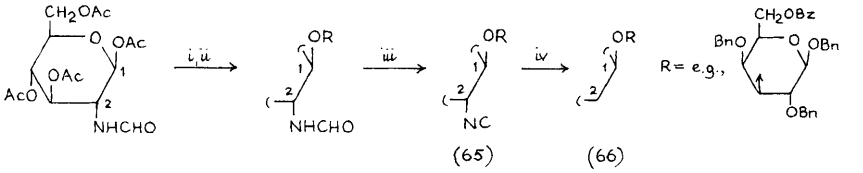
from ketone (63). The ribo-configurated amino-sugar (64) had to be obtained by reductive decyanation as shown (Scheme 14) because reduction ($LiAlH_4$) of the oxime derivative of ketone (63) unexpectedly gave the arabino-isomer.[43]

Glycofuranosyl formamide, isonitrile and isocyanate derivatives have been



Scheme 15

prepared from the corresponding glyco-furanosyl azides (Scheme 15).[44] The isonitriles (65) were formed as intermediates in the synthesis of β-linked 2-deoxy-D-



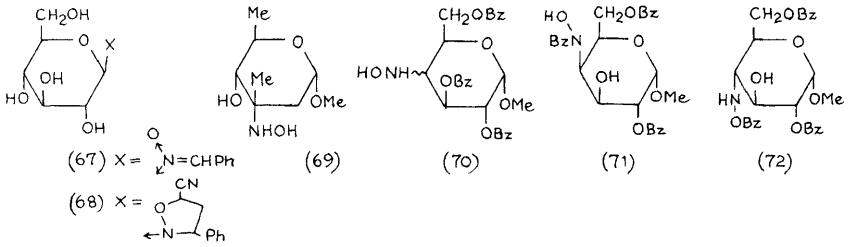
Reagents: i, AcCl, HCl; ii, ROH, AgOTf; iii, $POCl_3$, Et_3N; iv, Bu_3SnH

Scheme 16

arabino-hexose disaccharides (66) (Scheme 16), the isonitrile group being removed by radical reduction.[45]

The nitrone (67) has been prepared directly from D-glucose oxime and benzaldehyde without protecting groups, and shown to undergo dipolar cycloadditions with dipolarophiles such as acrylonitrile to give isoxazolidine (68) of undetermined stereochemistry.[46]

The novel hydroxylamino sugar (69) has been isolated from a new anthracycline antibiotic, viriplanin A.[47] The epimeric 4-hydroxylamino-sugars (70) were obtained by reduction ($NaBH_3CN$) of the corresponding 4-oxime derivative (cf., Vol.21, p.108); differences between the e.s.r. spectra of these two spin-labelled derivatives confirmed the sensitivity of e.s.r. to configurational changes.[48]

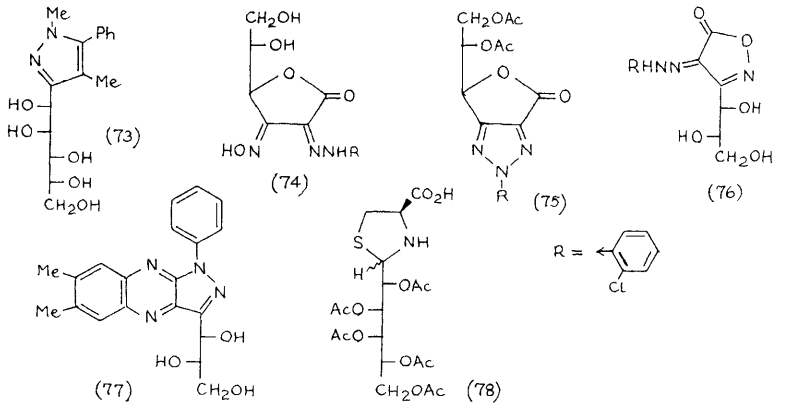


Ammonolysis of compounds (70) led to 3→4 benzoyl migration, O→N isomerisation

yielding compound (71) in the case of the 3,4-cis-compound, and O→O migration yielding compound (72) in the case of the 3,4-trans-compound.[49]

5 Hydrazones, Osazones and Related Heterocycles

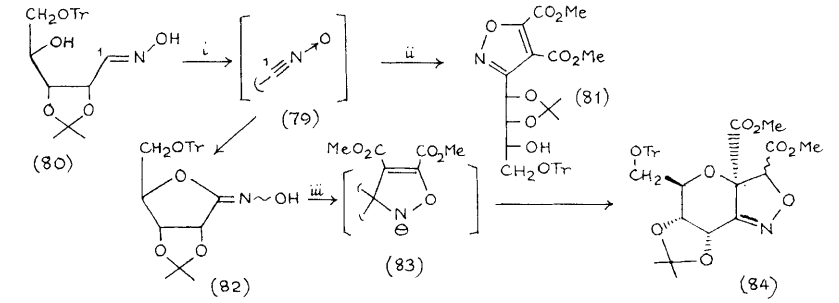
The synthesis of per-O-acetylated aldose N-methyl-N-(4-arylthiazole-2-yl)hydrazones has been described.[50] 3-Alditolyl-1-methylpyrazoles such as compound (73) have been obtained by condensation of the methylhydrazones of D-mannose and D-galactose with nitroalkenes.[51] 2-Hydrazone 3-oxime derivatives, e.g. (74), have been obtained from dehydro-L-ascorbic acid by sequential reaction with arylhydrazine then hydroxylamine. Cyclisation in acetic anhydride under reflux led to triazoles such as compound (75), whereas rearrangement yielded isoxazolidinones, e.g. (76).[52] Direct reaction of dehydro-L-ascorbic acid with two equivalents of arylhydrazines gave the 2,3-bis(arylhydrazones), which can exist as two geometrical isomers that were isolated in some cases. Reaction with acetone arylhydrazone, however, gave the 2-aryl-hydrazone derivative.[53] Pyrazolo[3,4-b]quinoxalines, e.g. (77), have been obtained from dehydro-L-ascorbic and dehydro-D-isoascorbic acids by sequential reaction with 1,2-diamino-4,5-dimethylbenzene then an arylhydrazine, and dehydrative ring closure (with NaOH).[54,55] A variety of heterocyclic products have been isolated from the reaction of kojic acid and arylhydrazines in aqueous acetic acid.[56]



6 Other Heterocycles

The synthesis and reactions of 1,2-dideoxy-hexopyrano[2,1-d]-oxazolines and -oxazolinium salts have been reviewed.[57] A reinvestigation of the reaction between L-cysteine and penta-O-acetyl-aldehydo-D-galactose or tetra-O-acetyl-aldehydo-L-arabinose revealed that, contrary to earlier reports, the product thiazolidines, e.g. (78), are a mixture of isomers at the newly formed chiral centre.[58]

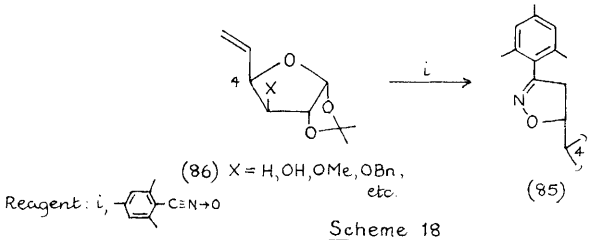
The nitrile oxide (79) generated from the D-ribose oxime (80) can be trapped with dimethylacetylene dicarboxylate (DMAD) to form the cycloadduct (81) (Scheme 17). In the absence of DMAD the D-ribono-1,4-lactone oxime (82) is



Reagents: i, NaOCl; ii, DMAD; iii, DMAD, Et_3N

Scheme 17

formed. This can then react with DMAD in the presence of a base to form the ionised spirocyclic adduct (83) that subsequently rearranges to the fused bicyclic system (84).[59] Anti-adducts (85) were formed with high π-facial stereoselectivity in the dipolar cycloaddition of mesitylenenitrile oxide to variously 3-substituted hex-5-enoses (86), best results being obtained with the 3-O-benzyl ether (Scheme 18).[60]

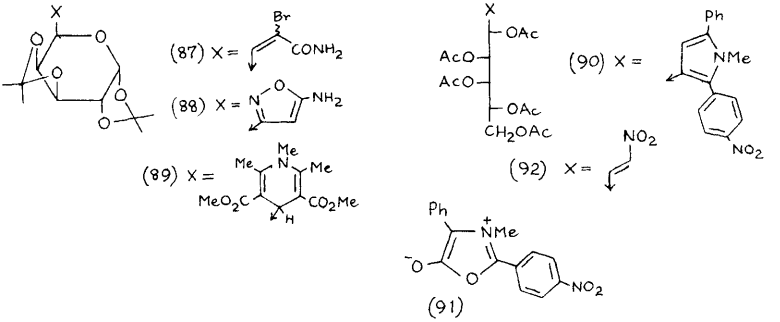


Scheme 18

New types of hydroxyamino- and hydroxyureido-sugars have been synthesized as potential antineoplastic agents. Thus, addition of hydroxylamine to the

bromoenose (87) led to the adduct (88).[61] Related syntheses and reactions of aziridines derived from compounds such as (87) are covered in Chapter 9.

Hantsch esters, such as (89), having monosaccharide substituents, have been synthesised from sugar aldehydes as chiral NADH models,[62] and used in the asymmetric reduction of several prochiral ketones with ee's up to 79% being attained.[63]



The 3-(D-galacto-pentitol-1-yl)pyrrole (90) was obtained by addition of the zwitterionic reagent (91) to the nitroalkene (92); analogous results were obtained for the D-manno-stereoisomers.[64]

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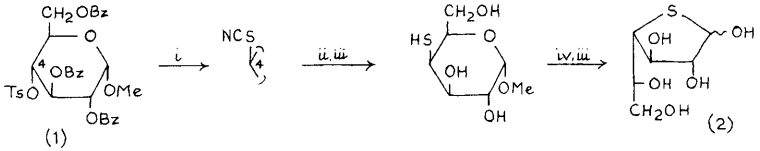
11
Thio- and Seleno-sugars

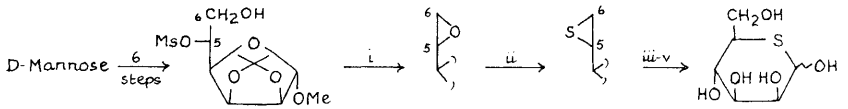
4-Thio-D-galactofuranose (2) has been synthesised from the methyl α-D-glucopyranoside derivative (1). The sulphur-containing substituent was introduced (Scheme 1) by nucleophilic displacement of the 4-tosyloxy group of the starting compound by thiocyanate ion with inversion of configuration[1].



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

Scheme 1

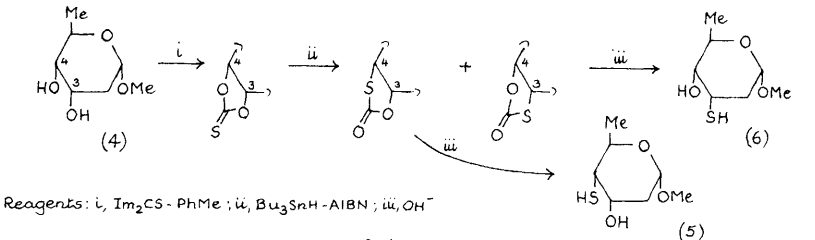
5-Thio-D-mannose (3), isolated from a marine sponge, is the first 5-thiosugar to be found in Nature. Its synthesis from D-mannose, which is outlined in Scheme 2, involves two stereochemical inversions at C-5.[2] Another new thiosugar, methyl 2,6-dideoxy-4-thio-α-D-ribo-hexopyranoside (5), a constituent of the calichemycins, a new class of antitumour antibiotics, has been prepared from the



Reagents: i, NaH-DMF; ii, $SC(NH_2)_2$, MeOH; iii, KOAc; iv, Ac_2O, Py; v, Et_3N, MeOH, H_2O

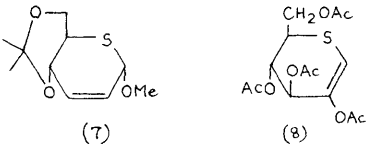
Scheme 2

readily available D-digitoxose derivative (4). Application of the tributyltin radical-catalysed O/S rearrangement of thionocarbonates allowed replacement of O-4 by a sulphur atom with retention of configuration. As indicated in Scheme 3 the O/S rearrangement was not selective and the desired product (5) and its 3-thio isomer (6) were obtained in roughly equal proportions.[3]

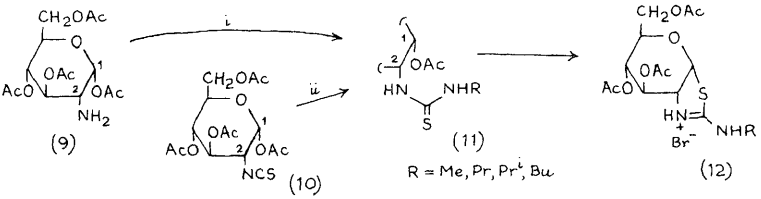


Scheme 3

The unsaturated 5-thioglucose derivatives (7) and (8) have been prepared and have been shown by ^{1}H-n.m.r. spectroscopy to assume the $^{S}H_5$ and $^{4}H_5$ conformations, respectively.[4]

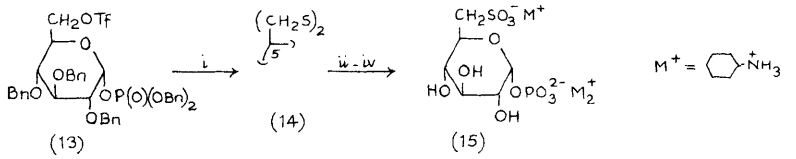


Thiourea derivatives (11) are available from 2-amino-2-deoxy-1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (9) or from the corresponding 2-isothiocyanate (10) by treatment with methyl isothiocyanate or a primary amine, respectively (Scheme 4). On exposure to hydrobromic acid they cyclise to give glucopyrano[2,1-d]-2-thiazolinium bromides (12).[5]



Scheme 4

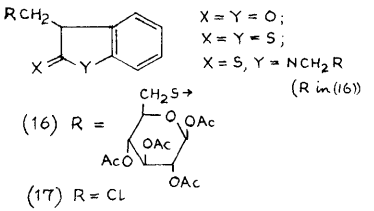
Scheme 5 shows the synthesis of 6-sulphono-α-D-glucopyranose 1-phosphate from the appropriately protected α-D-glucose 1-phosphate (13) via the disulphide (14). The product was isolated as the tris-cyclohexylammonium salt (15).[6] A convenient route to 6-thio derivatives of D-glucal from D-glucose is referred to in Chapter 13.

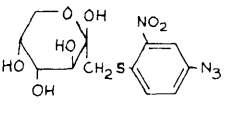


Reagents: i, Bu_4NSH, air; ii, MCPBA; iii, H_2, Pd/C; iv, NH_2, to pH 7

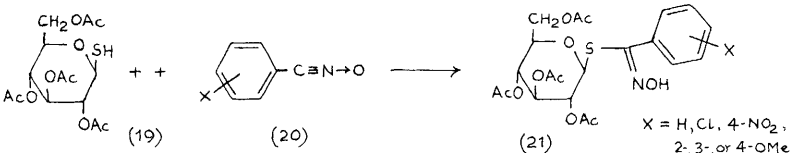
Scheme 5

Derivatives (16) of 6-thio-D-glucose were formed in 75-80% yield on treatment of 1,2,3,4-tetra-O-acetyl-6-thio-β-D-glucose with the chlorides (17),[7] and in the course of photoaffinity labelling studies the 1-(azidoaryl)thio-D-fructose derivative (18) was synthesised from 2,3 : 4,5-di-O isopropylidene-6-O-triflyl-D-fructopyranose by use of known methodology.[8] 1-Isoindolyl-(1-thio-β-D-glucoside) derivatives are mentioned in Chapter 3.



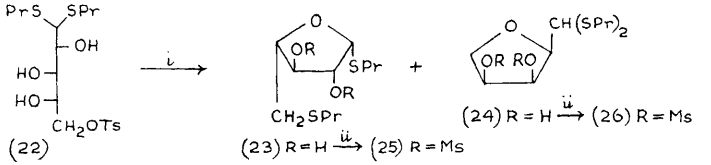


The glucosylthiol (19) underwent 1,3-addition to in situ generated, substituted benzonitrile oxides (20) as outlined in Scheme 6 to give thiohydroximate derivatives (21). The effects of the aromatic ring substituents on the course of this reaction



Scheme 6

was examined.[9] Attempts to prepare 2,5-anhydro-L-arabinose derivatives from acyclic 5-O-tosylates, by heating for example the tosylated dithioacetal (22) under the basic conditions specified in Scheme 7, were only moderately successful. An inseparable mixture was formed which contained the 1-thio-β-L-glycoside (23) as the main product and the target compound (24) as a minor constituent. The two compounds could be separated and isolated as their mesylates (25) and (26). The mechanism by which the 1-thio glycoside (23) is generated has been described before (see Vol. 13, 1979, p. 105).[10]



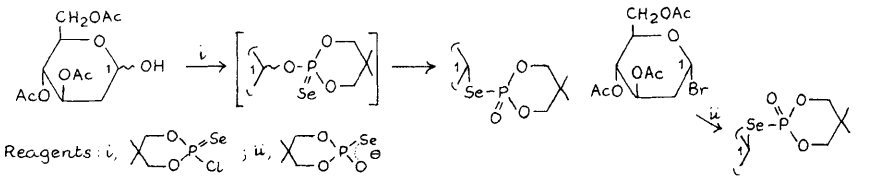
Reagents: i, Py or Collidine, with or without DMAP ; ii, MsCl - Py

Scheme 7

The copper(II) complexes of 1-thio-α- and -β-D-glucopyranose and 2-amino-2-deoxy-1-thio-β-D-glucopyranose and their peracetates have been synthesised by action of copper(II) acetate on the respective sodium thiolates, followed by acid catalysed acetylation, for an investigation of their anti-inflammatory activity.[11] The mesogenic properties of the C_4 - C_{10} dialkyl dithioacetals of ten standard pentoses and hexoses have been examined. Most of them form thermotropic liquid crystals with the notable exception of all L-rhamnose derivatives. A model has been proposed to correlate carbohydrate configuration and melting behaviour. Despite the intrinsic chirality of all carbohydrate mesogens no evidence for chiral mesophases was detected.[12]

In a simulation of the reaction of glucose and cellulose with hydrogen sulphide and polysulphide at ambient temperature in aqueous solution the formation of organic sulphur compounds was observed which yielded thiophene on pyrolysis/evaporation. By such a process carbohydrates in nature might be converted into sulphur compound which, being resistant to microbial attack, would be preserved in sediments.[13]

The first examples of 1-phosphonoselenates of a 2-deoxy sugar have been reported. Their synthesis is shown in Scheme 8.[14]



Scheme 8

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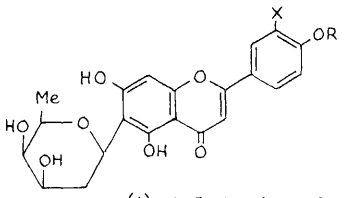
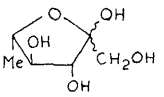
12
Deoxy-sugars

Reviews have been published on the use of carbohydrate free radicals in the synthesis of deoxy-sugars,[1] and the synthesis of deoxy-sugars generally.[2]

6-Deoxy-D-allose has been found as a terminal pyranosyl unit of a steroidal glycoside from Heleniopsis orientalis.[3] Two flavonoid C-β-D-oliosides (1) have been isolated from Cassia torosa leaves.[4] O- and C-Glycosylated benzanthraquinone antibiotics with complex deoxy-sugar oligosaccharide residues are covered in Chapter 19.

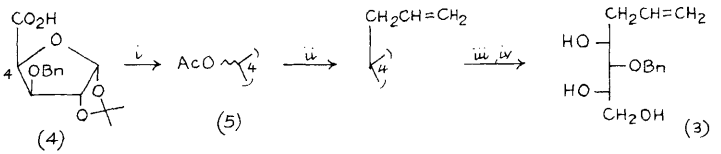


(1) X = R = H ; X = OH, R = Me



(2)

6-Deoxy-L-arabino-hexulose (2) has been obtained in 27% yield by isomerisation of L-rhamnose in pyridine under reflux.[5] The known precursor (3) of 2-deoxy-L-xylo-hexose (cf. Vol.21, p.123) has been synthesised from the D-xyluronic



(4) (5) (3)

Reagents: i, $Pb(OAc)_4$, Py ; ii, $CH_2{=}CHCH_2SiMe_3$, $MgBr_2$; iii, H_3O^+ ; iv, $NaBH_4$

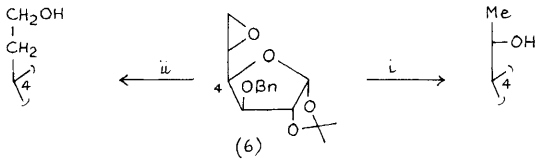
Scheme 1

acid derivative (4), via the chiral synthon (5) which is equivalent to D-tartaric aldehyde (Scheme 1). An equivalent precursor of 2-deoxy-L-ribo-hexose was obtained similarly from the C-3 epimer of compound (4).[6] 6-Deoxy-D-[U-^{14}C]-glucose has been synthesised in five steps and in 11.8% overall radiochemical yield from D-[U-^{14}C]glucose.[7]

A number of analogues of the Lewis b human blood group determinant tetrasaccharide, α-L-Fuc-(1→2)-β-D-Gal-(1→3)-[α-L-Fuc-(1→4)]β-D-GlcNAc-1→OMe,

in which the galactose residue is replaced by its deoxy- or deoxyhalo-derivatives have been synthesised to determine the role of this residue in binding.[8]

A remarkable, and so far unexplained, reversal in the ratio of secondary to primary alcohol product was observed in the one-pot reductive cleavage of 5,6-epoxide (6) in 1,2-dimethoxyethane under reflux, from 15:1 by use of lithium iodide



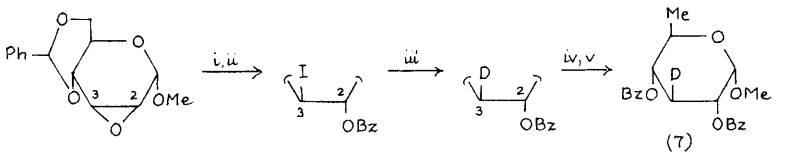
Reagents: i, LiI, Bu_3SnH, AIBN; ii, MgI_2, Bu_3SnH, AIBN

Scheme 2

to 1:5 using magnesium iodide (Scheme 2). The reaction is presumed to proceed via initial opening of the epoxide with halide ion.[9]

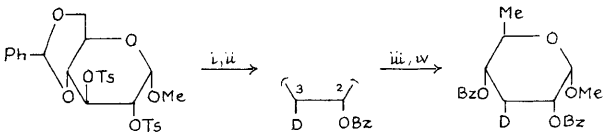
A further evaluation of the mechanism involved in the formation of deoxy-sugars on photolysis (254 nm) of sugar esters of aliphatic acids in HMPT-H_2O (95:5), and the competing formation of the corresponding alcohol derived by de-O-acetylation, has been published.[10] A number of deoxy- and deoxyhalo-analogues of α-D-glucopyranosyl phosphate have been synthesised, and their acid-catalysed hydrolyses studied. The deoxy-analogues hydrolysed faster, and the deoxyhalo-analogues slower, than the parent phosphate, the relative reactivity paralleling that which has been observed in the hydrolysis of glycosides.[11]

Specifically deuterated paratosides (3,6-dideoxy-D-ribo-hexosides) (7) and (8) have been synthesised as shown in Schemes 3 and 4, respectively, from D-glucose



Reagents: i, MeMgI; ii, Bz_2O, Et_3N, DMAP; iii, $NaBD_4$, NiCl, EtOH; iv, NBS, $BaCO_3$; v, Bu_3SnH

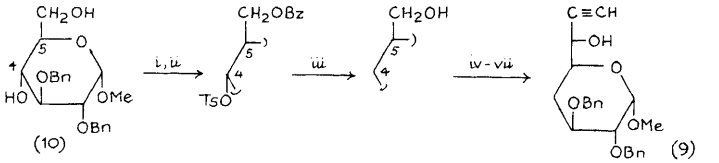
Scheme 3



Reagents: i, $LiAlD_4$; ii, Bz_2O, Et_3N; iii, NBS, $BaCO_3$; iv, Bu_3SnH

Scheme 4

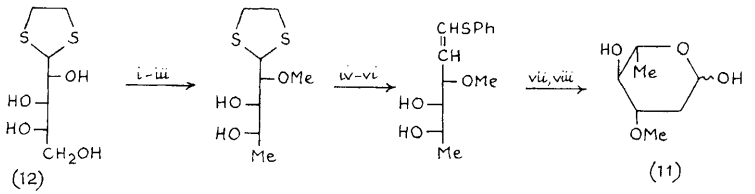
derived starting materials.[12] The 4-deoxy-acetylenic sugar derivative (9) has been



Reagents: i, BzCl, Py; ii, TsCl, Py; iii, LAH; iv, $(COCl)_2$, Me_2SO, Et_3N; v, $Me_3SiC{\equiv}CMgBr$, $MgBr_2$; vi, $AgNO_3$, EtOH; vii, KCN

Scheme 5

obtained from the methyl D-glucoside derivative (10) (Scheme 5),[13] and L-oleandrose (2,6-dideoxy-3-O-methyl-L-arabino-hexose) (11) from L-arabinose via the

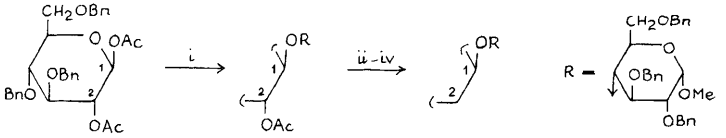


Reagents: i, TsCl, Py; ii, LAH; iii, CH_2N_2, $SnCl_2$, MeO~OMe; iv, Ac_2O, Py; v, HgO, $BF_3.OEt_2$; vi, $Ph_3P{=}CHSPh$; vii, NH_3, MeOH; viii, HgO, $HgCl_2$, H_2O

Scheme 6

dithioacetal (12) (Scheme 6),[14] reductive detosylation being employed in both cases to effect deoxygenation.

Radical reduction (with Bu_3SnH) of thioacylated sugars has featured in several deoxy-sugar syntheses. A new approach to β-linked 2'-deoxy-disaccharides



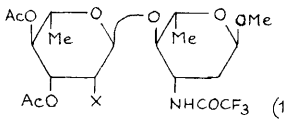
Reagents: i, ROH, Me_3SiOTf; ii, MeOH, MeONa; iii, NaH, CS_2, Imidazole, MeI; iv, Bu_3SnH, AIBN

Scheme 7

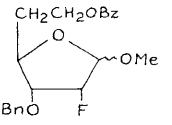
is exemplified in Scheme 7, in which the 2'-acetoxy substituent is removed by radical methodology. A related method involving the formation and radical reduction of an 2'-isonitrile from a 2'-formamido-disaccharide is covered in full in Chapter 10.[15] 2-Deoxy-C-glycosides have been obtained by reaction of 1,2-anhydro-3,4,6-tri-O-benzyl-β-D-mannopyranose with organocuprate reagents, and 2-deoxygenation of the product via radical reduction of the derived phenoxythiocarbonyl esters.[16] Improved syntheses of the 2-, 3- and 4-deoxy-

derivatives of methyl β-D-galactopyranosides have involved radical reductions of otherwise protected O-(imidazolethiocarbonyl)-derivatives.[17] 6-Deoxy-sucrose was prepared by hydrogenolysis of 6-S-(2-pyridyl)-6-thiosucrose, whereas 4-deoxy- and 3-deoxy-sucrose were obtained by radical reductions of thiocarbonyl derivatives.[18] Synthesis of, and the conformations adopted by, a variety of methyl β-D-galabiose analogues (1,4-α-linked disaccharides) modified in the non-reducing termini have been reported. These include the 2'-, 3'-, 4'- and 6'-deoxy-analogues, which were obtained by coupling methyl 2,3,6-tri-O-benzyl-β-D-galactopyranoside with glycosyl fluorides deoxygenated at C-3 (known), C-4 (obtained by reduction of a xanthate ester) or C-6 (from D-fucose), or with a D-galactal derivative using N-iodosuccinimide and deiodination of the product.[19] The synthesis of 3-deoxy-L-erythro-pentono-1,4-lactone, a new chiral building block, from ribitol is covered in Chapter 16.

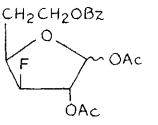
Radical reduction (with Bu_3SnH) of halogeno-sugars has featured in several deoxy-sugar syntheses. 4,6-Dideoxy-sucrose was obtained from 2,3,1',3',4',6'-hexa-O-benzoyl-6-deoxy-6-iodo-sucrose via chlorination (SO_2Cl_2) and reduction of the resulting 4-chloro-6-iodo-galactosucrose derivative. Its ability to inhibit various D-glucansucrases was compared with those of 3-, 4- and 6-deoxy-sucrose and 4-chloro-4-deoxy-D-galactosucrose. It was found that 6-deoxy-sucrose was a strong competitive inhibitor, but the conclusion was drawn that the hydroxy-groups at C-3 and C-4 of sucrose were important for binding.[20] 7-, 8- and 9-Deoxy- and 4,7-dideoxy-N-acetylneuraminic acids have been synthesised by radical reduction of the corresponding fully protected iodo-derivatives.[21] Their further conversion into deoxy-analogues of 2-deoxy-2,3-didehydro N-acetylneuraminic acid by introduction of a 2,3-double bond, and the topological features of these unsaturated analogues, and their behaviour as sialidase inhibitors, are covered in Chapter 13. The final step in the construction of the 4-epi-L-daunosamine-containing disaccharide (13) was radical deiodination of precursor (14), the synthesis of which is covered in Chapters 3 and 9.[22]



(13) X = H
(14) X = I



(15)

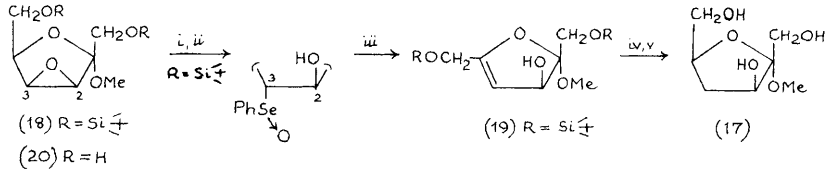


(16)

The 5-deoxy-fluoro-sugar derivatives (15) and (16) have been synthesised from D-glucose for incorporation into potential chemotherapeutic nucleosides.[23]

Improvements to Ogawa's method for the synthesis of 2-deoxy-β-glycosides, involving addition of arylsulphenyl esters of the desired aglycon to glycals, with

subsequent Raney nickel desulphurisation of the 2-arythio-products,[24] are covered in Chapter 3. The 4-deoxy-analogue (17) of methyl α-D-fructofuranoside was obtained either via selenide opening of the epoxide (18), selenoxide elimination to give alkene (19), and hydrogenation (Scheme 8), or directly by reduction ($LiAlH_4$) of the unprotected epoxide (20).[25]

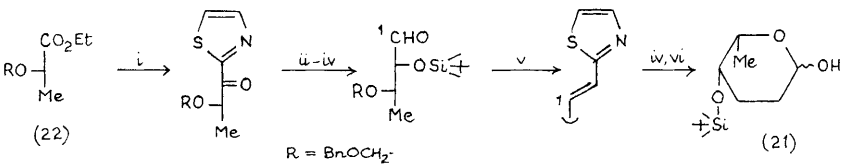


Reagents: i, PhSeNa; ii, H_2O_2; iii, $ClCH_2CH_2Cl$, Δ; iv, H_2, Pd/C; v, Bu_4NF

Scheme 8

A convenient synthesis of 5'-homoadenosine [i.e., 9-(5'-deoxy-β-D-ribo-hexofuranosyl)adenine] involved hydroboration of 3-O-benzoyl-5,6-dideoxy-1,2-O-isopropylidene-α-D-ribo-hex-5-enofuranose, obtained from diacetoneglucose.[26]

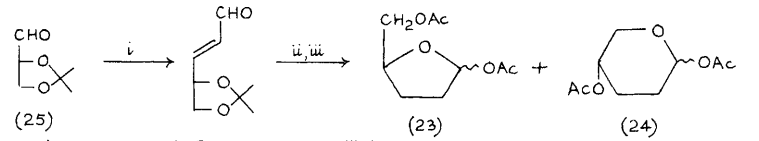
A number of deoxy-sugar syntheses have used non-carbohydrate starting materials. L-Rhodinose was obtained exclusively as its pyranose derivative (21) from ethyl (S)-lactate (22) using 2-lithiothiazole and 2-



Reagents: i, 2-Br-thiazole, BuLi; ii, $LiBu^s_3BH$; iii, $ClSiR_3$, imidazole; iv, MeI, then $NaBH_4$, then $HgCl_2$, H_2O; v, 2-$CH_2\overset{+}{P}Ph_3\bar{C}l$, $KOBu^t$; vi, H_2, Pd/C

Scheme 9

thiazolemethylenetriphenylphosphorane as masked aldehyde synthons (Scheme 9).[27] A separable mixture of the 2,3-dideoxy-D-pento-furanose and -pyranose diacetates (23) and (24), respectively, was obtained from 2,3-di-O-isopropylidene-D-

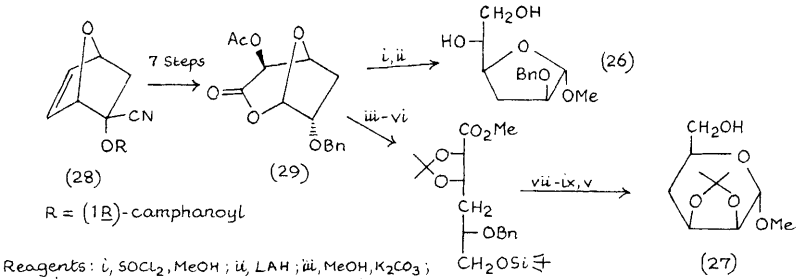


Reagents: i, Ph_3PCH_2CHO; ii, PtO_2, H_2, H_2O, HOAc; iii, Ac_2O-Py

Scheme 10

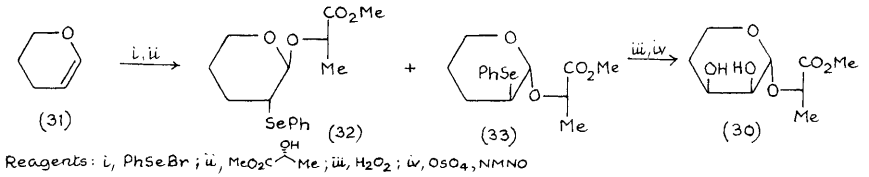
glyceraldehyde (25) (Scheme 10); they were required for use in the synthesis of

adenosine antagonists.[28] The 3-deoxy-D-arabino-hexofuranoside (26) and the 4-deoxy-D-lyxo-hexopyranoside (27) have been synthesised from the chiral Diels-Alder adduct (28) of furan with cyanovinyl (1R)-camphanate via the common intermediate



Scheme 11

(29) (Scheme 11).[29] Derivatives of 4-deoxy-D- and L-erythro-pentopyranoside, e.g. D-(30) (Scheme 12), are accessible from dihydropyran (31) via the easily separable diastereomeric phenylselenides (32) and (33).[30] Full details of the synthesis and



Scheme 12

enzymatic hydrolysis of a racemic 2,6-dideoxy-3,4-anhydro-sugar as part of the preparation of boivinosides (cf., Vol.18, p.128; Vol.20, p.134), have been published.[31] A study on the stereochemistry of epoxidation of Z,E-isomers of 1,1-dimethoxy-hex-3-en-5-ols and -4-en-3-ols, leading to all four possible dimethyl acetals of the 2,6-dideoxy-DL-hexoses, has been reported (cf., Vol.18, p.124; Vol.19, p.126),[32] and their configurations have been determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy.[33]

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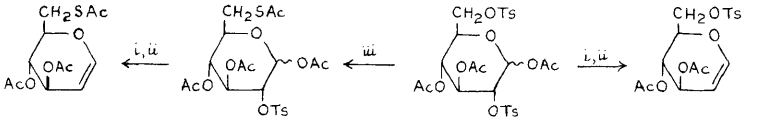
13
Unsaturated Derivatives

1 Glycals

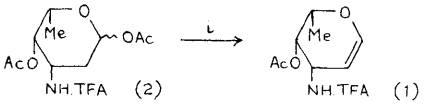
A study of the electrochemical reduction of tetra-O-acetyl-α-D-glucopyranosyl bromide in dipolar aprotic solvents with mercury electrodes to afford tri-O-acetyl-D-glucal has been reported.[1] A method for affording 6-functionalised D-glucal derivatives involves the use of tetra-O-acetyl-2,6-di-O-tosyl-D-glucopyranose as illustrated in Scheme 1.[2] The specific glycal derivative (1)



Reagents: i, HBr-HOAc ; ii, Zn-HOAc ; iii, KSAc-DMF

Scheme 1

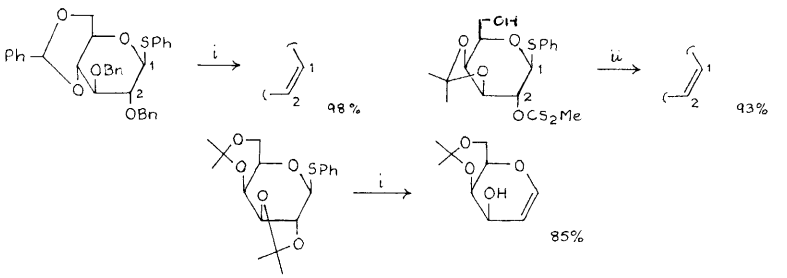
was produced from daunosamine via the substituted compound (2) as shown in Scheme 2.[3]



Reagents: i, Δ, xylene, silica gel

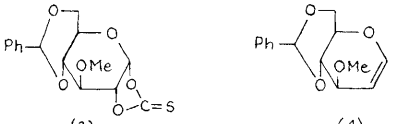
Scheme 2

Treatment of S-phenyl 1-thioglycoside derivatives, or their derived sulphones, with lithium naphthalamide in THF, affords the corresponding glycal derivatives in high yield, e.g. Scheme 3. The elimination can be carried out in the presence of acid- or base-labile protecting groups; in the latter cases deprotection occurs. A free radical induced synthesis was discovered in the same work, and is also illustrated in Scheme 3.[4,5] In related fashion, compound (3) afforded the glycal (4) on treatment with tributyltin hydride in the presence of a radical initiator.[6]

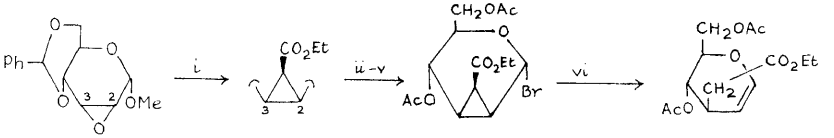


Reagents: i, Li naphthalenide ; ii, Bu_3SnH-AIBN

Scheme 3



A novel synthesis of a C-3-branched glycal derivative, by application of a cyclopropylmethyl radical ring-opening reaction, is illustrated in Scheme 4.[7]

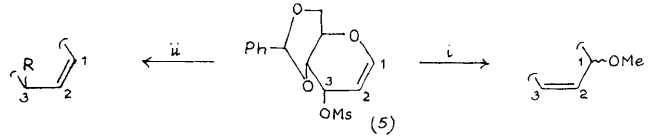


Reagents: i, $EtO_2CCH_2P(O)(OEt)_2$; ii, H_2-Pd/C ; iii, Ac_2O-Py ; iv, Ac_2O-H^+ ; v, Me_3SiBr ; vi, Bu_3SnH, AIBN

Scheme 4

An improved procedure for making O-benzylated glycal derivatives from acetylated analogues on the molar scale and without isolation of the unsubstituted derivatives and without chromatography has been reported. Tri-O-benzyl-D-glucal was obtained directly in 70% yield and other pentose and hexose analogues were similarly produced.[8] Selective acetylation of D-glucal using vinyl acetate as a source and a Candida lipase gave the 6-ester in 90% yield, whereas a Pseudomonas enzyme gave the 3,6-diacetate in 92% yield. Conversely, the latter catalyst afforded the 4,6-diester when used to cleave tri-O-acetyl-D-glucal. Similar studies were carried out in the D-galactal series and also with vinyl benzoate. In this way, selective procedures were developed and, for example, a route to 3-O-acetyl-6-O-benzoyl-D-glucal was reported.[9]

Treatment of the allylic mesylate (5) with various alkyl or alkynyl Grignard reagents gave mainly the products of direct displacement, whereas methylmagnesium bromide afforded the α,β-products of S_N2' reaction (Scheme 5). Lithium dimethylcuprate, on

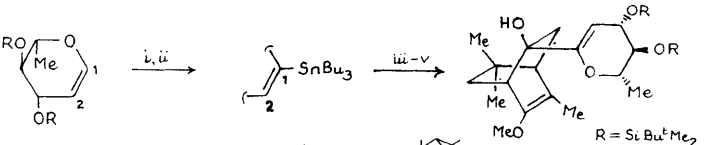


Reagents: i, MeMgBr; ii, RMgBr (R = Alkyl (except Me) or alkynyl)

Scheme 5

the other hand, reacted in the former way to give the C-3-methylglycal. These observations were rationalised in terms of HSAB theory.[10]

A different type of C-substitution of a glycal derivative is illustrated in Scheme 6. It was found not to be applicable to

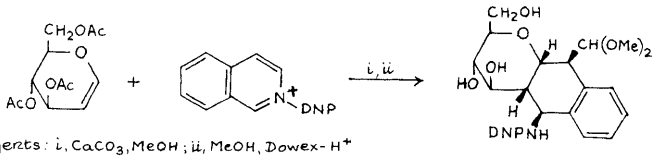


Reagents: i, KOBut; ii, Bu_3SnCl; iii, BuLi; iv, $CeCl_3$; v,

Scheme 6

several other glycals, and the product did not undergo oxy-Cope rearrangement as did the analogue with an unsubstituted dihydropyran ring.[11]

Reference is made in Chapters 13 and 24 to the synthesis of β-lactams by the addition of trichloroacetyl isocyanate to glycal derivatives followed by periodate cleavage of the sugar rings, and bis(trichloroethyl)azodicarboxylate adds to such compounds to afford a route to 2-amino-2-deoxyglycosides (Chapter 9). A novel cycloaddition reaction is illustrated in Scheme 6A.[11A]

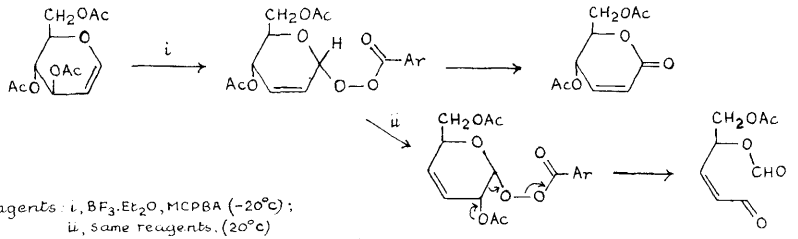


Reagents: i, $CaCO_3$, MeOH; ii, MeOH, Dowex-H^+

Scheme 6A

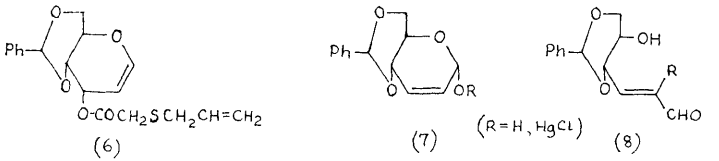
The allylic rearrangement reaction by which tri-O-acetyl-D-glucal affords 4,6-di-O-acetyl-2,3-dideoxy-D-erythro-hex-2-enose has been examined in detail; oxidation of the product, or of the

6-O-trityl analogue, gave the corresponding 2,3-unsaturated aldonolactones. A more direct and efficient method for making such unsaturated lactones involves low temperature treatment of glycal esters with small proportions of boron trifluoride etherate and 1.2 equivalents of m-chloroperbenzoic acid. A range of glycals were oxidised in this way with high efficiency, but if the reactions were conducted at room temperature or with more than 0.5 equivalents of catalyst, ring cleavage occurred and pentenal derivatives were formed following an allylic acetate rearrangement (Scheme 7).[13] Oxymercuration-demercuration of the D-allal

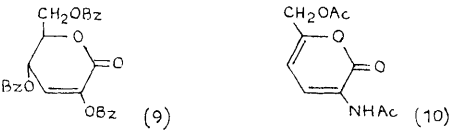


Scheme 7

derivative (6) in the presence of alcohols provides a new way of making unsaturated glycosides (7) together with the aldehydes (8).[14]



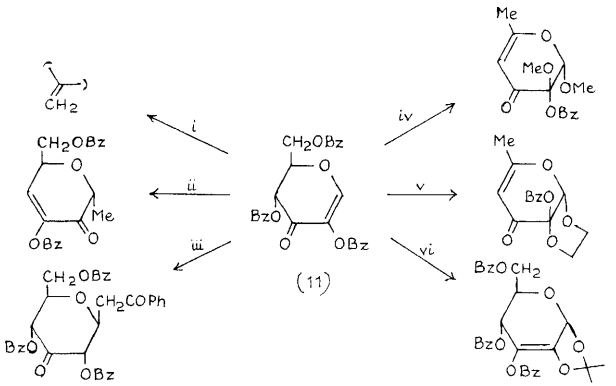
A simple route to 2-hydroxyglycal esters involves treatment of esterified glycosyl bromides with cesium fluoride,[15] and the reaction of such glycal derivatives with boron trifluoride etherate and m-chloroperbenzoic acid affords enones such as compound (9). The unusual pyranone (10) was obtained, however,



when 2-N-acetylamino-tri-O-acetyl-D-glucal was subjected to this reagent.[13]

Compound (11) and analogues (e.g. of maltose) are available from otherwise substituted 3-hydroxypyranoid compounds via the

derived 3-ulose derivatives. Some reactions of the dihydropyran are illustrated in Scheme 8.[16]

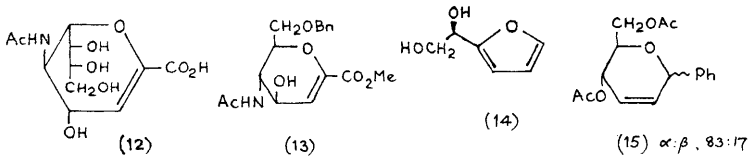


Reagents: i, CH_2Br_2, Zn-$TiCl_4$; ii, $LiMe_2Cu$; iii, $PhC(OTMS)=CH_2$, $ZnCl_2$; iv, K_2CO_3, MeOH, DMSO; v, K_2CO_3, DMSO; vi, $h\nu$ - Me_2CO

Scheme 8

1-Cyano-glycal and 1-cyano-hydroxylglycal derivatives have been produced by elimination reactions applied to the products of photobromination of esterified glycosyl cyanides, the reagents used were, respectively, zinc, pyridine and mercury(II) cyanide in nitrobenzene in the presence of silver triflate.[17]

7-, 8- and 9-Deoxy- and 4,7-dideoxy-analogues of the N-acetylneuraminic acid derivative (12) were made as potential sialidase inhibitors; results indicated that the 4-OH and 7-OH and a planar α-surface are important for enzymic recognition and binding.[18] The related compound (13) has been made by methoxycarbonylation of a 2,3-unsaturated phenylthioglycoside derivative (Chapter 16).

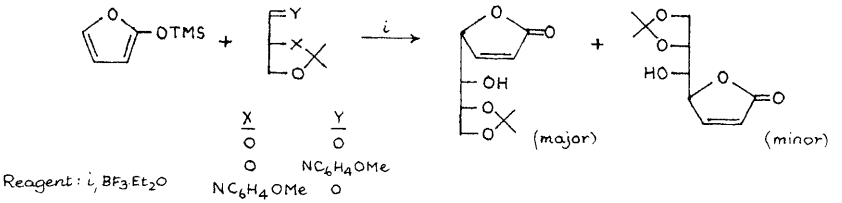


2 Other Unsaturated Derivatives

The uses of 2′,3′-cyclicthionocarbonates (with trimethyl phosphite), 2′,3′-cyclic orthoesters (heated with acetic anhydride) and 3′-O-acetyl-2′-bromo-2-deoxy derivatives (with zinc/copper) as

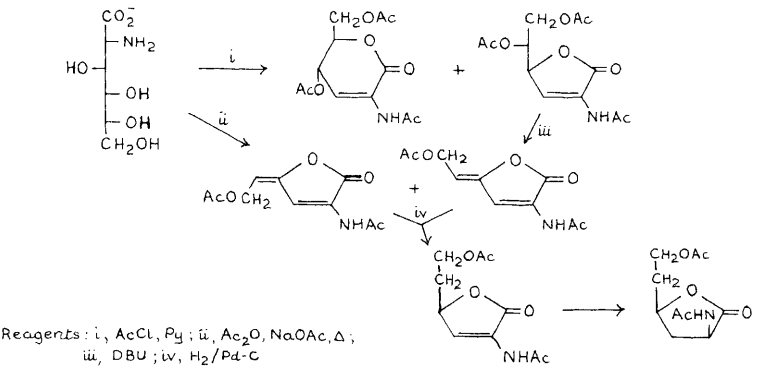
means of access to 2′-unsaturated nucleosides have been compared; the last of them was found to be most suitable.[19]

A novel synthesis of enantiomercially pure 2,3-dideoxyhept-2-enono-1,4-lactones is illustrated in Scheme 9,[20] and related



Scheme 9

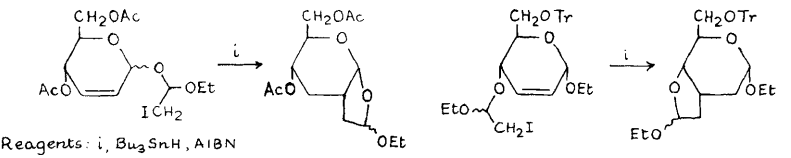
substances were obtained on acetylation of 2-amino-2-deoxy-D-gluconic acid (Scheme 10).[21]



Scheme 10

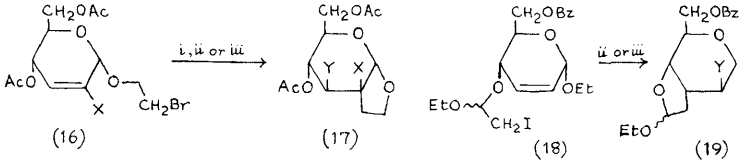
Ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside, on treatment with alkali followed by acid, gives the furan (**14**) in almost quantitative yield,[22] and the analogous glycosyl phenylsulphone affords access to the phenyl C-glycosides (**15**).[23]

Intramolecular cyclisations induced by free radicals have afforded stereospecific means of introducing branch-points at C-2 or C-3 of saturated pyranoid compounds via 2,3-unsaturated precursors (Scheme 11).[24] Related work showed these principles



Scheme 11

could be applied to give analogous products having oxygenated substituents at C-2 of the product's pyranoid ring and carbon-bonded substituents at C-2 and C-3 (Scheme 12).[25]

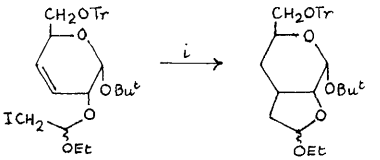


(16) (17) (18) (19)

Reagents: i, Bu_3SnH (16) X = H → (17) X, Y = H
(16) X = OAc → (17) X = OAc, Y = H
ii, Bu_3SnH, $MeO_2CCH=CH_2$ (16) or (18) X = H → (17) or (19) X = H, Y = $CH_2CH_2CO_2Me$
iii, Bu_3Sn (16) or (18) X = H → (17) or (19) X = H, Y = $CH_2CH=CH_2$

Scheme 12

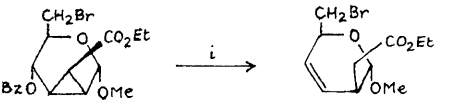
An analogous reaction has been applied to a 3-enopyranoside derivative (Scheme 13),[24] and a member of this class of compound



Reagents: i, Bu_3SnH, AIBN

Scheme 13

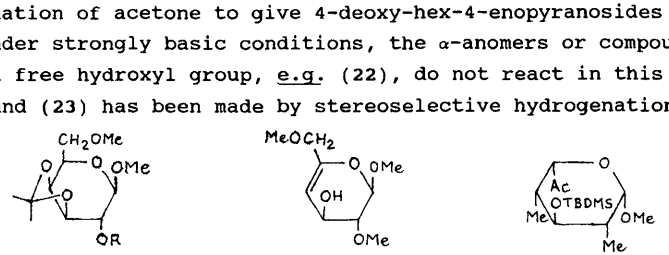
bearing a branching group at C-2 has been made by photochemical ring-opening of a 2,3-cyclopropa-substance (Scheme 14; cf. Scheme 4).[7]



Reagents: i, hν, N-methylcarbazole, $Mg(ClO_4)_2$

Scheme 14

Whereas β-D-galactopyranosides, e.g. (20), undergo elimination of acetone to give 4-deoxy-hex-4-enopyranosides (e.g. 21) under strongly basic conditions, the α-anomers or compounds with a free hydroxyl group, e.g. (22), do not react in this way.[26] Compound (23) has been made by stereoselective hydrogenation of a



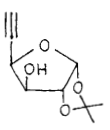
(20) R = Me
(22) R = H

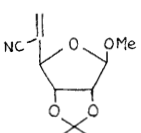
(21)

(23)

4-enoside in the course of the development of a synthesis of erythronolide B from 1,6-anhydro-β-D-glucopyranose.[27]

In the area of 5,6-unsaturated furanoid compounds, the alkyne (**24**) was made from 6-chloro-6-deoxy-1,2:3,5-di-O-isopropylidene D-galactose by treatment with lithiumamide in liquid ammonia,[28] and the 5-cyanoalkene (**25**) from the 6-nitroalkene by the addition of the elements of hydrogen cyanide and the removal of nitrous acid with triethylamine.[29] Application of the Claisen rearrangement (triethyl orthoacetate) to the enol (**26**) gave the octuronate epimers (**27**) in equal proportions, and the (Z)-starting material gave similar results. In the case of the analogous 3-hydroxy-D-ribo-alkenes, the E-isomer gave no stereoselectivity, but the Z-compound afforded the D-allo- and D-altro-5-C-vinyl octuronates in the ratio 7:1.[30]


(24)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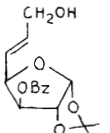
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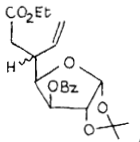
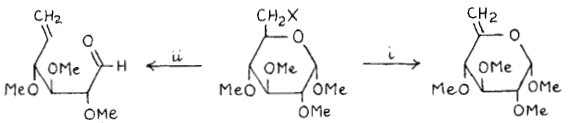

(27)

Methyl 6-bromo-6-deoxy-2,3,4-tri-O-methyl-α-D-glucopyranoside (or the chloro or iodo analogues) underwent loss of hydrogen halide to give the 6-deoxy-5-enoside (**28**) on treatment with potassium-graphite laminate, whereas reaction with zinc-silver couple-graphite caused attack at the halogen centre and ring opening (Scheme 15).[31] A lecture on the use of organometallic methods in carbohydrate synthesis included the description of the use of Tebbe's reagent to produce exo-alkenes related to (**28**) and hence C-linked disaccharides.[32] A further report described the conversion of trimethylsilylated aldonolactones into the difluoromethylene exo-alkenes and hence difluoromethyl C-glycosides (Chapter 3).



Reagents: i, C_8K; ii, Zn/Ag-C

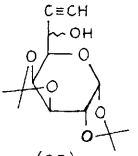
X = Br, Cl, I

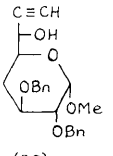
(28)

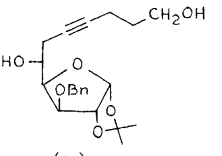
Scheme 15

Displacement reactions have been studied in the cases of the 7-ynes (**29**), and the Mitsunobu reaction of derived sulphonates was regio- and stereo-selective. The displacement of the tosyloxy

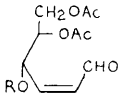
group by benzoate gave mixed products including allenic benzoates.[33] Synthesis of the 4-deoxy compound (30) was accomplished from the corresponding 6-aldehyde (by use of trimethylsilylacetylenemagnesium bromide) in connection with studies on the synthesis of amipurimycin A.[34] The extended chain alkyne (31) was made from the 5,6-D-gluco-epoxide by treatment with $LiC{\equiv}C(CH_2)_3OLi$ which is available by reacting tetrahydrofurfuryl chloride with lithium in liquid ammonia.[35]

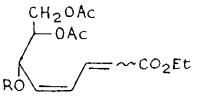

(29)

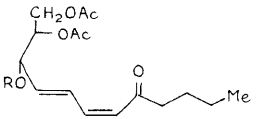

(30)


(31)

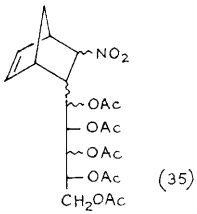
Treated with mercury(II) sulphate in aqueous dioxane followed by acetic anhydride and pyridine, D-lactal gave compound (32) which was chain extended to the two acyclic unsaturated compounds (33) and (34).[36] Other literature data suggest these


(32)


(33) R = Ac_4-β-D-Gal-p


(34)

should all be (E)-compounds. Several isomers of (35) were produced on Diels-Alder reaction of cyclopentadiene with penta-O-acetyl-2,3-dideoxy-1-nitro-D-gluco-, D-galacto- and D-manno-hept-2-enitol. Each was degraded to a nitrobornene-6-aldehyde, known isomers of which were obtained from isomers of (35) which had previously been characterised by X-ray diffraction analysis.[37]


(35)

Other acyclic unsaturated derivatives which have been used in the preparation of C-glycosidic compounds are noted in Chapter 3.

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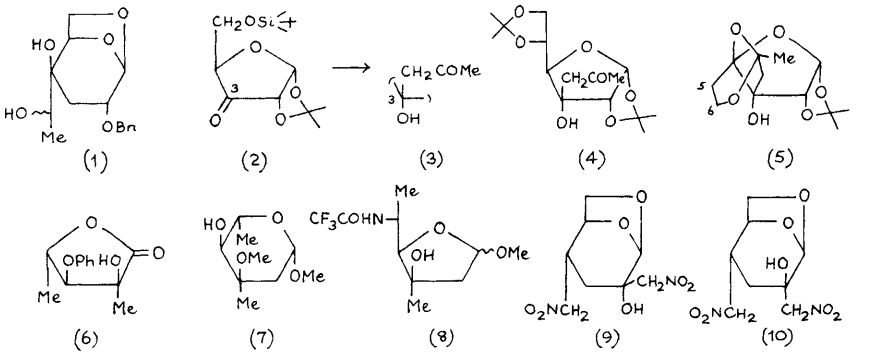
14
Branched-chain Sugars

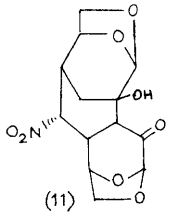
1 Compounds with an R-C-O- Branch

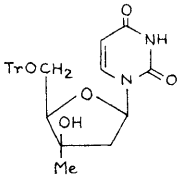
The diastereomers (1) as well as the compounds epimeric at C-4 have been prepared from levoglucosan as intermediate compounds for the total synthesis of isomers of yersinioses [3,6-dideoxy-4-C-(1-hydroxyethyl)-xylo-hexoses],[1] and the same group has reported such a synthesis.[2] The addition of acetone under basic conditions (K_2CO_3, H_2O) to ketone (2) affords a good yield of adduct (3), whereas with other bases or other active methylene compounds only complex mixtures were obtained. When the same conditions (K_2CO_3, H_2O, acetone) were applied to 1,2:5,6-di-O-isopropylidene-α-D-glucofuran-3-ulose only 15% of the adduct (4) was isolated along with 56% of the product (5) of rearrangement. A mechanism was proposed to explain the formation of (5).[3] The synthesis of methyl (2R,3S)-[3-$^2H_1$]-2-hydroxyisocaproate (+)-methoxy(trifluoromethyl)phenylacetyl ester from D-glucose is described in Chapter 24.

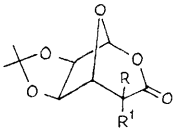


The lactone (6), prepared by a stereocontrolled aldol condensation followed by resolution of the enantiomers, has been converted into methyl cladinoside (7).[4] Some branched 5-amino-2,5,6-trideoxy-hexose derivatives (eg (8)) have been prepared from a 1,5-dideoxy-pent-2-ulose derivative.[5] Treatment of levoglucosenone with a basic excess of nitromethane has afforded products (9) and (10), whereas

when limited quantities of nitromethane were used another product (11) was obtained.[6] When 2'-O-tosyl-5'-O-trityluridine was allowed to react with a large excess of methylmagnesium iodide only a small amount of the expected product (12) was isolated as well as products of methyl incorporation in the base moiety.[7] 6-Deoxy-5-C-methyl-DL-ribo-hexofuranose and 5-C-methyl-DL-talo-hexofuranose

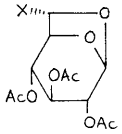

(11)

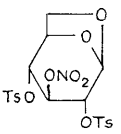

(12)

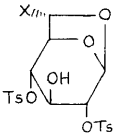

(13) R = Me, CH_2OBn; R^1 = Me
(14) R = R^1 = H

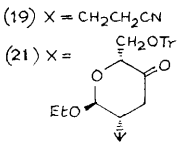
derivatives have been prepared by way of enolate alkylation products (13) of lactone (14).[8] The generation of alkoxy radicals from the corresponding nitrate esters of branched alcohol compounds is discussed in Chapter 7.

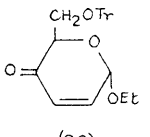
Adducts (15) and (16) were produced when bromide (17) was treated with tert-butyl isocyanide and allyltributyltin respectively. When the nitrate ester (18)


(15) X = CN
(16) X = $CH_2CH=CH_2$
(17) X = Br

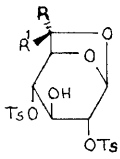

(18)

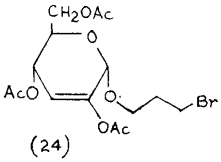



(19) X = CH_2CH_2CN
(21) X =


(20)

was allowed to react with Bu_3SnH in the presence of acrylonitrile the branched derivative (19) was obtained, and if acrylonitrile was replaced by enone (20) a moderate yield of (21) could be obtained. When the nitrate ester of alcohol (19) was then treated with Bu_3SnH the endo-substituted epimer (22) was obtained because of exo attack of the hydrogen atom. If the reaction was performed in the presence of acrylonitrile the principal product was the bis-alkylated adduct (23).[9]


(22) R = H, R^1 = CH_2CH_2CN
(23) R = R^1 = CH_2CH_2CN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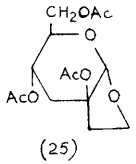

(25)

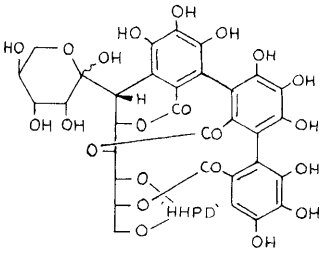
Radical cyclisation of bromoethylglycoside (24) leads to the bicycle (25).[10] The intramolecular photochemical cyclisation of a carbohydrate ketone onto the benzylic centre of a benzyl ether is covered in Chapter 5.

2 Compounds with an R-C-N Branch

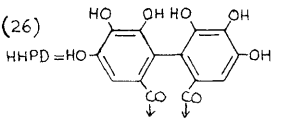
The four isomeric methyl 2,4,6-trideoxy-4-C-methyl-4-trifluoroacetamido-L-hexopyranosides (L-ribo-, L-arabino, L-xylo, and L-lyxo-) have been synthesised from L-threonine.[11] The synthesis of some branched-chain derivatives of daunosamine is discussed in Chapter 10. A new naturally occurring branched amino-sugar eremosamine is covered in Chapters 9 and 19.

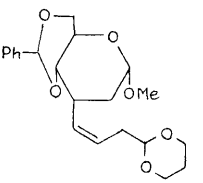
3 Compounds with an R-C-H, R-C-R or C=R Branch

Grandinin (26), a complex novel branched ketose derivative, has been isolated from



(26)

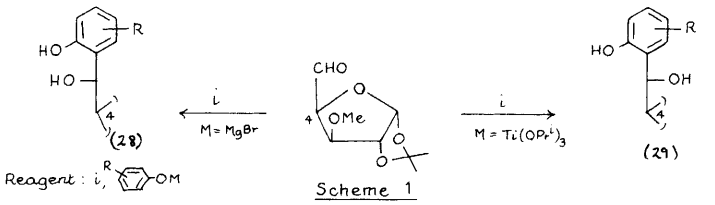




(27)

various plant sources.[12] The synthesis from D-glucose of olefin (27), a common intermediate for the synthesis of actinobolin, bactobolin, ramulosin and 6-hydroxy-ramulosin, has been described.[13] Some C-methyl and C-ethyl derivatives of methyl β-D-galactobioside have been used in a study of the binding between uropathogenic E. coli bacteria and human P erythrocytes.[14] Methyl 3-O-benzoyl-2,4,6-trideoxy-2,4-di-C-methyl-α-L-talopyranoside and 2,4,6-trideoxy-2,4-di-C-methyl-L-galactitol have been prepared starting from methyl 4,6-dideoxy-4-C-methyl-α-L-talopyranoside,[15] and methyl 4,6-dideoxy-4-C-methyl-α-L-mannopyranoside has been converted into methyl 2,4,6-trideoxy-2,4-di-C-methyl-α-L-gluco-, manno- and altro- pyranosides.[16,17]

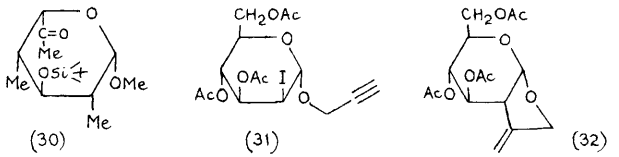
5-C-(2-Hydroxyaryl)-furanoses with either the D-gluco- (28) or L-ido- (29) configuration can be obtained from 1,2-O-isopropylidene-3-O-methyl-α-D-xylo-



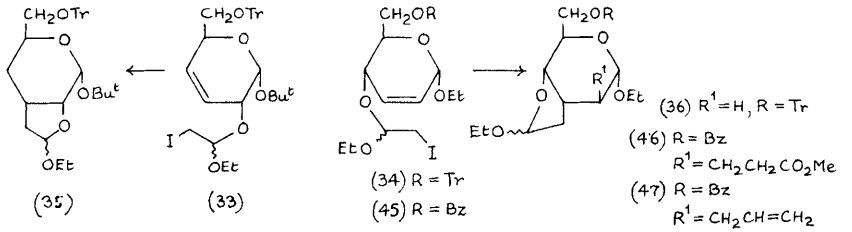
Scheme 1

pento-1,5-dialdofuranose (Scheme 1).[18] This procedure has been extended to other carbohydrate aldehydes.[18a] A general strategy for the synthesis of erythronolide B from levoglucosan has been outlined, and the synthesis of the branched heptose derivative (30) has been achieved.[19] A branched-chain derivative used in the synthesis of L-daunosamine and L-acosamine is covered in Chapter 9.

The stereoselectivity of intermolecular free radical reactions has been reviewed including the use of carbohydrate-based radicals for forming branched-chain sugars.[20] A number of intramolecular radical cyclisations affording C-branched compounds have been reported. A 2-deoxy-2-iodo-glycoside on treatment with Bu_3SnH affords a C-2 radical which may cyclise onto an appropriate functional

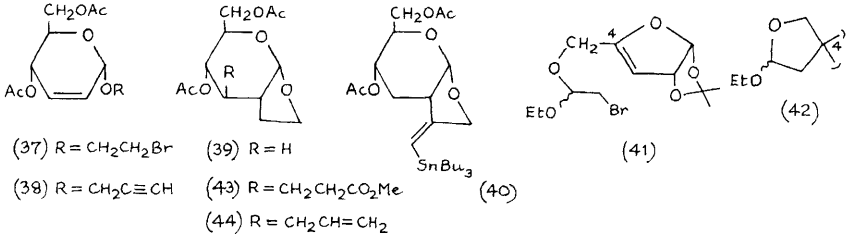


group on the aglycone. For example, iodide (31) gave the bicyclic adduct (32).[21] Radicals derived from haloacetal protecting groups may also cyclise onto an olefin.



Thus iodoacetals (33) and (34)afforded cyclised products (35) and (36), respectively, when treated with Bu_3SnH, and glycosides (37) and (38) under the same conditions gave the C-2 alkyl products (39) and (40), whereas the corresponding 3-bromopropyl glycoside afforded the product only of reduction of the aglycone.[22] Similarly the bromoacetal (41), with Bu_3SnH, gave the cyclic product (42) as the major stereoisomer at C-4.[23] Such cyclisations have also been performed in the presence

of intermolecular radical traps so that the initial radical produced on cyclisation may undergo reaction other than simple reduction. Treatment of bromoethyl glycoside (37) with Bu_3SnH in the presence of methyl acrylate or allyltributyltin

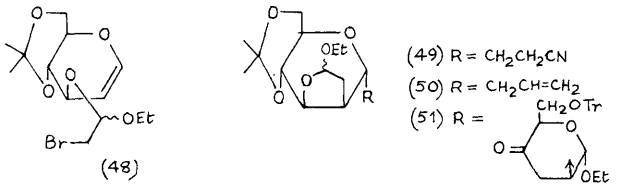


(37) R = CH_2CH_2Br (39) R = H (41) (42)

(38) R = $CH_2C{\equiv}CH$ (43) R = $CH_2CH_2CO_2Me$ (40)

(44) R = $CH_2CH{=}CH_2$

afforded the C-2, C-3 doubly branched derivatives (43) and (44) respectively. Similarly, iodoacetal (45) gave the doubly branched compounds (46) and (47),[10] and bromoacetal (48) gave rise to C-2 branched C-glycosides (49) and (50).



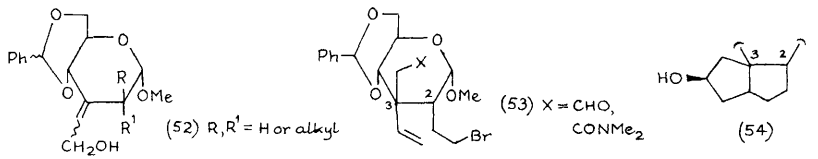
(48) (49) R = CH_2CH_2CN

(50) R = $CH_2CH{=}CH_2$

(51) R =

When enone (20) was used as the radical trap the adduct (51) was produced in good yield.[24] Radical cyclisations of some ω-iodo-aldehyde, nitrile, and α,β-unsaturated ester compounds is discussed in Chapter 24.

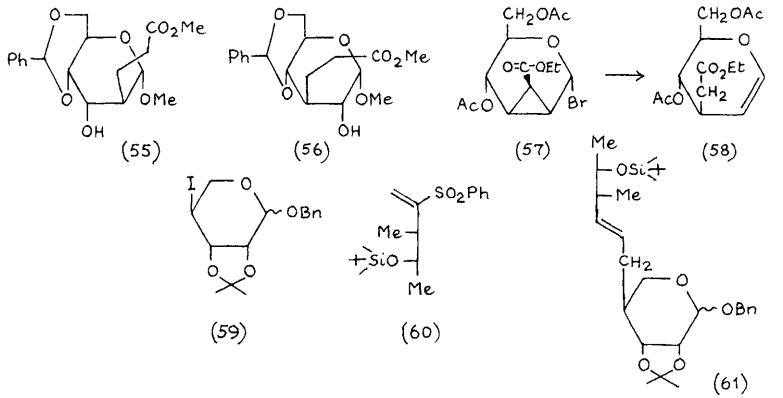
The stereochemistries of the Claisen rearrangement products of some compounds derived from allylic alcohols (52) have been studied.[25] These products were converted into derivatives [eg (53)] that were subjected to radical cyclisation



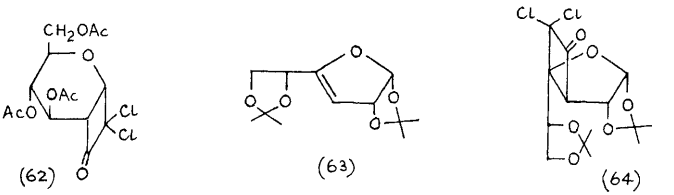
(52) R,R' = H or alkyl (53) X = CHO, $CONMe_2$ (54)

procedures as an approach to compounds bearing the diquinane carbon skeleton [eg (54)]. Many modifications of the process were described and the relative radical trapping characteristics of the -CHO, $-CONMe_2$ and -CN groups were evaluated.[26] Some radical cyclisations have been effected on carbohydrate derivatives with the aldehyde group as a radical acceptor. Moderate yields were generally obtained.[27]

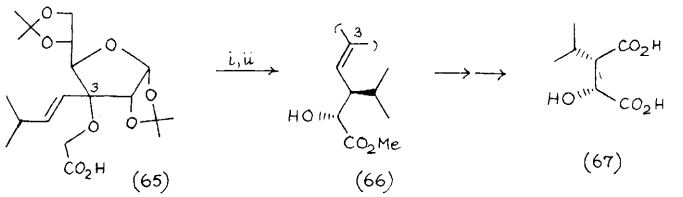
A novel procedure has been developed for the electrophilic opening of epoxides. Treatment of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside with Cp_2TiCl and excess of a radical trap such as methyl acrylate gave rise to branched products (55) and (56) as well as some products of elimination of water or methanol from the starting epoxide.[28] Radical reduction of the glycosyl bromide (57) is accompanied by rearrangement of the cyclopropylmethyl radical intermediate so that olefin (58) is the product obtained.[29] The C-4 radical derived from iodide (59) adds to the α,β-unsaturated sulphone (60) affording the undecose derivative (61).[30]



Full details on the periodate cleavage of the [2+2] cycloadducts of glycals and trichloroacetyl isocyanate have been published.[31] Dichloroketene undergoes [2+2] cyclo-additions to carbohydrate enol ethers affording the expected products. Thus, tri-O-acetyl-D-glucal gave adduct (62), and the hex-3-ene (63) gave rise to (64).[32]

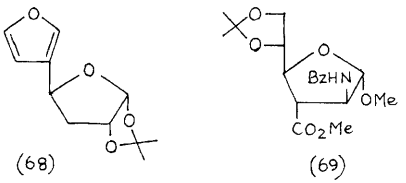


The stereoselectivity of the Claisen rearrangement undergone by some carbohydrate allylic alcohols in the presence of ethyl orthoacetate and ethyl orthopropionate has been studied.[33,34] A [2,3]-Wittig rearrangement on the carbohydrate template (65) gave olefin (66) (Scheme 2) which opened a new route to the 3-alkylmalic acid (67).[35]



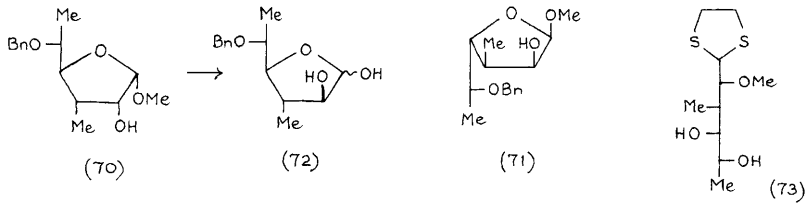
Scheme 2

The furyl-tetrahydrofuran (68) and its C-4 epimer were synthesised from 3-deoxy-1,2-O-isopropylidene α-D-erythro-pento-1,5-dialdofuranose and its C-4 epimer, and these products were proposed as convenient chiral precursors of furanoterpenes.[36] Some 2-amino-2-deoxy-3-C-branched D-manno- and D-altro-



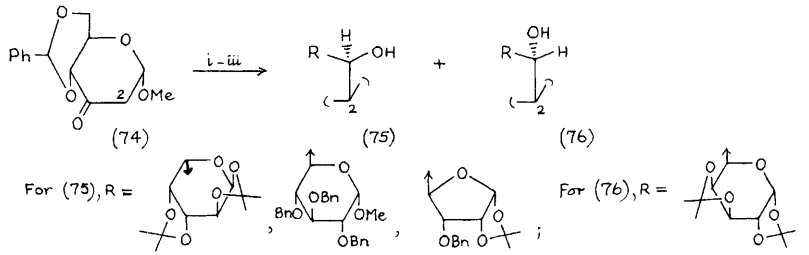
hexose derivatives, e.g. (69), have been synthesised from 2,3-O-isopropylidene-D-glyceraldehyde.[37] Some extension of earlier work (Vol. 20, p.148) on the base-promoted condensation of carbohydrate-derived dialdehydes with active methylene compounds has been published.[38]

A full account has appeared of work described earlier (Vol. 21, p.144) on the synthesis of methyl D- and L-3,6-dideoxy-3-C-methyl-hexofuranosides via a homoaldol reaction. [Two of these formulae, (92) and (94), in Vol. 21 should be transposed.][39] In an extension of this work the D-allo- and D-talo-furanosides (70) and (71) have been converted via displacement (CsOAc, DMSO) of the derived



triflate esters into the D-altro- and D-galacto-hexose derivatives (72) and (73), respectively. The latter compounds are intermediates used for the chiral synthesis of the rifamycin ansa chain.[40]

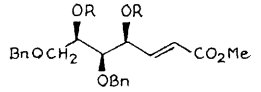
Aldol condensations with ketone (74) occur exclusively onto the β-face to give either adduct (75) or (76) (Scheme 3) depending on the complexing properties of



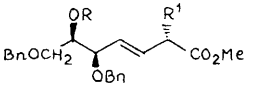
Scheme 3

the carbohydrate aldehydes RCHO.[41] The cross-aldolisation of a chiral enol silyl ether and 2,3-O-isopropylidene-D-glyceraldehyde leading to some octose derivatives is described in Chapter 2.

Treatment of the D-xylose-derived enonate (77) with $Me_2CuLi.BF_3$ afforded only the reductive elimination product (78), whereas the dimesylate (79) with the same reagent furnished the α-alkylated product (80). Similarly, use of $PrCu(CN)Li.BF_3$ and $BuCu(CN)Li.BF_3$ with enonate (79) afforded high yields of

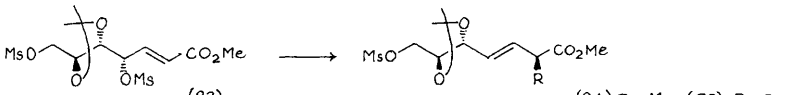


(77) R = Ac (79) R = Ms



(78) R^1 = H, R = Ac
(80) R^1 = Me, R = Ms
(81) R^1 = Pr, R = Ms
(82) R^1 = Bu, R = Ms

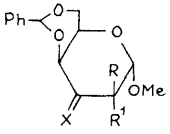
alkylated products (81) and (82), whereas the L-arabinose-derived enonate (83) with



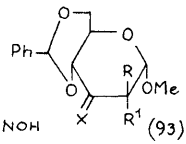
$MeCu(CN)Li.BF_3$ and $BuCu(CN)Li.BF_3$ gave alkylation products (84) and (85) respectively.[42] When 4,6-O-benzylidene-3-O-mesyl-D-allal was allowed to react with Grignard reagents (RMgBr, R = various alkyl and alkynyl groups) the corresponding 3-C-alkyl or alkynyl-4,6-O-benzylidene-3-deoxy-D-glucal was the major product except where R = Me when the nucleophile was incorporated at C-1. However, use of $MeMgBr/CuBr.SMe_2$ or Me_2CuLi with the above D-allal derivative afforded 4,6-O-benzylidene-3-deoxy-3-C-methyl-D-glucal.[43]

The gem-dimethyl compounds (86) and (87) were prepared by direct alkylation of the parent ketones (88) and (89), and the derived oximes (90) and (91)

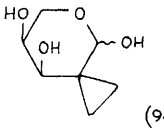
have been subjected to a cyclopalladation sequence (Na_2PdCl_6-NaOAc then $Pb(OAc)_4$-Py-$NaBH_4$) which selectively functionalised the equatorial methyl groups



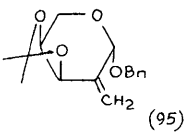
(86) R = R¹ = Me, X = O
(88) R = R¹ = H, X = O
(90) R = R¹ = Me, X = NOH
(92) R = Me, R¹ = CH_2OAc, X = NOH



(87) R = R¹ = Me, X = O
(89) R = R¹ = H, X = O
(91) R = R¹ = Me, X = NOH
(93) R = Me, R¹ = CH_2OAc, X = NOH



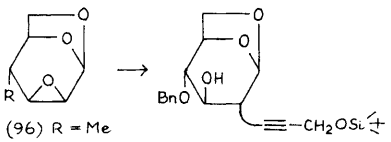
(94)



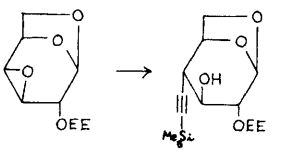
(95)

affording esters (92) and (93) respectively.[44] The 2-spirocyclopropyl-2-deoxy-L-erythro-pentose (94), a potential suicide inhibitor of β-galactosidase, has been prepared via dichlorocarbene addition to olefin (95).[45]

Treatment of epoxide (96) with $Et_2AlC{\equiv}CCH_2OSiMe_2{}^tBu$ afforded products with little selectivity between C-2 and C-3 attack by the nucleophile, whereas benzyl ether epoxide (97), under the same conditions, gave the C-2 branched compound (98) in quantitative yield. Similarly, when epoxide (99) was allowed to react with

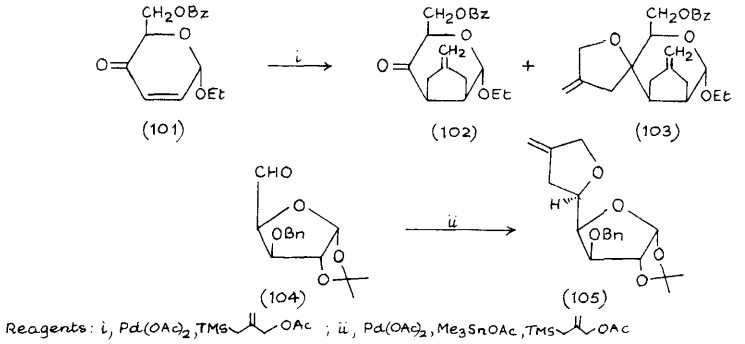


(96) R = Me
(97) R = OBn
(98)



(99)
(100)

$Et_2AlC{\equiv}CSiMe_3$ the expected trans-diaxial ring opening product (100) was produced in nearly quantitative yield.[46] The palladium-catalysed trimethylenemethane cycloaddition has been applied to the carbohydrate Michael acceptor (101) furnishing the cyclopentane adduct (102). In the presence of excess of reagent, the bis-adduct (103) was formed. This reaction may be extended to carbonyl compounds in general–particularly when an organotin co-catalyst is used. Thus aldehyde (104) gave stereospecifically the branched adduct (105) (Scheme 4).[47] The same cycloaddition reaction applied to α,β-unsaturated sulphones is discussed in Chapter 24.



Scheme 4

The coupling of an allylic organotin reagent with a carbohydrate aldehyde affording a branched higher sugar is mentioned in Chapter 17. The formation of 2',3'-dideoxy-3'-C-cyano-2'-substituted thymines is covered in Chapter 20, and the synthesis of blocked sugars bearing a terminal 1-cyanovinyl group is discussed in Chapter 10. The incorporation of an HCHO unit into an α,β-unsaturated lactone by the latter's reaction with hydroxylamine and formaldehyde is outlined in Chapter 16.

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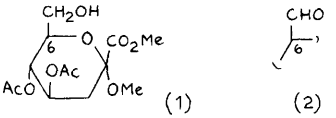
15
Aldosuloses, Dialdoses, and Diuloses

1 Aldosuloses

Optimum conditions for the electro-oxidation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose to the corresponding 3-ulose have been developed[1]. In a study of the hydration of methyl 4,6-O-benzylidene-2-bromo- and 2-chloro-2-deoxy-α- and β-D-xylo-hexopyranosid-3-ulose in acetone solution, only the β-D-xylo-derivatives were observed to hydrate[2] and in another investigation the isomeric composition of freshly prepared D-ribo-hexos-3-ulose in D_2O has been examined by ^1H-n.m.r. spectroscopy[3]. Full details have been published on the regioselective mono-oxidation of unprotected glycosides by reaction of O-stannyl derivatives with bromine[4].

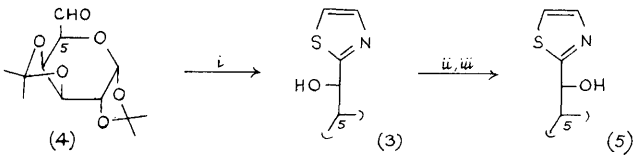


(1) (2)

Oxidation of alcohol (1) to the corresponding aldehyde (2) without subsequent elimination of acetic acid can be achieved by photolysis of the corresponding pyruvoyl ester[5]. Some aldol condensations between a sugar ketone and some chiral aldehydes are mentioned in Chapter 14.

2 Dialdoses

The thiazole adduct (3) obtained from aldehyde (4) and 2-trimethylsilylthiazole, can be converted to the 6-epimer (5) by an oxidation-reduction sequence (Scheme 1),

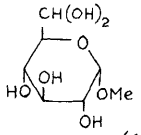


(4) (3) (5)

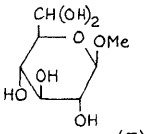
Reagents: i,  ; ii, $KMnO_4$; iii, K-Selectride

Scheme 1

and hydrolysis of adducts (3) and (5) illustrates the iterative chain extension of an aldehyde-sugar derivative[6]. A study of the hydrated dialdoses (6)-(8) has determined that the C-6 aldehydes are very electrophilic and that acetals, thioacetals and gem-diamines are easily made. Reduction of (6) with $NaBD_4$ afforded the (S)-alcohol, whereas (8) gave the corresponding (R)-isomer and (7)



(6)



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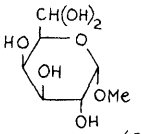
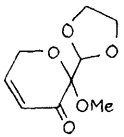


(8)

gave a 1:1 mixture of (R) and (S) alcohols[7]. The coupling of a carbohydrate organotin derivative with a sugar aldehyde to produce higher sugars is covered in Chapters 14 and 17, and the synthesis of a higher carbon acetylenic sugar from a dialdose derivative is discussed in Chapter 13. The arylation of a sugar aldehyde to give 5-C-(2-hydroxyaryl)-xylofuranoses is referred to in Chapter 14.

3 Diuloses

A racemic synthesis of the ethylene acetal derivative (9) of cortalcerone has been achieved[8].



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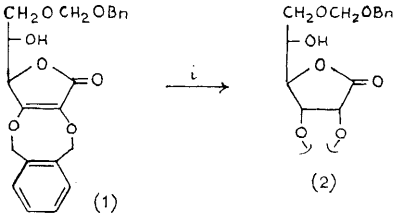
16
Sugar Acids and Lactones

1 Aldonic and Aldaric Acids

A review has appeared on carbohydrate-containing amphiphiles with amide linkages, these compounds being prepared by reaction of aldonolactones of glucose or maltose with alkylamines or by interaction of *N*-(2-aminoethyl) aldonamides with C_6-C_{20} alkanoic acids.[1]

An improved procedure has been reported for the conversion of calcium D-gluconate into D-glucono-1,5-lactone under acidic conditions,[2] whilst cellobiono-1,5-lactone can be obtained by electrochemical oxidation of cellobiose or by lactonization of calcium cellobionate over a strong-acid cation exchange resin.[3] The oxidation of D-lyxose by reaction with various metal ions gives mainly lyxonic acid.[4]



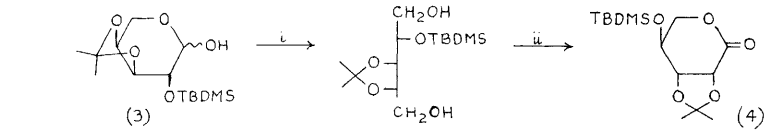
Reagents: i, Rh(Diphos-4)(NBD)BF_4, H_2, CH_2Cl_2

Scheme 1

L-Ascorbic acid can be easily converted into (1) (Scheme 1); hydroxyl-directed homogeneous hydrogenation of (1) gave (2), which could be deprotected to L-talono-1,4-lactone by catalytic hydrogenolysis.[5] A way of effecting exchange of functionality between C-1 and C-5 of aldopentoses relies upon the regioselective oxidation of acyclic 1,5-diols in which one hydroxyl group is sterically hindered; the method is illustrated in Scheme 2 by the conversion of the L-arabinose derivative (3) into the L-lyxono-1,5-lactone (4), and similar chemistry was used to interconvert L- and D-ribose derivatives.[6]

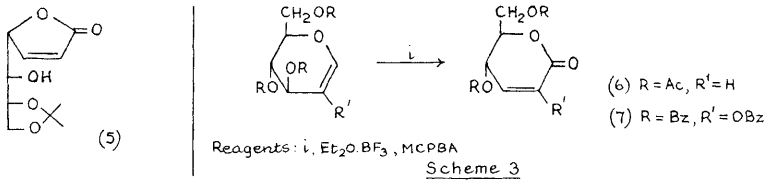
The 2,3-dideoxy-hept-2-enono-1,4-lactone (5) was obtained as the major product from the BF_3-catalysed reaction of isopropylidene-D-glyceraldehyde and 2-trimethylsilyloxyfuran.[7] A simple and generally applicable one-pot procedure for the preparation of pyranoid 2-enonolactones and enol lactones

from glycal and hydroxyglycal esters is illustrated in Scheme 3 by the formation of (6) and (7) in 84% and 91% yield respectively.[8]



Reagents: i, $NaBH_4$; ii, $RuH_2(PPh_3)_2$, Ph–C(=O)–Me

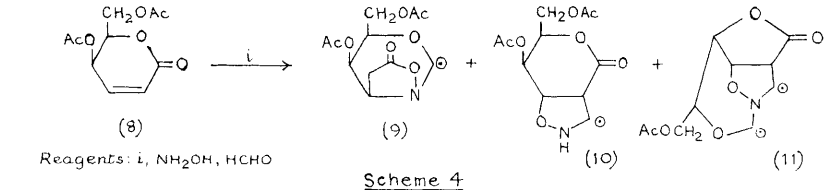
Scheme 2



Reagents: i, $Et_2O.BF_3$, MCPBA

Scheme 3

When the racemic unsaturated lactone (8) (Scheme 4) was allowed to react with hydroxylamine and formaldehyde, the Michael adduct (9) was formed at lower temperatures, whilst the nitrone cycloadduct (10) and its rearrangement product (11) predominated at higher temperatures; methylene groups originating from formaldehyde are indicated in the formulae. The structure of (11) was secured by X-ray crystallography.[9]



Reagents: i, NH_2OH, HCHO

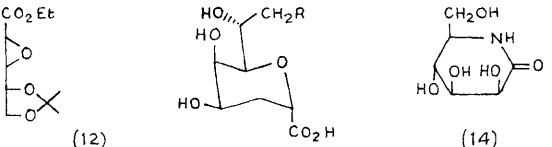
Scheme 4

The anhydroribonic acid derivative (12) has been prepared from isopropylidene-D-glyceraldehyde.[10] Several 8-substituted analogues (13) of 2-deoxy-β-KDO have been prepared and shown to be inhibitors of CMP-KDO synthetase, although they did not display antibacterial activity.[11] A number of similar 2-deoxy compounds are discussed together with their ulosonic analogues in the next section.

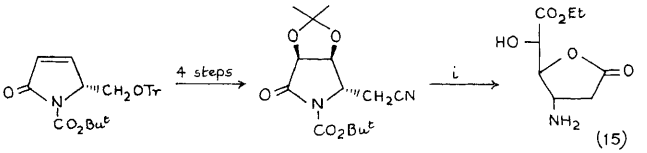
A full account has been given of the synthesis of D-mannonolactam (14) from L-gulonolactone (see Vol. 22, p. 94).[12]

A pyroglutamate derivative has been converted as outlined in Scheme 5 into the amino-substituted aldaric lactone (15).[13] A paper on the formation of unsaturated lactones of 2-amino-2-deoxy-D-gluconic acid is discussed in

Chapter 13, and some anhydroaldonic acids which can be regarded as *C*-glycosides are mentioned in Chapter 3.



(12) (13) R = H, F, NH_2 (14)

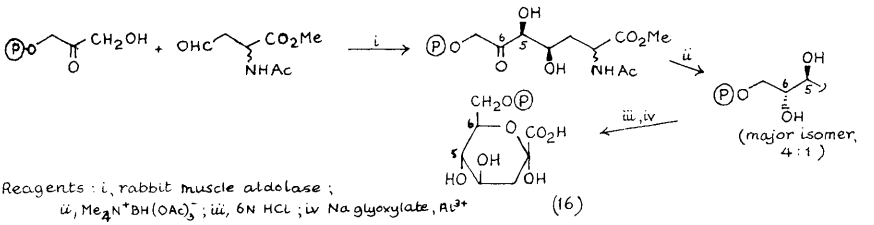


Reagents : i, HCl, EtOH

Scheme 5

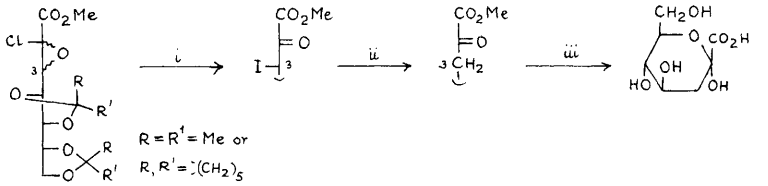
2 Ulosonic and Ulosaric Acids

As part of a major review of enzymic synthesis of carbohydrates, Whitesides and coworkers have discussed the current situation regarding enzyme-catalysed syntheses of 3-deoxyulosonic acids.[14] The same group have described the combined enzymatic-chemical route to 3-deoxy-D-*arabino*-heptulosonic acid-7-phosphate (DAHP,16) outlined in Scheme 6.[15]



Reagents : i, rabbit muscle aldolase ; ii, $Me_4N^+BH(OAc)_3^-$; iii, 6N HCl ; iv Na glyoxylate, Al^{3+} (16)

Scheme 6

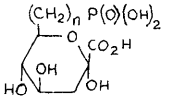


Reagents: i, MgI_2 ; ii, $NaHSO_3$; iii, H^+

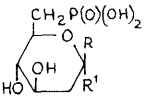
Scheme 7

A chemical route to the non-phosphorylated heptulosonic acid is indicated in Scheme 7.[16,17] The phosphonate analogues (17) and (18) of DAHP(16) have been synthesized, along with the analogues (19) and (20)

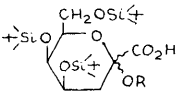
of 2-deoxy-DAHP, and these compounds were evaluated as inhibitors of dehydroquinate synthase from *Pisum sativum*; (17) and (20) proved inhibitory, but (18) and (19) did not.[18,19] Knowles and coworkers have independently reported routes to (17) and (18), together with the corresponding carbocyclic analogues,[20] and to 2-deoxy-α-DAHP and its carbocyclic analogue;[21] these compounds were used in elegant studies of the mechanism of dehydroquinate synthase from *E.coli*.



(17) n = 1
(18) n = 2

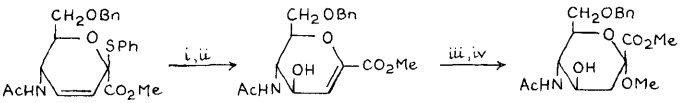


(19) R = CO_2H, R' = H
(20) R = H, R' = CO_2H



(21)

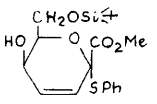
Methods previously used in the D-*arabino*-series (Vol. 22, p.17-18) have been applied to the synthesis of derivatives (21) of 3-deoxy-D-lyxo-heptulosonic acid.[22] Treatment of thioglycoside (22), prepared by acylation of a sulphur-stabilized C-1 carbanion as described previously for similar systems (Vol. 21, p.131-132), as indicated in Scheme 8 gave rise to the 4-acetamido-4-deoxy derivative (23) related to DAHP; a [2,3]-sigmatropic rearrangement of an allyl sulphoxide is the key to the synthesis, and similar chemistry applied to (24) gave 3-deoxy-D-*xylo*-heptulosonic acid systems.[23]



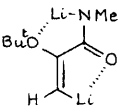
(22) (23)

Reagents: i, MCPBA; ii, Et_3N, MeOH; iii, $Hg(OCOCF_3)_2$, MeOH; iv, Ph_3SnH

Scheme 8



(24)



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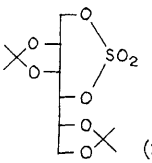
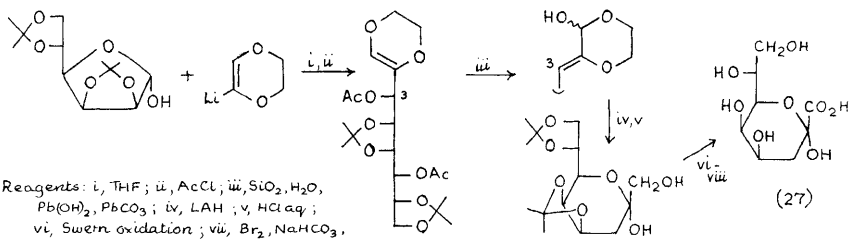


(26)

The synthesis of 3-deoxy-D-*manno*-2-octulosonic acid (KDO) and its derivatives continues to attract attention. The Cornforth-type synthesis of KDO from D-arabinose and oxaloacetic acid has been improved by the use of $NiCl_2$ to effect rapid decarboxylation, and similarly 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) could be made in high yield from D-mannose and oxaloacetate.[24] Schmidt and coworkers have given a full account of their route to KDO (Vol. 18, p.152), and also describe various *O*-acylated derivatives and

the *N*-methylamide.[25] The same group has reported a rather similar synthesis but using the simpler C_3-synthon (25); although the yield and *manno*-selectivity are not as high in the key addition to di-isopropylidene-aldehydo-D-arabinose, the subsequent manipulations to form KDO are considerably easier.[26] A synthesis of KDO reported this year is conceptually very similar to an earlier route (Vol. 21, p.156), involving the interaction of the cyclic sulphate (26) with the lithium derivative of 2-ethoxycarbonyl-1,3-dithiane to assemble the functionality of KDO.[27] A new '$C_6 + C_2$' synthesis of KDO (27) is outlined in Scheme 9,[28] and a further report has appeared on the use of α-silyloxy-phosphonate anions to effect the appropriate two-carbon extension of



Scheme 9

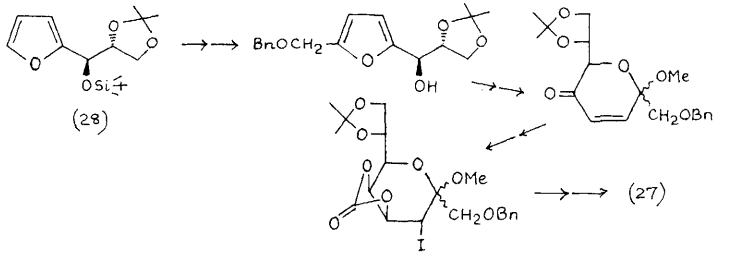
D-mannose derivatives. (see Vol. 22, p. 161).[29] A new stereoselective total synthesis of (+)-KDO (27) proceeds via the adduct (28) from 2-furyllithium and isopropylidene-D-glyceraldehyde (Scheme 10).[30] A full account has been given of a KDO synthesis by free-radical extension of a mannose derivative at C-6 (see Vol. 22, p. 162),[31] and there has been a further report on the preparation of 3-deoxy-L-*gulo*-2-octulosonic acid [the C-7 epimer of (27)] by similar methods to those previously used (see Vol. 22, p. 162).[32]

The reactions outlined in Scheme 11 have been used for extension of hexose and pentose derivatives at C-1 to give products which are derivatives of 2-ulosonic acids, but no way could be found to deprotect oxime (29).[33]

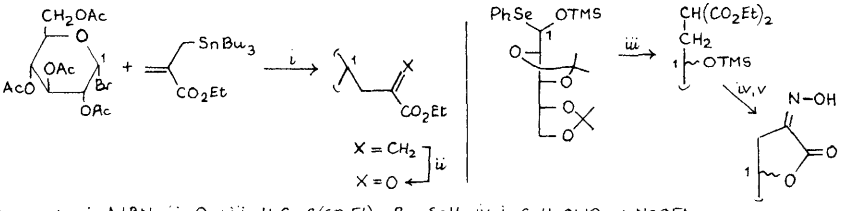
The 7-O-(α-D-galactopyranosyl) derivative of KDO has been isolated and characterized from the inner core region of the lipopolysaccharide of E.coli EH 100.[34]

A 3-diazo-oct-2,4-diulosonate is referred to in Chapter 10.

Further examples have been given of the use of acylneuraminate pyruvate lyase to catalyse the reaction of pyruvate with D-lyxose, 2-deoxy-D-*xylo*-hexose, D-glucose, D-xylose, 4-deoxy-D-*lyxo*-hexose and 2-azido-2-deoxy-D-mannose to give neuraminate analogues (see Vol. 21, p.161).[35] The formation of (30) from the reaction with 2-azido-2-deoxy-D-mannose has been described in more

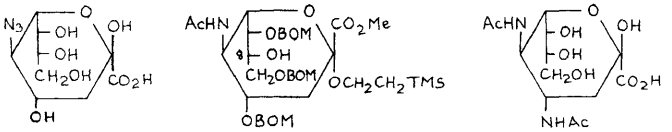


Scheme 10



Scheme 11

detail.[36] Various naturally-occurring acylated and *O*-methylated derivatives of *N*-acetylneuraminic acid (Neu*N*Ac) have also been made enzymically.[37] A number of derivatives of Neu*N*Ac, suitable for the preparation of Neu*N*Ac (2→8)Neu*N*Ac disaccharides, have been reported; the trimethylsilylethylglycoside (31) is typical.[38] Derivatives of 8-epi-Neu*N*Ac were also made by similar chemistry, inverting stereochemistry at C-8 by reaction of a mesylate with CsOAc/18-crown-6.[39] Other references to glycosides and oligosaccharides of Neu*N*Ac are given in Chapters 3 and 4.



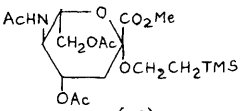
The 7-, 8-, and 9-deoxy-, and 4,7-didedeoxyderivatives of Neu*N*Ac have been prepared by treatment of the appropriate fully-protected iododerivatives with Bu_3SnH; [40] the side -chain conformations of these analogues were studied by n.m.r., and their substrate properties towards CMP-sialate synthase were determined. All were good substrates except for the 8-deoxyanalogue, and these findings could be correlated with side-chain shape (see Vol. 21, p.229 for earlier work with side-chain epimers).[41] The same series of deoxyanalogues of Neu*N*Ac were also converted into the corresponding

2,3-enes; the topographical features of these were determined, as was their behaviour as sialidase inhibitors in comparison with the 2,3-ene derivative of Neu*N*Ac itself. [42] The 4-acetamido-4-deoxy analogue (32) of Neu*N*Ac has been made by a double-inversion sequence, and this was also found to be activated by CMP-sialate synthase, in accordance with predictions. [43] Some fluoro analogues of Neu*N*Ac are mentioned in Chapter 8.

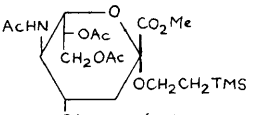
Periodate-borohydride degradation of partially-protected Neu*N*Ac derivatives was used to prepare truncated analogues of Neu*N*Ac such as (33)[44] and (34)[45] (i.e. derivatives of 5-acetamido-3,5-dideoxy-L-*arabino*-2-heptulosonic acid[44] and 5-acetamido-3,5-dideoxy-D-*galacto*-2-octulosonic acid[45]) suitable for use in the synthesis of modified sialonconjugates.

Routes have been developed for the synthesis of the 9-*O*-, 4-*O*-, 7-*O*-, and 7,8-di-*O*-acetylated derivatives of the 4-methylumbelliferyl-α-glycoside of KDN.[46] The synthesis of the α-glycoside itself is mentioned in Chapter 3, and an enzymic synthesis of 9-*O*-acetyl-Neu*N*Ac is discussed in Chapter 7.

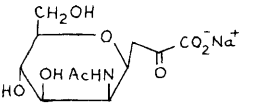
The α-Neu*N*Ac-(2→8)-α-Neu*N*Ac(2→3)- unit of ganglioside GD1b can form a spirocyclic lactone between the two sialosyl units in the presence of traces of acid, [47] whilst treatment of the ganglioside with DCC in DMSO gives a dilactone, the second lactone involving *O*-2 of the galactose residue to which the di-sialosyl unit is attached.[48]



(33)



(34)



(35)

The intermediate aldehydes produced from the sialosyl units of a glycoprotein by periodate treatment have been reductively aminated with glycine and cyanoborohydride. The resultant glycine-modified sialic acids were isolated by mild acid hydrolysis and characterised.[49] Reductive amination has also been used to bond KDO and Neu*N*Ac to 1,6-hexanediamine; the saccharide-1-(6-aminohexyl)amines obtained were converted to isothiocyanates and coupled to bovine serum albumin for immunological studies.[50]

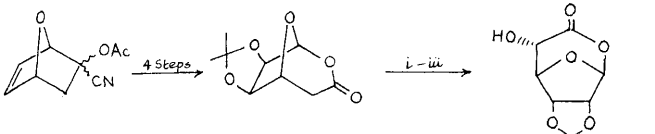
Heating of the sodium salt of Neu*N*Ac at 140° for 3h gave the crystalline anhydroderivative (35) in 53% yield.[51]

KDN has been shown to exist in its free form in the fertilised eggs of salmon.[52] Examination of the cell wall of the green alga *Tetraselmis striata* has revealed the presence of 3-deoxy-*lyxo*-2-heptulosaric acid [previously isolated from another source (Vol 22, p. 165)], and the 5-*O*-methyl ether of KDO, the first such methylated derivative found in nature, together with KDO itself.[53]

3 Uronic Acids

Enzymic oxidation of methyl α- or β-D-galactopyranoside to the corresponding aldehydes using galactose oxidase, followed by chemical oxidation with O_2/Pt-C gives high yields of methyl α- and β-*O*-galactopyranosiduronic acids.[54] The use of *O*-levulinoyl esters as protecting groups has been advocated during chromate oxidation to form uronic acid derivatives, since this group is not prone to migration. It was also reported that fully protected 6-*O*-monomethoxytrityl sugars could be converted directly by Jones reagent into uronic acid derivatives.[55]

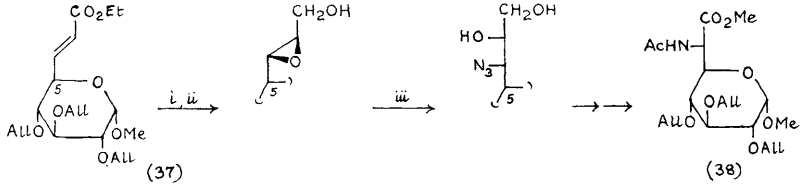
A 'naked-sugar' approach has been used (Scheme 12) to prepare the racemic allofuranuronosyl 6,1-lactone (36) from the Diels-Alder adduct of furan and α-acetoxyacrylonitrile.[56]



Reagents: i, LDA ; ii, TMSCl ; iii, MCPBA (36)

Scheme 12

The unsaturated ester (37) was converted into the α-aminoacyl glycoside (38) as indicated in Scheme 13.[57] Use of unsaturated esters of type (37) for the formation of higher sugars via hydroxylation is described in Chapter 2.

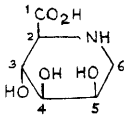


Reagents : i, DIBAL ; ii, Bu^tOOH, $Ti(OPr^i)_4$, (−)-diisopropyl tartrate ; iii, $Ti(N_3)_2(OPr^i)_2$

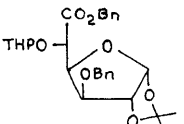
Scheme 13

An improved route has been developed for the synthesis of the iminomannuronic acid (39) (see vol. 21, p. 176), in which a protected 6-azido-6-deoxy-D-glucofuranose is reduced and cyclized onto C-2 with inversion of configuration (glucose carbons indicated).[58]

The glucuronic acid derivative (40) was prepared by treating the 6,3-lactone with BaO, $Ba(OH)_2$ and benzyl bromide in DMF, whereby both lactone opening and ether formation occurred in situ.[59]

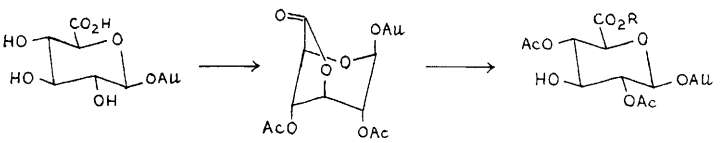


(39)



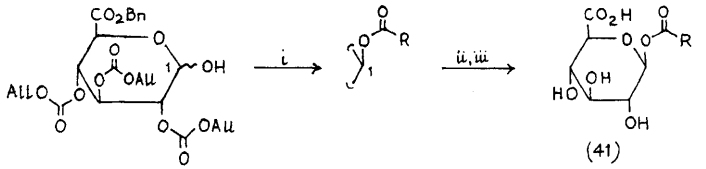
(40)

When alkyl hexopyranosiduronates are treated with acetic anhydride, per-acetylated uronolactones are formed, which undergo selective alcoholysis giving uronic esters with a free hydroxy group; the β-D-*gluco*-case of Scheme 14 is illustrative.[60]



Scheme 14

A new method has been developed for the formation of 1-*O*-acyl-β-D-glucuronic acids (41), the metabolic conjugates of carboxylic acids, which are highly liable to undergo acyl migration to O-2 and/or hydrolysis at pH>8; the product is generated under very mild conditions as indicated in Scheme 15.[61]



(41)

Reagents: i, RCO_2H, PPh_3, DEAD; ii, $Pd(PPh_3)_4$; iii, H_2, Pd/C

Scheme 15

Pre-column enzymic conversion to glucuronides was used to determine the enantiomeric purity of some novel chiral phenolic dopamine antagonists, using reversed-phase HPLC.[62]

Nucleosides of glycuronic acids are covered in Chapter 20.

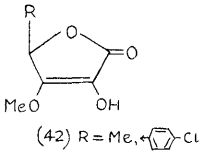
4 Ascorbic Acids

A report has appeared on the optimization of the conversion of D-glucose into ascorbic acid via di-*O*-isopropylidene-L-sorbose.[63]

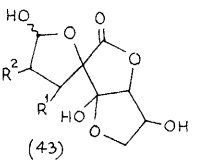
The antioxidant activity of isoascorbic acid has been reviewed.[64] The kinetics and mechanism of oxidation of L-ascorbic acid by ferricyanide in alkaline medium,[65] by Cu(II),[66] and by sodium perborate in perchloric acid[67] have been studied. L-Ascorbate was used as reducing agent in work on the

kinetics of reduction of potassium dichromate and pyridinium chlorochromate in acidic media,[68] and kinetics of electron-transfer from ascorbate to various Ru(III) species have been shown to exhibit a first-order dependence on both ascorbate and the oxidant, and an inverse first-order dependence on hydrogen ion concentration.[69] L-Ascorbic acid is stabilised against autoxidation by 3-alkyl-2-thiohydantoins, with the sulphur atom binding superoxide anion radicals and hydroxy radicals.[70]

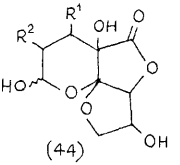
Further studies (see Vol. 22, p. 167) have been reported on the photo oxygenation of L-ascorbic acid derivatives, involving the reactions of 3-*O*-methyl-L-ascorbic acid and the analogues (42).[71]



(42) R = Me,

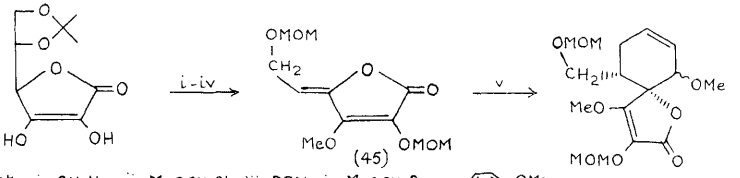


(43)



(44)

Interaction of ascorbic acids with α,β-unsaturated aldehydes has led to adducts of types (43) and (44).[72] The diene (45), accessible in four steps from 5,6-*O*-isopropylidene-L-ascorbic acid, undergoes cycloaddition with various electron-rich dienes, one example being indicated in Scheme 16. The resultant (racemic) spirocyclic lactones have the skeleton and key functionality of the 'top half' of chlorothricolide.[73]



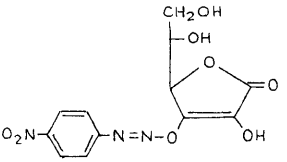
(45)

Reagents: i, CH_2N_2; ii, $MeOCH_2Cl$; iii, DBN; iv, $MeOCH_2Br$; v,

Scheme 16

Treatment of L-ascorbic acid with *p*-nitrophenyldiazonium tetrafluoroborate gives the diazoderivative (46).[74] It has been shown that the 3,4-enediol form of 2,3-diketogulono-δ-lactone is formed in about 10% yield from dehydroascorbic acid under nitrogen in neutral solution.[75]

8-*C*-Ascorbyl-(-)-epigalloylcatechin 3-*O*-gallate (47) has been isolated from commercial oolong tea.[76] In a study of the interaction of amines with ascorbigens, compounds (48) gave amides of type (49), which could be acetylated to give L-*xylo*-hex-3-ulosonamides (50) (Scheme 17).[77]
The ninhydrin-positive substance formed in the initial stages of the browning reaction between dehydroascorbic acid and glycyl leucine has been identified as *N*-[(2-nitrilo-2-deoxy-L-ascorbic acid) acetyl]leucine.[78] Similar



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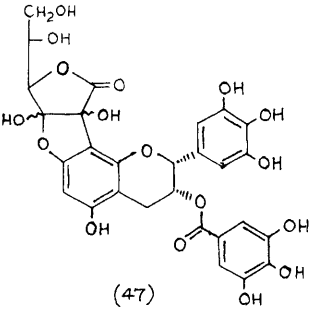

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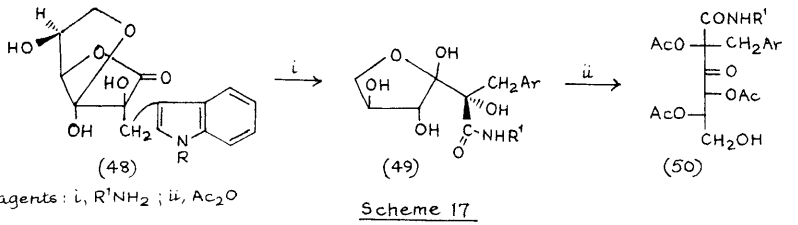

Reagents: i, R^1NH_2 ; ii, Ac_2O

Scheme 17

compounds can be obtained from other glycyl dipeptides, but non-glycyl dipeptides do not form such products.[79] Some other nitrogenous compounds derived from dehydroascorbic acid are mentioned in Chapter 9.

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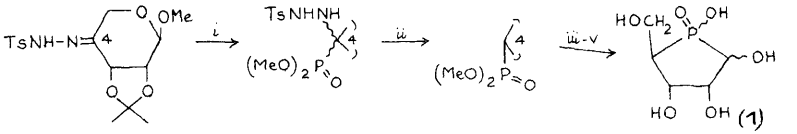
17
Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

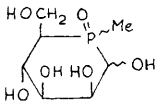
The D-ribofuranose derivative (1) with a hydroxyphosphinyl group in the hemiacetal ring has been synthesised (Scheme 1),[1,2] and the same group have described the



Reagents: i, $HP(O)(OMe)_2$, CF_3SO_3H; ii, $NaBH_4$, THF; iii, $NaH_2Al(OCH_2CH_2OMe)_2$; iv, HCl aq, PrOH; v, H_2O_2 aq

Scheme 1

preparation of xylopyranose derivatives with ethyl- and phenyl-phosphinyl and phenylphosphinothioyl units in the hemiacetal ring[3]. The methylphosphinyl analogues (2) of D-mannose have been synthesised and three isomers were isolated as their pentaacetates[4]. An improved approach to the hydroxyphosphinyl D-glucose analogue (3) has been reported[5]. A novel approach to racemic phenylphosphinyl tetrose derivatives (4) utilised the alkene (5) as starting material[6].



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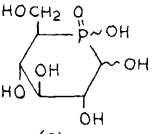
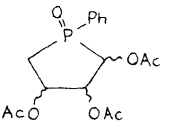


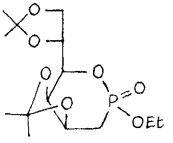
(3)



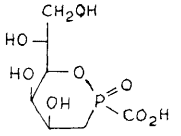
(±)(4)

(5)

The phosphonate (6) has been synthesised in an attempt to prepare analogue (7) of β-KDO, but several different attempts to effect the conversion of (6) into (7)

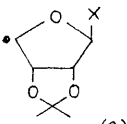


(6)



(7)

were unsuccessful[7]. Radicals, eg (8), have been shown to add to vinyl phosphonates giving rise to isosteric phosphonate analogues, eg (9), of nucleosides[8]. D-lyxose has been converted into the D-glyceric acid phosphonate isostere (10)[9], and the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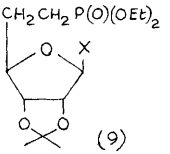
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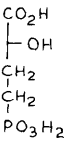
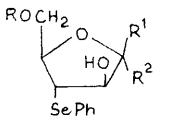

(10)

synthesis of some phosphonate analogues of 3-deoxy-D-arabino-heptulosonic acid is covered in Chapter 16. Some diphenylphosphinyl sugar derivatives have been converted into perchlorate complexes of rhodium and used as catalysts for the asymmetric hydrogenation of alkenes affording products with moderate optical yield[10].

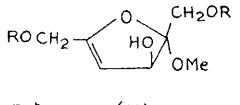
2 Other Carbon-bonded Derivatives

A review covering selenium and tellurium derivatives of carbohydrates has been published[11]. The selenium-containing D-fructose derivatives (11) and (12) were obtained from the corresponding 3,4-anhydro compounds, and then were mesylated to give exceptionally stable β-sulphonyloxyselenides that did not undergo elimination even at elevated temperatures. The former was oxidised to the selenoxide which underwent syn-elimination affording alkene (13)[12]. Treatment of glycal (14) with phenylselenyl triflate and an alcohol (R^1OH either a simple alcohol or another saccharide) afforded only α-glycosides (15), which after deselenylation with Bu_3SnH


R = $SiBu^tPh_2$

(11) $R^1 = CH_2OR$, $R^2 = OMe$

(12) $R^1 = OMe$, $R^2 = CH_2OR$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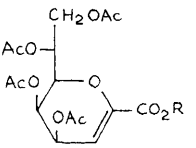
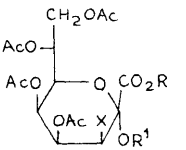
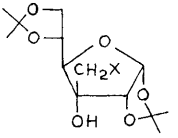

(14) R = Bu, Me


R = Bu, Me

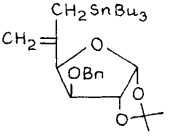
(15) X = SePh

(16) X = H

gave the α-glycosides (16) of KDO[13]. Addition of trimethyl-stannylmethyl lithium to 1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-ulose gave the branched chain derivative (17) which on treatment with iodine afforded the stannyl iodide (18)[14]. The stannylated derivative (19) has been utilised in a $TiCl_4$-catalysed coupling



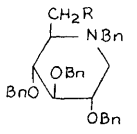
(17) X = $SnMe_3$
(18) X = $SnMe_2I$



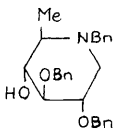
(19)

reaction with a carbohydrate aldehyde[15].

Reductive oxygenation ($NaBH_4$, O_2, DMF) of organomercurial (20) is known to afford alcohol (21) along with 5% of the by-product (22). If the reaction is performed with only a slow stream of air (rather than a vigorous flow of pure oxygen) the by-product (22) becomes the major product and is isolated in 68% yield. The radical (23) is postulated as an intermediate[16]. An oxymercuration-demercuration reaction of a D-allal derivative is mentioned in Chapter 13. Addition of dimethylphenylsilylmethyl magnesium chloride to methyl 2,3,4-tri-O-benzyl-α-D-manno-1,6-dialdo-pyranoside afforded adduct (24) which was oxidised to the L-glycero-D-manno-heptopyranoside (25)[17].



(20) R = HgBr
(21) R = OH



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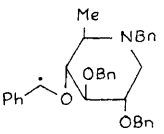
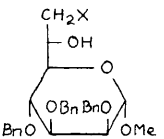


(23)



(24) X = $SiMe_2Ph$
(25) X = OH

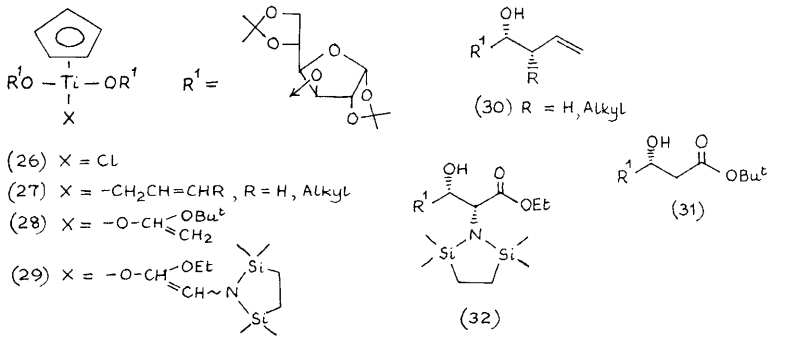
3 Oxygen-bonded Derivatives

The dimethylphosphinothioyl group [-P(S)Me_2] has been advocated for the protection of carbohydrate hydroxyl groups. Derivatives are formed from the alcohols by use of $Me_2P(S)Cl$ in the presence of DBU and are stable to moderately acidic or basic conditions. Cleavage is effected with $BnMe_3NOH$[18]. Some glucopyranosyl dimethylphosphinothiolate derivates treated with alcohols in the presence of iodine and catalytic trityl perchlorate, have afforded the β-glucopyranosides stereoselectively in good yields[19]. Treatment of 2,4-O-methylene-D-glucitol with phosphorus trichloride gave 2,4-O-methylene-D-glucitol-1,3:5,6-bis-O-(chlorophosphite)[20].

The interactions of boric acid or borate with shikimic and quinic acids in aqueous solutions have been studied by ^{11}B- and ^{13}C-n.m.r., with various species in

equilibria being identified[21]. In an extension of an earlier study the borate complexes in aqueous solution of D-allose, D-talose and D-psicose have been examined by ^{11}B- and ^{13}C-NMR. The spectra were used to determine the site and extent of chelation and showed that the sugars were complexed in the furanose form[22]. Similarly, ^{11}B-NMR spectroscopy has been used to study the complexation of borate ions with xylitol, ribitol and arabinitol in aqueous solution at high pH values[23]. A study by FAB Mass Spectrometry of the reaction of butaneboronic acid with eleven mono-saccharides is mentioned in Chapter 22.

Some organotin ethers of carbohydrate derivatives have been synthesised as potential pesticides[24,25] and the selected acylation of some cyclic dibutylstannylene compounds is discussed in Chapter 7. Treatment of cyclopentadienyltitanium trichloride with 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose affords adduct (26) which may be transformed into the chiral organometallic reagents (27)-(29). These react with aldehydes (RCHO) to give products (30)-(32), respectively, with high stereoselectivity[26-29].



Adducts of D-glucose and Zn(II) Cd(II) and Hg(II) ions of the form M(D-glucose)$X_2.H_2O$ (X = Br or Cl) have been isolated and characterised by FTIR, ^1H-NMR spectroscopy and molar conductivity measurements[30]. Association constants determined for the interactions of $CaCl_2$ and KCl with ribose, arabinose, lyxose, xylose, glucose, mannose, galactose, talose and allose in dilute water solutions by an electro-chemical method were distinctly smaller than those determined by NMR methods in more concentrated solutions[31]. The complexation of Cu(II), Ni(II) and Co(II) ions by D-galactosamine solutions has been studied by potentiometric and spectroscopic methods[32]. Complexes of Pb(II) and a number of carbohydrates have been isolated as solids and investigated by FTIR, ^1H- and ^{13}C-NMR methods, but no specific structures have been concluded[33]. Cobalt(III) complexes containing glycosylamines formed from ethylenediamine and aldoses (D-mannose, L-rhamnose or D-ribose) have been synthesised[34].

Potentiometric and spectroscopic studies have shown that D-galacturonic acid and D-glucuronic acid are effective ligands for oxovanadium(IV) ions[35]. The stoichiometry of the reduction of Fe^{3+} by D-galacturonic acid has been determined to be 4:1 (reduced Fe^{2+} : oxidised galacturonic acid)[36]. A full report has appeared on the study with ^{13}C-enriched D-glucose of the C-2 epimerisation of aldoses promoted by Ni(II) diamine complexes[37]. The alkali-metal cation complexes of a cyclic tetrasaccharide made up of peracetylated (1→6)-β-D-glucopyranosyl residues have been studied by ^1H-NMR spectroscopy in $(CD_3)_2CO$ and CD_3NO_2 solutions. The relative ligand affinities were in agreement with the ligand cavity size calculated from molecular models (3.3 Å)[38]. Copper(II) complexes of 1-thioglucoses are discussed in Chapter 11.

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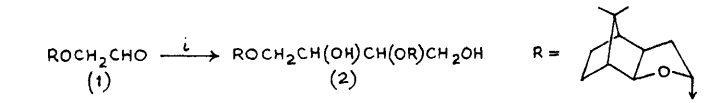
18
Alditols and Cyclitols

1 Alditols

1.1 Acyclic Alditols. - Chain-shortening of aldoses to the next lower alditol by decarbonylation has been accomplished by heating in N-methyl-2-pyrrolidinone in the presence of chloro(triphenylphosphine)rhodium (II).[1]

Asymmetric aldolysation of glycolaldehyde has been achieved using the asymmetric acetal derivative (1) with triethylamine or calcium hydroxide; the mixture of tetritol stereoisomers (2) obtained after borohydride reduction showed small stereoselectivities for L over D and erythro over threo isomers.[2]



Reagents: i, Et_3N or $Ca(OH)_2$; ii, $NaBH_4$

Scheme 1

Mono-O-hydroxyethyl-D-glucitol peracetates have been synthesized as reference compounds for the g.c.-m.s. analysis of hydrolysates of O-(hydroxyethyl)-starch and -cellulose.[3]

A crown ether incorporating one residue of D-mannitol has been used as an asymmetric coating for silica chromatography columns which allow baseline resolution of racemic phenylglycine.[4]

3-O-Hexosyl-D-arabinoses, prepared by Zemplen degradation of (1→4)linked aldonobiononitrile octabenzoates, have been reduced to the corresponding hexosyl-D-arabinitols to facilitate n.m.r. analysis.[5]

The selective cleavage of carbon-carbon bonds in sugars can be achieved under relatively mild hydrogenolytic conditions using a ruthenium complex catalyst; thus, besides D-mannitol and D-glucitol, D-fructose yielded up to 30% of glycerol.[6]

2-D N.m.r. techniques have been used to give a full assignment of ^1H and ^{13}C signals for mannitol hexaacetate.[7]

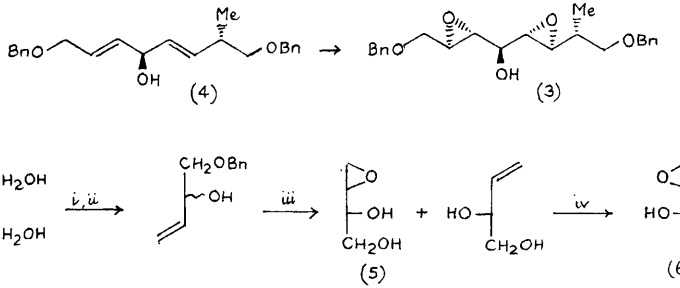
1.2 Anhydro-Alditols. - Unambiguous syntheses of 1,2-anhydro-3,4; 5,6-di-O-isopropylidene-D-glucitol and -D-mannitol from D-glucono-1,5-lactone have been described; the claimed stereospecificity of an

earlier synthesis of the latter is questioned.[8]

Microsynthesis of dianhydro-hexitols from 1,5- and 1,6- anhydro precursors has employed a tosylation procedure.[9]

2,5-Anhydro-derivatives of DL-ribitol and DL-arabinitol,[10] and 2,5:3,4-dianhydro-1-halo-1-deoxypentitols,[11] have been prepared from xylitol using tosyl intermediates, and another study of the cyclization of pentitols under tosylating conditions has been reported.[12]

The diepoxy branched-chain octitol (3) has been synthesized from the corresponding diene (4) by sequential Sharpless epoxidations with L- and then D-tartrate auxiliary.[13] Likewise, cis-butene-1,4-diol has been converted to the but-3-en-1,2-diol and hence, by Sharpless oxidation, to the isomeric epoxides (5) and (6) (Scheme 2).[14]



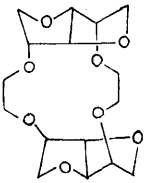
Reagents: i, $HgSO_4$, H_2SO_4, H_2O; ii, NaH, BnBr; iii, $Ti(OPr^i)_4$, Pr^i_2(-) tartrate, Bu^tO_2H; iv, as iii, but with (+) tartrate

Scheme 2

The rearrangement of epoxides formed by base-catalysed reactions of 2,6-dibromo-2,6-dideoxy-D-mannitol and -D-glucitol has been investigated; depending on conditions, dianhydro-sugars containing 3-or 5-membered anhydro-rings were obtained, together with D-glucitol or D-mannitol.[15] The solvolysis of 1,6-dibromo-1,6-dideoxy-galactitol, a cytostatic agent, has been studied; 3,6-anhydro-1-bromo-1-deoxy-DL-galactitol, which is biologically inactive, is readily formed.[16]

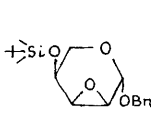
The alkylation of 1,4:3,6-dianhydro-D-mannitol with ethane-1,2-diol derivatives leads to compounds of interest as chiral complexing and phase transfer reagents, including the dimeric compound (7).[17,18]

The selective esterification of a 1,5-anhydro-D-galactitol is mentioned in Chapter 7, and a biguanido derivative of a 2,5-anhydro-hexitol is referred to in Chapter 9.

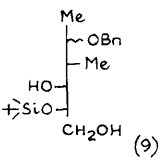


(7)

1.3 Branched-Chain Alditols. - Reaction of sugar oxiran derivatives with excess of trimethylaluminium yield branched-chain deoxy-alditol derivatives, e.g., (8) → (9), in an unusual ring opening, chain extension process. The conversion of the benzyl glycoside (10) to the alditols (11) was also described.[19]



(8)



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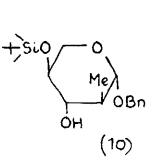

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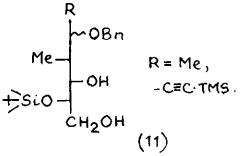
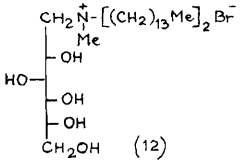


(11)

1.4 Amino-Alditols. - Diaminodideoxytetritols have been prepared by standard procedures from butene-diol, mannitol, and tartaronitrile precursors to give stereoisomers of 1,4- or 2,3-diamino compounds which were then complexed with platinum to give analogues of the anti-cancer drug cisplatin.[20]

The chiral quaternary salt (12) of 1-amino-1-deoxy-D-glucitol, derived from N-methyl-D-glucamine, has been used in conjunction with N-benzyloxycarbonylphenylalanylhistidine, a chiral active catalyst, to effect enantioselective hydrolysis of enantiomeric esters.[21]

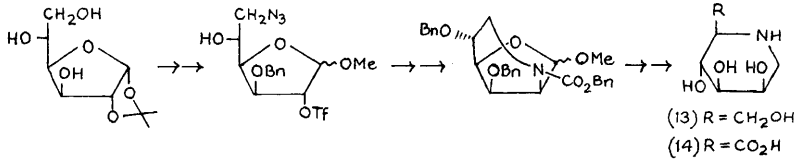


(12)

Oligosaccharide 1-deoxy-1-(4-trifluoroacetamidophenyl)amino-alditols can be oxidized to the corresponding reducing oligosaccharides with hydrogen peroxide, or to the corresponding 1-amino-1-deoxy-alditols with ceric ammonium nitrate.[22]

A 4-step synthesis of 1-deoxynojirimycin from L-sorbose has been described involving a 6-azido-L-sorbose intermediate which undergoes cyclization concomitantly with reduction to give the required compound.[23]

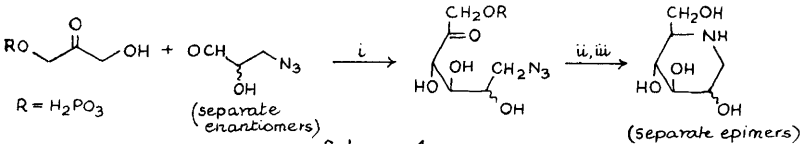
Full details of the synthesis of deoxymannojirimycin and D-mannonolactam from L-gulonolactone have been published (see Vol.22, p.94); the report includes syntheses of the L-enantiomers from D-gulonolactone.[24] New syntheses of deoxymannojirimycin (13) and the corresponding pipecolic acid (14) have been described (Scheme 3),



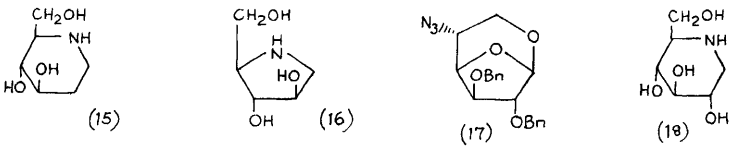
Scheme 3

a key improvement being efficient intramolecular displacement of the 2-triflate by the 6-amino group in both anomers.[25]

A combined enzymatic/chemical synthesis of imino-alditols used fructose 1,6-diphosphate aldolase to generate 6-azido-ketohexoses (as outlined in Scheme 4) which could be catalytically reduced to deoxynojirimycin and deoxymannojirimycin. By use of appropriate azido-aldehydes, fagomine(15) and 1,4-dideoxy-1,4-imino-D-arabinitol (16) were similarly prepared.[26] Microbial epimerization of 1-deoxynojirimycin to 1-deoxymannojirimycin has also been reported.[27]



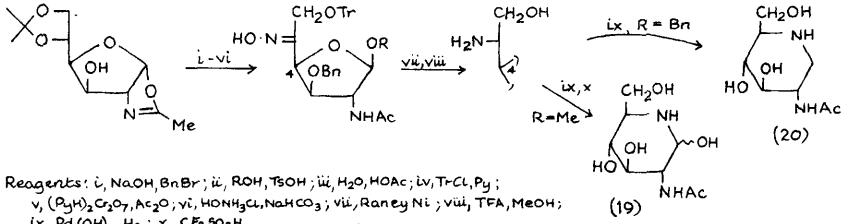
Scheme 4



A paper on the use of 1,6-anhydro-hexoses for oligosaccharide synthesis includes a conversion of 1,6-anhydro-2,3-di-O-benzyl-β-D-glucofuranose to the corresponding 5-azido-5-deoxy analogue (17) by a double inversion sequence, and hence to 1-deoxy-nojirimycin (18).[28] A synthesis of 2-acetamido-2-deoxynojirimycin (19) and its 1-deoxy analogue (20) utilizes the N-acetyl-D-glucosamine derivative (21) as outlined in Scheme 5.[29]

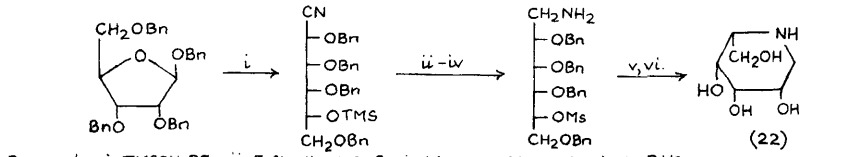
A synthesis of the L-talo isomer (22) of 1-deoxynojirimycin

utilizes a chain elongation procedure from D-ribose with cyanotrimethylsilane, as indicated in Scheme 6.[30]



Reagents: i, NaOH, BnBr; ii, ROH, TsOH; iii, H_2O, HOAc; iv, Tr-Cl, Py; v, $(PyH)_2Cr_2O_7$, Ac_2O; vi, $HONH_3Cl$, $NaHCO_3$; vii, Raney Ni; viii, TFA, MeOH; ix, $Pd(OH)_2$, H_2; x, CF_3SO_3H

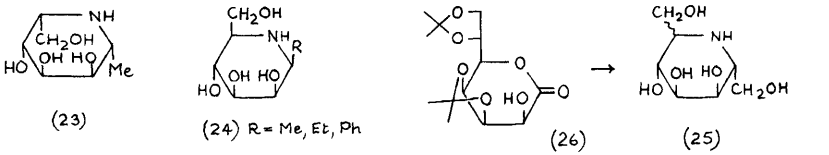
Scheme 5



Reagents: i, TMSCN, BF_3; ii, $FeCl_2$; iii, MsCl, Py; iv, LAH; v, NaOAc, EtOH; vi, H_2, Pd/C

Scheme 6

Fleet's group has reported syntheses of the nojirimycin analogues (23) and (24) from 5-azido-5-deoxy-hexono-ɣ-lactone precursors using organometallic reagents,[31] and of the 2,6-dideoxy-2,6-imino-heptitols (25) from the heptonolactone (26) derived from diacetone mannose by use of the Kiliani reaction. These imino-heptitol

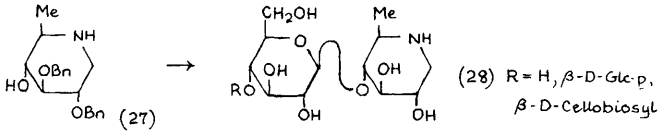


epimers show opposite selective inhibitory activity against α-fucosidase as against α-mannosidases; one inhibits the former, whilst the other inhibits the latter.[32]

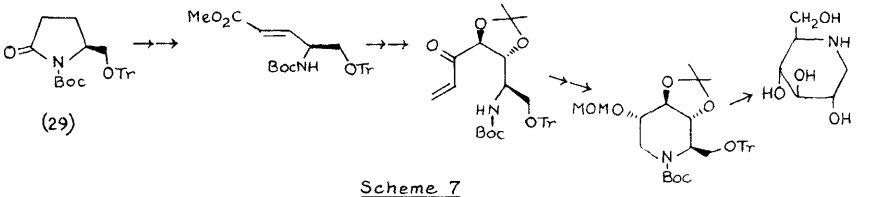
2-Amino-2-deoxy-D-mannitol has been isolated as a minor byproduct from a broth of S. lavendulae which produces moranoline (1-deoxynojirimycin).[33] N-Substituted 4-O-α-D-glucopyranosyl-moranoline derivatives have been enzymatically synthesized using soluble starch and a glucosyltransferase with the parent moranoline.[34] Alternatively, the parent disaccharide has been alkylated to give a series of N-alkylated derivatives which were assessed as sucrase and maltase inhibitors.[35]

The 1,6-dideoxy-nojirimycin derivative (27), obtained by a

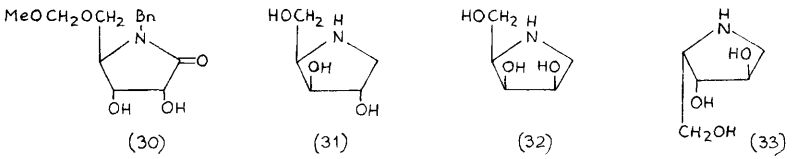
reductive-oxygenation modification of a previously reported procedure for making 1-deoxynojirimycin from a 6-bromo-6-deoxy-glucoside derivative (see Vol.19,p.170,ref.40), has been converted to oligosaccharide derivatives (28) in quest of endo-cellulase inhibitory activity.[36]



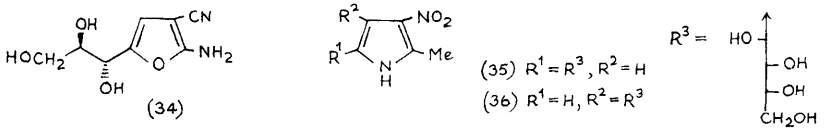
A synthesis of 1-deoxynojirimycin from non-carbohydrate precursors involves the conversion of (S)-pyroglutamic acid to the lactam (29), followed by the sequence outlined in Scheme 7 which uses standard reactions.[37] The same starting material was used to prepare the lactam (30) and hence the 1,4-dideoxy-1,4-imino-D-xylitol (31), selective benzylation at O-2 allowing routine inversion at C-3.[38] Other papers describe the synthesis of the isomeric imino-D-lyxitol (32) from D-glucose,[39] and of the imino-L-xylitol (33) from D-mannose.[40] A paper on the synthesis of swainsonine from mannose mentioned in Chapter 24 includes a practical synthesis of 1,4-dideoxy-1,4-imino-D-mannitol.



Scheme 7



1.5 Polyhydroxyalkyl-Heterocycles. - Knoevenagel condensation of D-ribose with malononitrile gave the trihydroxypropylfuran (34).[41]

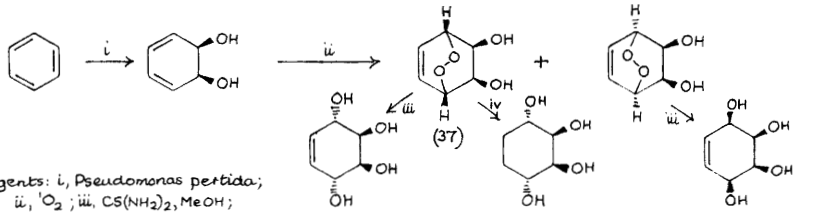


Condensation of 2-amino-2-deoxy-D-glucose and 1-amino-1-deoxy-D-fructose with nitromethane led to tetrahydroxybutylpyrrole derivatives (35) and (36) respectively.[42] 5'-Phosphates of a variety of D-ribityl-substituted pyrimidines and pteridines have been synthesized.[43]

2 Cyclitols

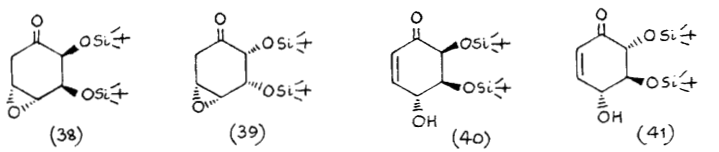
2-O-(β-L-Arabinopyranosyl)-myo-inositol has been identified as a main constituent of tea, although it is essentially tasteless.[44]

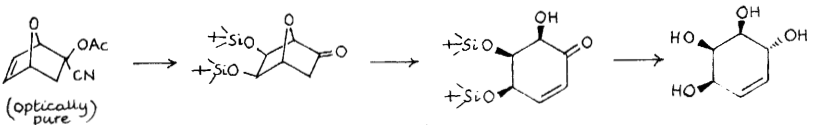
Conduritol isomers have been stereospecifically prepared from benzene as shown in Scheme 8.[45] Irradiation of the disilyl ether



Scheme 8

of the peroxide (37) gave the rearranged epoxyketones (38) and (39) which were further rearranged using triethylamine to give the isomers (40) and (41).[46] An alternative synthesis of (-)-conduritol used Vogel's "naked sugar" approach as indicated in Scheme 9.[47]

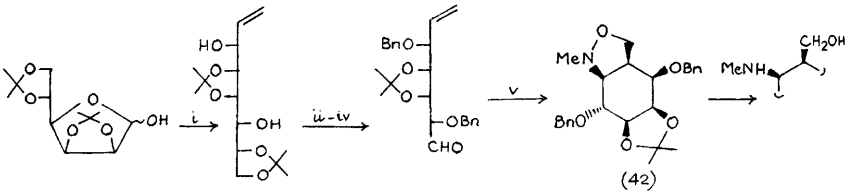




Scheme 9

Cyclopentane and cyclohexane compounds have been prepared by employing chelation-controlled stereoselective vinylmagnesium bromide additions to aldose sugars, and subsequent construction of the carbocyclic rings by intramolecular nitrone cyclization using Bernet and Vasella's methodology as illustrated for the amino-

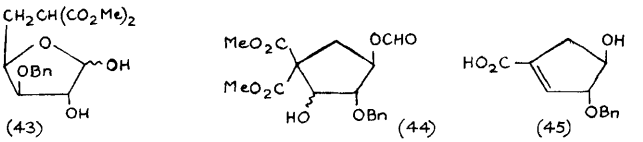
cyclitol (42), made from D-mannose, as outlined in Scheme 10.[48]



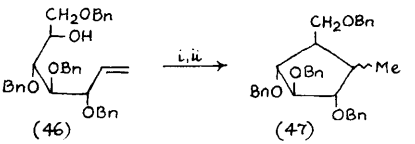
Reagents: i, ⟋MgBr ; ii, BnBr, NaH ; iii, H_3O^+ ; iv, $NaIO_4$; v, MeNHOH

Scheme 10

The xylose derivative (43), on periodate oxidation, gave an aldose which underwent spontaneous Knoevenagel cyclization to the cyclopentane (44) which could be conventionally converted to ψ-α-L-arabinofuranose and ψ-β-D-ribofuranose via the cyclopentene (45).[49]



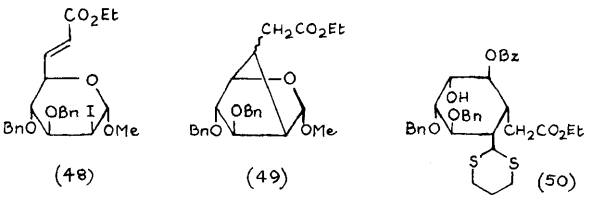
Carbohydrate alkenes derived by Wittig reaction of aldohexoses undergo radical cyclization to cyclopentane analogues, e.g., (46) → (47)(Scheme 11). The stereochemistry of cyclization was found to depend mainly on the substituent at C-2 of the original sugar.[50]



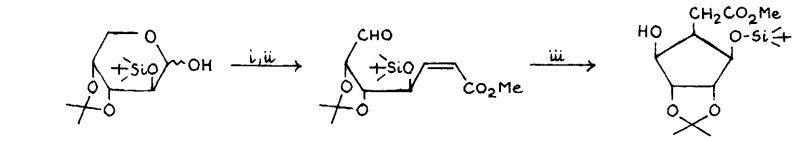
Reagents: i, $(N\text{-}O)_2CS$; ii, Bu_3SnH

Scheme 11

The unsaturated iodo-sugar (48), obtained from 3,4-di-O-benzyl-D-glucal, underwent reductive cyclization with tributylstannane leading to the cyclopentane isomers (49); the cyclohexane derivative (50) was similarly made.[51]



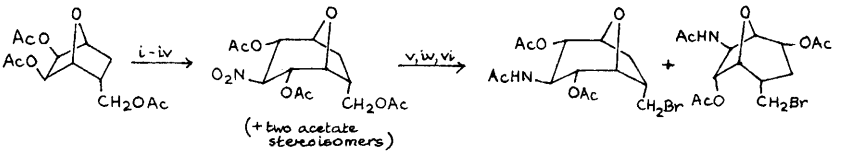
Another reductive coupling technique has been applied to unsaturated carbohydrate aldehydes, giving cyclopentanes with high stereoselectivity following samarium diiodide reduction, as exemplified in Scheme 12.[52]



Reagents: i, $Ph_3P{=}CHCO_2Et$; ii, PDC; iii, SmI_2, THF, MeOH (-78°)

Scheme 12

Pseudoheptanose derivatives have been prepared by ring enlargement of an oxabicyloheptane compound using nitromethane on a dialdehyde intermediate as illustrated in Scheme 13; the derived anhydro compounds resisted anhydro-ring cleavage.[53]

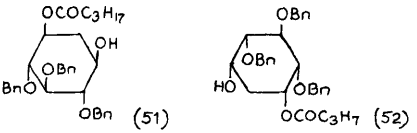


Reagents: i, NaOMe; ii, $NaIO_4$; iii, $MeNO_2$, OMe^-; iv, Ac_2O; v, H_2, Pd/C; vi, HBr, HOAc

Scheme 13

Pseudo-3-amino-3-deoxy-DL-hexopyranoses have been synthesized by the nitromethane cyclization procedure from pseudo-α-galactose, the gluco isomer predominating; the β-isomer reacted less selectively.[54] The same starting material has been used to prepare pseudo derivatives of 4-amino-4-deoxy, 4,7-diamino-4,7-dideoxy, and 4-amino-4,7-dideoxy-α-DL-glucopyranose by standard reactions.[55]

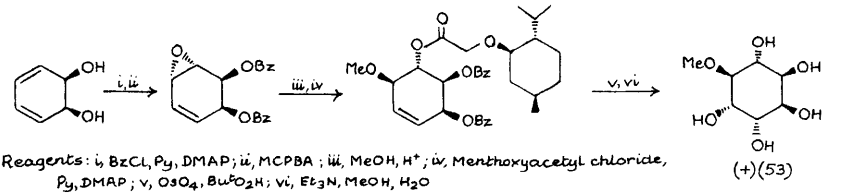
Selectively substituted symmetrical deoxyinositols (51) and (52) have been made following borohydride reduction of inosose derivatives.[56] Pseudo-2-acetamido-2-deoxy-DL-hexopyranoses have been prepared conventionally.[57]



(51) (52)

Optically pure isomers of 1,4,5,6-tetra-O-benzyl-myo-inositol have been obtained after separation of diastereoisomeric 2,3-acetals of myo-inositol with L- or D-camphor.[58]

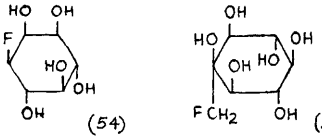
The benzene microbial oxidation product mentioned above has also been used to prepare (+)-pinitol (53) and its enantiomer as outlined in Scheme 14, the diastereoisomeric menthoxyacetic esters being readily separated.[59]



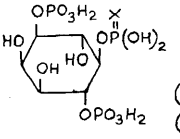
Scheme 14

Acetalated myo-inositol derivatives have been converted by standard reactions into intermediates required for the total synthesis of sugarotoxin and some of its analogues, which are 6-O-acyl derivatives of myo-inositol.[60] Quebrachitol reacts with DAST to a deoxy-fluoro derivative which, on demethylation, gave the fluoro-inositol (54), a cellular replication inhibitor.[61] Deoxy-fluoro-myo-inositols have been prepared, and their behaviour as substrates for phosphatidyl-inositol synthetase has been reported.[62] 2-C-fluoromethyl-myo-inositol (55) has been prepared conventionally from an exocyclic oxiran precursor.[63]

Many papers have appeared on myo-inositol phosphates and their analogues. Recent developments in their synthesis have been reviewed.[64] Syntheses of (-)-myo-inositol 1,4,5-triphosphate (56) have


(54)

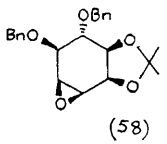
(55)


(56) X = O
(57) X = S

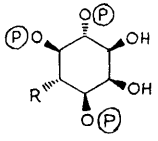
been reported from myo-inositol precursors,[65-67] and also from (-)-quinic acid.[68] Both enantiomers have been synthesized, using D-pinitol and L-quebrachitol respectively to obtain enantiomeric 1,2,5-tri-O-benzoyl-3,4-di-O-benzyl-chiro-inositol intermediates which were inverted to the required myo-inositol derivatives using a triflate ester displacement procedure.[69] Synthesis of racemic myo-inositol 1,4,5-triphosphate has been reported, together with the corresponding 5-phosphorothiolate analogue (57) which is phosphatase resistant, using known 2,3,6-tri-O-benzyl-4,5-O-isopropylidene-myo-inositol.[70]

The inositol derivative (58), previously reported as a product of

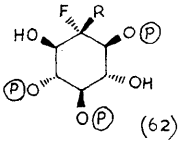
benzene oxidation (see Vol.21,p.179,ref.57), has been used to prepare the 6-deoxy analogues (59)-(61) of myo-inositol 1,4,5-triphosphate.[71] Another paper reports conversion of a myo-inositol derivative to the mono- and di-fluoro-scyllo-inositol analogues (62) using standard reactions.[72] TIPS-Protected derivatives of myo-inositol have been used to prepare its 4-mono, 5-mono, 1,3,4-tris, and 1,3,4,6-tetrakis-phosphate ester derivatives.[73] The 2- and 6-deoxy-myo-inositol 1-phosphate derivatives (63) and (64) respectively have been prepared, and then used to show that both the 2- and the 6-hydroxy group of myo-inositol 1-phosphate are involved in the mechanism of its hydrolysis by inositol monophosphatase.[74]



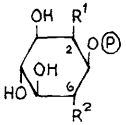
(58)



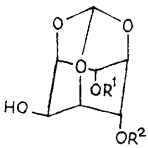
(59) R = H
(60) R = Me
(61) R = F



(62) R = H or F

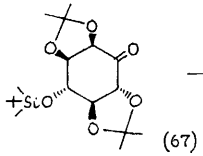


(63) R^1 = H, R^2 = OH
(64) R^1 = OH, R^2 = H

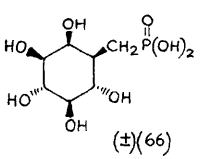


(65) R^1, R^2 = H, Bn, Au

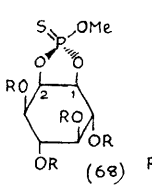
Myo-inositol orthoformate has been used to prepare 4- and 6-substituted derivatives, e.g. (65), and from these 2-mono, 4-mono, 1,3-bis, and 1,3,4,5-tetrakis-phosphate esters were prepared.[75] (See also Vol. 21, p.183.) Selective phosphorylation of (+)-2,3:5,6-di-O-isopropylidene-myo-inositol has been used to synthesize inositol phospholipid analogues.[76] This same precursor has been used to prepare the non-hydrolysable phosphonate analogue (66) of myo-inositol 1-phosphate via the intermediate inosose (67).[77]



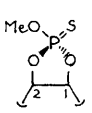
(67)



(±)(66)



(68)



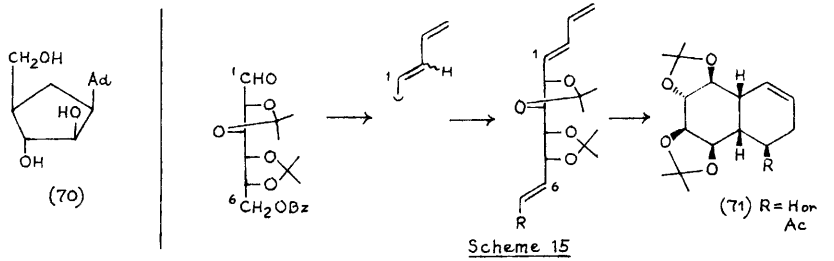
(69)
R = Bn or H

Full details of the synthesis of myo-inositol phosphate esters from racemic dicyclohexylidene ketal precursors have been published (see Vol. 21, p.183); phosphorylation has been improved using Bartlett's tetrabenzyl pyrophosphate procedure in this work.[78]

Epimeric forms (isomeric at phosphorus) of a myo-inositol phospholipid incorporating a thiophosphate group have been prepared; the isomeric derivatives (68) and (69) were also synthesized.[79]

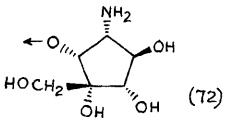
The regio- and stereo-selective synthesis of inosamines and inosadiamines utilizing Diels-Alder reactions with nitroso compounds has been reviewed.[80]

Xylose, previously converted to ψ-D-arabinofuranose (see Vol.21, p.182), has now been used to prepare (+)-cyclaradine (70) via ψ-β-D-arabinosylamine.[81] Intramolecular Diels-Alder reactions of sugar-based decatrienes have been used to prepare the decatetrol derivatives (71) as outlined in Scheme 15.[82]



Scheme 15

Incorporation of ^{13}C-labelled glucose into hopane triterpenoids revealed that the tetrol sidechain is derived from D-ribose, and that the novel carbocyclic pentofuranose unit (72), attached to this tetrol, is derived from a hexose linked between C-1 and C-5.[83]



(72)

The incorporation of an inosamine into the complete synthesis of hygromycin A, the structure determination of mannostatins A and B, and the synthesis of carbocyclic nucleoside antibiotics are mentioned in Chapter 19, and the synthesis of phospholipids incorporating pyranosyl-myo-inositol units is referred to in Chapter 3. Carbocyclic nucleosides are covered in Chapter 20.

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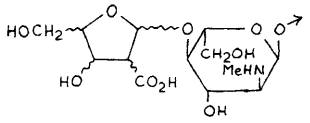
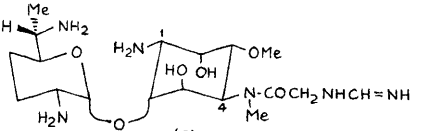
19
Antibiotics

1 Amino-Glycoside Antibiotics

Two new streptomycin analogues, ashimycins A and B, have been isolated from the fermentation broth of S. griseus; these are streptomycin derivatives modified in the L-glucosamine unit, ashamycin A (1, part structure) carrying a glycosidically linked branched-chain sugar acid (the stereochemistry has not been established).[1]



(1)



(2)

A blocked mutant of istamycin-producing S. tenjimariensis converts fortimicin B to 1-epidactimicin (2)(with C(1)-NH_2 inversion and N-4 acylation).[2]

The biosynthesis of fortimicin antibiotics has been studied, and common features in their production by S. sannanensis and Micromonospora olivosterospora have been recognized.[3]

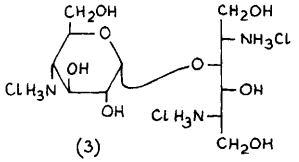
(+)-Validoxylamine A has been prepared by deoxygenation of a validoxylamine B derivative, and validamycins A and E have been synthesized.[4] The imino bond of validoxylamine A derivatives has been cleaved using N-bromosuccinimide to give a mixture of inosamine and inosose derivatives useful for reconstructing modified validoxylamine compounds.[5]

Syntheses have been reported for (-)-sannamine (2-deoxy-fortamine)[6] and its C-6 epimer, (±)-sporamine.[7]

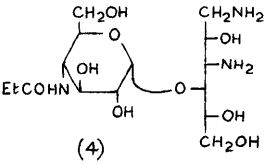
The mechanism and stereochemistry of the biosynthesis of 2-deoxystreptamine and neosamine C by S. ribosidificus have been investigated using labelled 6-^{2}H-D-glucoses.[8]

The sorbistin analogues (3) and (4) have been synthesized by coupling azido-precursors to the separate units using modified forms of standard glycosidation procedures.[9]

A synthesis of spectinomycin has been reported, together with that of an analogue (C-5' n-butyl replacing C-methyl) which shows enhanced antimicrobial activity and is the only analogue active against anaerobic bacteria (see also Vol. 17, p. 174, ref. 40).[10]



(3)



(4)

A total synthesis reported for the pseudo-tetrasaccharide α-glucosidase inhibitor acarbose and its hydroxylated analogue adiposin involved converting 1,6-anhydromaltotriose into 3",4"-anhydro analogues which were then condensed with 4,7:5,6-di-O-isopropylidenevalienamine.[11] A synthesis of dihydroacarbose is referred to in Chapter 4.

2 Macrolide Antibiotics

Two new 16-membered macrolide antibiotics, cirramycins F-1 and F-2, have been isolated from mutant strains of S. cirralus, which produces cirramycins A and B. Compared with cirramycin B, which contains L-cinerulose → D-mycaminose as a substituent disaccharide, cirramycin F-1 has rhodinose and cirramycin F-2 has L-amicetose instead of L-cinerulose in the disaccharide.[12]

Izenamycins, newly isolated from Micromonospora, contain 4'-deoxy-mycosamine glycosidically linked to a tylonolide 16-membered macrolide ring.[13] X-Ray analysis has established the absolute configuration of mycinamicin IV, a 16-membered macrolide containing D-desosamine and D-mycinose separately attached.[14] Mycinamicin VIII, a key intermediate in the biosynthesis of mycinamicins, has been characterized as the desosamine glycoside of the macrolide.[15] Vacidin A has also been completely characterized and shown to contain an aromatic and heptaene 38-membered ring with attached mycosamine.[16] A crystal structure of (14R)-14-hydroxy-6-O-methylerythromycin A has been reported.[17]

16-Deformyl-4'-deoxydesmycosin has been prepared by a method which involved standard 4'-deoxygenation of the mycaminose residue.[18]

The biosynthesis of cytovaricin, a macrolide antibiotic containing D-cymarose, has been studied, and its ^{13}C n.m.r.spectrum assigned.[19]

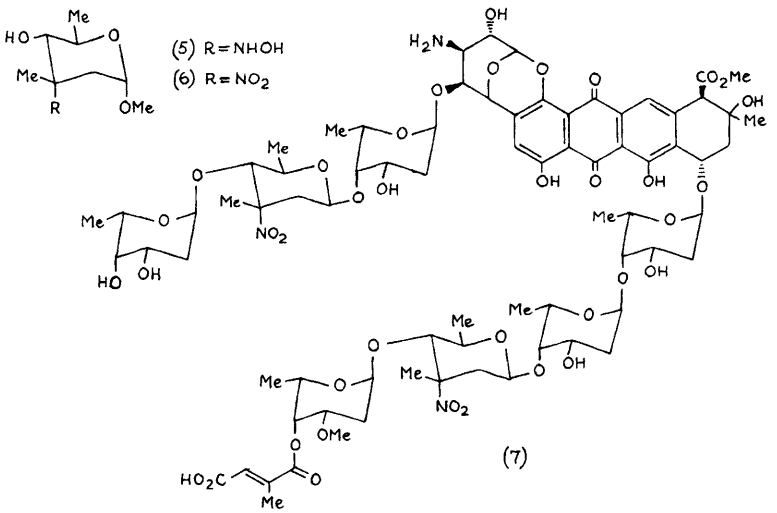
Analogues of 8,9-anhydroerythromycin A 6,9-hemiacetal have been prepared in which the N,N-dimethylamine of the desosamine was replaced by other N,N-dialkylamine units; the N-ethyl,N-methyl analogue gave the best, desired gastrointestinal motor stimulating

activity.[20] Significant enhancement also occurred on quaternization of the desosamine dimethylamino group with small, unsaturated alkyl groups, notably with a propargyl residue.[21] 4"-Acyl,-alkyl, and -deoxy-tylosin derivatives have been prepared via a 3",4"-O-dibutylstannyl intermediate, and evaluated as antimicrobial agents.[22]

3 Anthracycline and Related Polycyclic Antibiotics

The synthesis and pharmacology of new antitumour anthracyclines developed between 1983-1986 have been reviewed.[23]

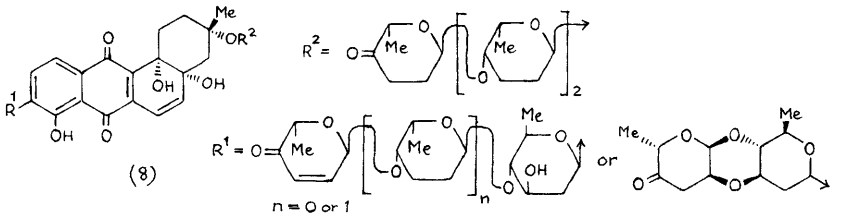
Viriplanin A, a new member of the nogalomycin group of antibiotics, has been characterized; it contains a novel hydroxyamino-sugar, isolated as methyl 2,3,6-trideoxy-3-hydroxyamino-3-C-methyl-α-D-ribo-hexopyranoside (5), which on oxidation gave methyl α-D-decilonitroside (6); viriplanin D, a photo-oxidation product of viriplanin A, has the full structure (7); the authors suggest that



the L-configuration previously attributed to decilonitrose obtained from anthracycline antibiotics should be corrected to D.[24]

Three new platelet aggregation inhibitors (8) have been isolated from S. matensis culture broth. As O- and C-glycosylated benzanthraquinones, they are closely related to antibiotics previously reported (see Vol. 16, p.199; Vol. 18, p.120).[25]

Anthracycline F 84 0020 (a 2,6-dideoxy-β-D-lyxo-hexopyranoside) has been prepared in a multistep procedure from lactose.[26]



(8)

2,6-Dideoxy-α-L-arabino- and -lyxo-hexopyranosyl derivatives of daunomycinone have been synthesized by coupling glycals with daunomycinone and N-iodosuccinimide followed by dehalogenation with tributylstannane; use of the deuterio-stannane reagent gave the 2'-axially labelled isomers.[27] 2'-C-Methyl-daunomycins have been prepared by coupling the daunomycinone with the appropriate 2-C-Methyl-3-amino-sugar obtained from methyl 4,6-O-benzylidene-2-C-methyl-α-D-ribo-hexopyranosid-3-ulose by standard reactions.[28] Semi-synthetic 14-chloro analogues of rubomycin and carminomycin have been synthesized, including N-formyl derivatives of the antibiotics prepared using formic acid with N-hydroxysuccinimide and dicyclohexylcarbodiimide.[29]

The biosynthesis of angucycline antibiotics urdamycins A-D has been studied; feeding S. fradiae with [1-^{13}C]-glucose showed that the C-glycoside unit and the three sugars (two L-rhodinose and D-olivose) arise from glucose.[30]

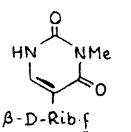
6-Deoxy-2-O-methyl-α-L-talopyranosyl derivatives of daunomycinone and adriamycinone, made by standard procedures from a fucose precursor, show improved antitumour activity compared with daunorubicin and doxorubicin respectively.[31] Corresponding 3-amino-2,3,6-trideoxy-2-fluoro-α-L-talopyranosyl compounds were also made, but these showed no improvement in activity compared with the 3-hydroxy-sugar analogues.[32] Compounds with high antileukaemic activity have been prepared by coupling 4-demethoxy-9-hydroxymethyl-9-deacetyl-daunorubicinone with 2-deoxy-L-fucose, 2-deoxy-L-rhamnose, and 2,6 dideoxy-2-iodo-α-L-mannose using a Koenigs-Knorr procedure.[33] N-Salicylidene derivatives of pirarubicin , obtained from the antibiotic with aryl aldehydes, showed greater in vitro activity than did the parent compound.[34] Semi-synthetic anthracycline antibiotic analogues have been made incorporating an hydroxyethyl spacer between the tetracycline aglycone and the sugar.[35] 4'-Epi-N-trifluoroacetyl [14-^{14}C] daunorubicin has been converted to 4'-iodo-4' [14-^{14}C]-deoxydoxorubicin hydrochloride.[36]

FAB-m.s. on underivatized retamycins (which incorporate a trisaccharide sidechain) have been recorded, allowing sequencing of the carbohydrate moiety.[37]

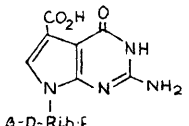
The glycosylation of anthracyclinone is also referred to in Chapter 3.

4 Nucleoside Antibiotics

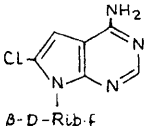
3-Methylpseudouridine (9) has been isolated from the fermentation broth of Nocardia lactamdurans.[38] 5'-O-Acyl derivatives of 5-fluoro-uridine[39] and 3'- and 5'-O-alkyl derivatives of 2'-deoxy-5-fluoro-uridine[40] have been synthesized in the search for enhanced antitumour activity, some enhancement being achieved with some derivatives in each case.



(9)



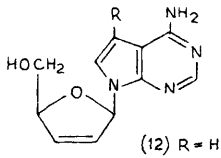
(10)



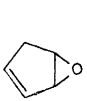
(11)

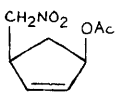
Cadeguomycin (10) and its ara- and 2'-deoxy-analogues have been synthesized.[41,42] Standard coupling procedures have been used to prepare 6-chlorotubercidin (11) and its 3',5'-cyclic phosphate, an analogue of the anticancer 8-chloro-cAMP; the 4-substituted isomer of (11) was also obtained.[43]

The unsaturated sugar analogues (12) of anti-HIV nucleosides have been prepared,[44] and a large scale route to the thymine analogue of (12)(from thymidine) has been described.[45] The biosynthesis of ara-A, 2'-chlorodeoxycoformycin, 2'-amino-2'-deoxyadenosine, and nucleosidin has been studied using labelled oxygen and hydrogen derivatives; in each case adenosine appeared to be incorporated intact.[46] The synthesis and antitumour activity of modified nucleosides is also referred to in Chapter 20.

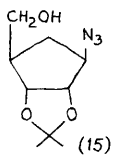


(12) R = H, CN, $CONH_2$


(13)



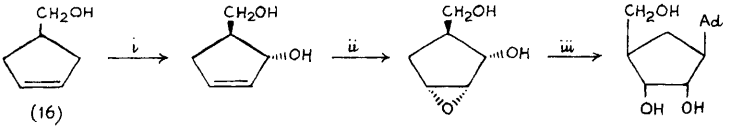
(14)



(15)

Several syntheses of aristeromycin have been reported. The (-)-isomer has been made from a cyclopentenone mentioned previously (see

Vol. 21, p. 194),[47] and a 21-step procedure from D-glucose has been described.[48] (±)-Aristeromycin has been prepared from the cyclopentene-oxiran (13) via the nitromethyl intermediate (14) and the azide (15).[49] An alternative approach utilized the (hydroxymethyl)-cyclopentene (16) in the 3-step stereoselective synthesis outlined in Scheme 1.[50]

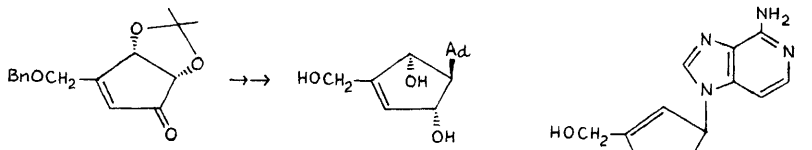


(16)

Reagents: i, SeO_2 ; ii, MCPBA ; iii, NaH, DMF, Adenine

Scheme 1

The racemic cyclopentenone (17), obtained as a byproduct in a synthesis of neplanocin A, has been used to make (±)-neplanocin F (18).[51] A similar starting material has been used to make 3-deaza-neplanocin A (19), which shows antiviral properties and is a powerful inhibitor of S-adenosyl-homocysteine hydrolase.[52] This enzyme has been used to oxidize neplanocin A to the corresponding 3'-keto analogue; sodium cyanoborohydride reduction of this ketone was neither regio- nor stereo-specific, yielding 5 products by 1,4 as well as 1,2 reduction.[53]



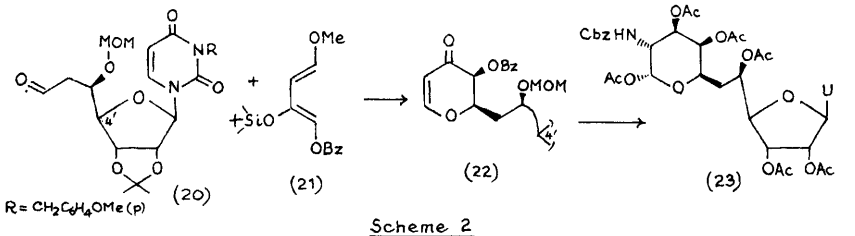
(17) (±)(18) (19)

A biosynthetic study of aristeromycin using labelled precursors has found that the cyclopentane ring is generated by C-C bond formation between C-2 and C-6 of D-glucose; the authors propose oxidation at C-5 or C-4 occurs leading to a cyclopentenone derivative.[54]

Other carbocyclic nucleosides which show some antibiotic activity are mentioned in Chapter 20.

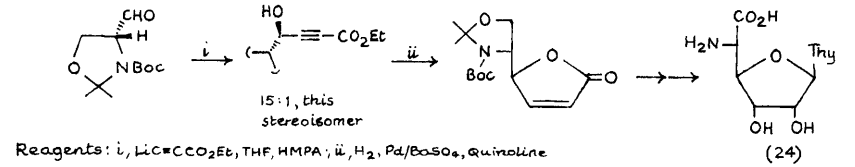
Protected subunits of tunicamycins have been synthesized. Cyclocondensation of the aldehyde (20), derived from uridine, with the butadiene (21) gave the dihydropyrone derivative (22) after desilylation, and by further manipulation, the tunicamycin subunit (23) (Scheme 2).[55]

An asymmetric synthesis of thymine polyoxin C (24) has been



Scheme 2

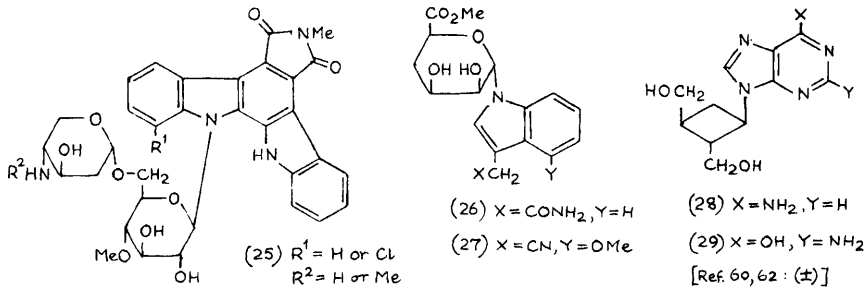
achieved as outlined in Scheme 3.[56]



Scheme 3

Two new nikkomycins have been isolated from the broth of S.tendae, nikkomycins pseudo-Z and pseudo-J, differing from the Z and J components by having a C-glycosidic link from the allofuranuronic acid and the C-5 of uracil instead of the usual N-glycoside bond.[57]

Relatives of rebeccamycin, containing an additional amino-sugar residue attached to the 4-O-methyl-β-D-glucose unit, have been isolated from Actinomadura melliaura. Structure (25) summarizes these new compounds, AT 2433-A1, -A2, -B1, and -B2.[58,59]



Various synthetic approaches to bicyclic nucleosides, including octosyl acids and the ezomycins, have been reviewed.[60]

The antibiotics neosidomycin (26) and the related SF-2140 (27) have been synthesized by conventional procedures from the corresponding 4-deoxy-hexose, confirming the α-N-glycoside linkage in these compounds.[61]

Carbocyclic analogues (28)[62,63] and (29)[63,64] of oxetanocin-A and oxetanocin-G, respectively, have been synthesized, and shown to possess high antiviral activity. Use of a chiral titanium catalyst in forming the cyclobutane precursor by a 2+2 cycloaddition process gave a highly enantioselective reaction (>98% e.e.).[63]

A 3-O-acrylyl ether of D-allose has been used to prepare a derivative of the sugar moiety of octosyl acids.[65]

5 Glycopeptide Antibiotics

Eromomycin, a new glycopeptide antibiotic produced by actinomycete INA 238, which is less toxic and more potent than the related vancomycin, contains a unit of D-glucose and two units of a new aminosugar, eromosamine (3-amino-2,3,6-trideoxy-3-C-methyl-L-arabino-hexopyranose), one (2-O-α) linked through glucose as a disaccharide.[66,67] Another new vancomycin relative, antibiotic A 42867, produced by a Nocardia strain, differs from vancomycin in the carbohydrate units, having α-glucopyranose attached to α-rhamnopyranose as a disaccharide and vancosamine attached to the peptide core.[68]

Ramoplanin, (A-16686), obtained from Actinoplanes, has been identified as a glycolipodepsipeptide antibiotic, in which a dimannosyl disaccharide (α-D-man p 1→2α-D-man p→O-tyrosine) is attached to a 17-membered cyclic polypeptide core.[69]

Two new analogues of teichoplanin have been isolated as minor components of the complex from Actinoplanes teichomyceticus, RS-3 and RS-4, which have 6-methyloctanoic and nonanoic acid residues respectively attached as amide substituents to the two glucosamine units which are separately attached to the cyclic peptide core.[70]

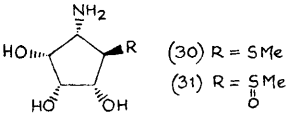
Antibiotic A 82846 B, a close relative of eromomycin mentioned above, has been shown to be identical to chloroorienticin A, and its hydrolysis products are identical to those of chloroorienticin B and C (see Vol. 22, p. 199).[71]

Eighty N-alkylated vancomycins have been prepared in which vancosamine and/or N-methylleucine is/are substituted; these compounds exhibited greater antibiotic activity that the parent or N-acylated analogues.[72]

A complete ^{13}C n.m.r. assignment of peplomycin has been made. It contains a 3-O-carbamoyl-α-D-mannosyl-(1→2)-α-D-gulosyl disaccharide residue attached to an acyclic peptide chain.[73]

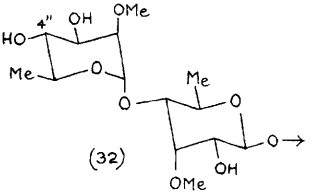
6 Miscellaneous Antibiotics

Mannostatins A an B, newly discovered inhibitors of α-D-mannosidase, have been identified as the amino-methylthio-cyclopentanetriol derivatives (30) and (31) respectively.[74,75]



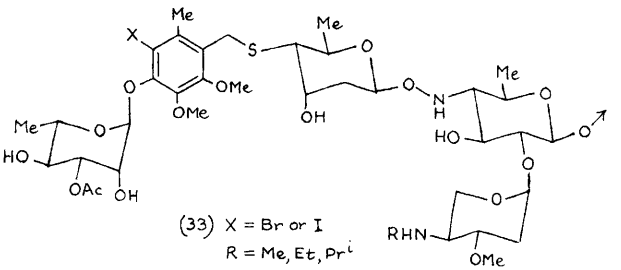
(30) R = SMe

(31) R = S(=O)Me



A novel member of the efrotomycin family of antibiotics, UK-69753, obtained from a Amycolatopsis orientalis strain, has been identified as the 4"-de-O-methyl analogue of efrotomycin, containing the disaccharide unit (32) attached to factumycin, an acyclic polyene amide.[76] Another pair of acyclic polyene antibiotics, glucopieridinols A_1 and A_2, which contain a β-D-glucopyranosyl unit glycosidically linked, have been isolated from a Streptomyces strain (sp. OM-5689).[77] Aleurodiscal, an antifungal sesquiterpenoid from Aleurodiscus mirabilis, contains a glycosidically linked β-D-xylopyranose unit.[78] An alkaloid antibiotic, hatomamicin (YL-0358M-A), obtained from a culture filtrate of Saccharopolyspora, is a glycoside of rhodinose.[79]

Calicheamicins, a novel family of antitumour antibiotics produced by Micromonospora echinospora ssp. calichensis, contain the part structure (33); seven components were identified.[80]

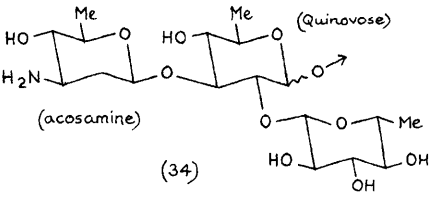


(33) X = Br or I

R = Me, Et, Pr^i

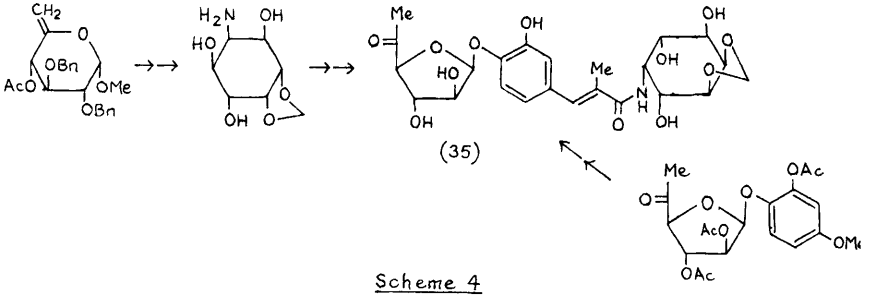
Aculeximycin, a new basic glycosidic antibiotic produced by Streptosporangium albidum, includes five monosaccharide units; a branched trisaccharide chain, aculexitriose (34), is accompanied by separate units of D-mannose and L-vancosamine.[81] New inhibitors of

cyclic-nucleotide phosphodiesterase, KS-501 and KS-502, have been isolated from the fungus Sporothrix sp. KAC-1985, and shown to contain β-D-galactofuranose as a phenolic glycoside.[82]



(34)

A complete synthesis of hygromycin A (35) is outlined in Scheme 4.[83]



Scheme 4

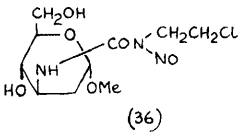
Coumamidines γ1 and γ2, isomeric compounds isolated from an Actinomycete strain, have been characterized as the amino-sugar derivatives of a cinnamamide complex; the same carbohydrate units are present in the related cinodines, which are glycocinnamoylspermidines (see Vol. 12, p. 153, ref. 63, structures (15) and (16)).[84]

Further work on the structure of the antibiotic complex sporaviridin has been reported (see Vol. 17, p. 181; Vol. 18, p. 186); six components have been characterized, differing in one unit of the viridapentaose chain (see Vol. 18) or in the aglycone, which is a polyhydroxy C_{47}, 34-ring macrolide.[85]

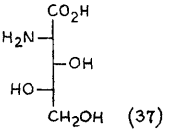
9-β-D-Arabinofuranosyladenine 2',5'-cyclic phosphate shows antiviral activity.[86] (See also Chapter 20)

N-Nitroso-ureido derivatives of di- and tri-deoxy sugars have been prepared, all of which showed significant antitumour activity; of those compounds synthesized, (36) was most active.[87]

A multistep, stereoselective synthesis of (+)-polyoxamic acid (37), a constituent of polyoxins, employed an aldehydo-L-threose derivative prepared from L-tartaric acid.[88] Another synthesis



(36)



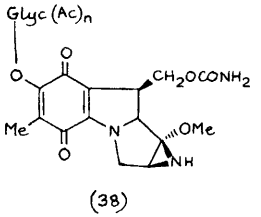
(37)

starting from L-arabinose is noted in Chapter 24. A synthesis of the enzyme inhibitor 2-deoxy-β-KDO is referred to in Chapter 16.

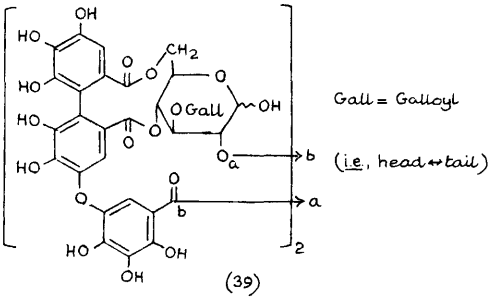
Buchanan's group has reviewed its work on the synthesis of the antiprotozoal antibiotic anisomycin, extended to necine bases of the pyrrolizidine alkaloids; routes from D-ribose and D-erythrose to a key pyrrolidine intermediate using highly stereoselective reactions are included.[89]

L-Arabinose has been used in a new total synthesis of the antibiotic patulin (23% overall yield).[90] 7-O-β-D-Glycosyl-9a-methoxymitosanes (38) have been prepared using glucose, lactose, glucosamine and galactosamine (Koenigs-Knorr conditions), and their antibiotic activities have been studied.[91]

A dimeric hydrolysable tannin, oenothein B (39), which shows antitumour and antiviral activity, has been obtained from the leaves of Oenothera erythrosepala.[92] 3-O-Digalloyl-1,2,6-tri-O-galloylglucose has been isolated from the freshwater alga spirogyra varians, and shown to be an antibiotic and an α-glucosidase inhibitor.[93] (See also Chapter 7.)



(38)



(39)

The biosynthesis of the aglycone of the disaccharide glycosides benanomicins A and B has been studied.[94]

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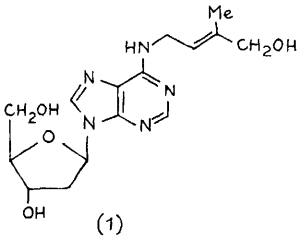
20
Nucleosides

A new cytokinin, the 2'-deoxy-derivative (1) of zeatin riboside, has been isolated from the culture filtrate of *Pseudomonas amygdali*; it was also synthesised conventionally, together with its α-anomer.[1]

3-Methyluridine[2] and 5'-deoxyxanthosine[3] have been isolated from normal human urine. The 4-pyridone nucleoside (2) has also been isolated from the same source; the analogous 2-pyridone, which had been previously synthesized (Vol. 19, p.194), was also found, and was prepared by oxidation of nicotinamide mononucleotide with ferricyanide followed by treatment with phosphatase.[4] 3-Hydroxyuridine, isolated from the rain forest tree *Baillonella toxisperma*, has potent plant growth regulatory properties.[5]



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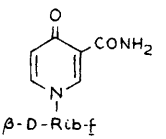


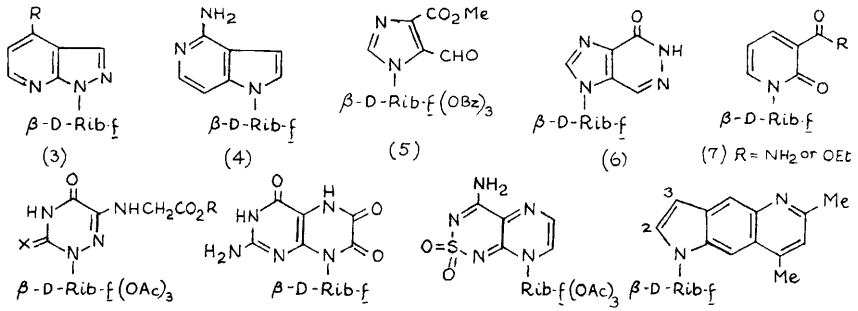
(2)

1 Synthesis

A two-part review has been published, in Russian, on the use of monosaccharides in nucleoside synthesis.[6]

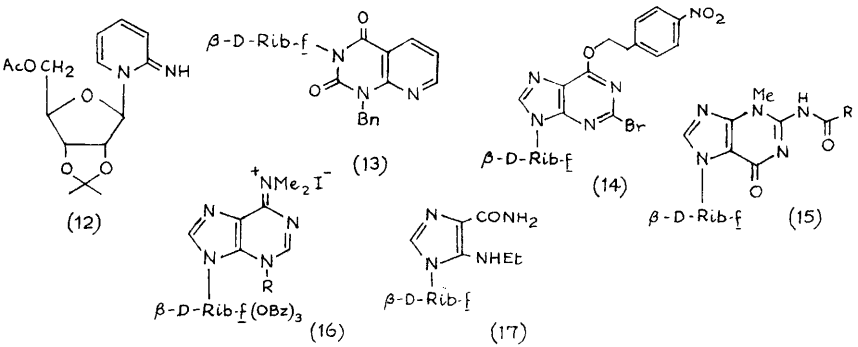
The use of the sodium-salt glycosylation procedure for synthesis of β-D-ribofuranosyl, -arabinofuranosyl and 2-deoxy -β-D-ribofuranosyl systems has also been reviewed,[7] and this technique has been applied to the preparation of pyrazolo[3,4-*b*]pyridine nucleosides (3) (together with 2'-deoxy- and arabino-analogues),[8,9] and pyrrolo[3,2-*c*]pyridines such as 3-deazatubercidin (4),[10,11] where again 2'-deoxy systems were also prepared.[11] The protected imidazole nucleoside (5) was made in a similar manner, and reaction with hydrazine then led to the imidazo[4,5-*d*]pyridazinone(6) (2-aza-3-deazainosine).[12]

Conventional condensation procedures have been used to prepare 2-pyridone nucleosides of type (7),[13] 6-aza- and 2-thio-6-azauracil derivatives of type(8),[14] 1-β-D-ribofuranosyl derivatives of nitrobenzimidazoles,[15] chloroindazoles,[16] and 6- and 7-*p*-chlorophenyllumazines,[17] and 2-



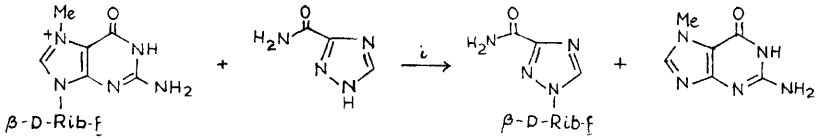
methylthiopteridine-N^8-ribosides, from which 8-β-D-ribofuranosylleucopterin (9) was available.[18] Conditions have been found for the formation of the N^8-isomer (10) as major product of the ribosylation of the pyrazino[2,3-c]1,2,6-thiadiazine dioxide.[19] The pyrroloquinoline (11), and the β-D-glucopyranosyl analogue, have been prepared by MnO_2 oxidation of the 2,3-dihydro derivatives,[20] whilst the pyridine derivative (12) has been reported as formed by reaction of 2-aminopyridine with the 1'-*O*-tosyl sugar derivative, 4-aminopyridine also giving the analogous product.[21] The pyrido[2,3-*d*] pyrimidine nucleoside (13), and related pyrrolo[2,3-*d*]pyrimidine systems have been prepared by ribosylation of 1-benzyl-6-chlorouracil and annulation of the second ring using Pd(II) dehydrocyclization.[22]

M.J. Robins has reviewed his group's work on methods for obtaining high yields of the N^9-regioisomers in the formation of guanine nucleosides (see Vol. 21, p.201), and for kinetic formation of the N^7-isomers (see also Vol. 22, p. 206).[23] R.K. Robins and coworkers have also described the highly regioselective formation of (14) by Vorbrüggen-type coupling, and its use for making guanosine and inosine analogues.[24] The N^7-ribosylated derivatives (15) of N^3-methyl guanosine were prepared by fusion or chloromercuri methods,



and the N^9-isomer (made from an imidazole nucleoside) underwent thermal rearrangement to (15).[25] The *N,N*,3-trialkyl adenosine derivatives (16, R=Me,Et) were prepared by $SnCl_4$-catalysed glycosylation; the N^3-ethyl compound underwent hydrolysis to the imidazole (17).[26]

Enzymic methods of nucleoside synthesis continue to attract attention, and the synthesis of radiolabelled ribo- and deoxyribonucleosides by transglycosylation catalysed by crude *E.coli* homogenates has been reviewed.[27] A promising method for the enzymic synthesis of nucleosides is illustrated by the example of virazole synthesis in Scheme 1; the use of N^7-methyl guanosine



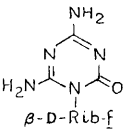
Reagents: i, Purine nucleoside phosphorylase

Scheme 1

makes the reaction essentially irreversible, and this method removes the need for the use of more than one enzyme or for the isolation of the intermediate ribose-1-phosphate. 3-Deazaadenosine could be prepared similarly in good yield.[28] 8-Azaguanosine, ^{14}C-labelled in the sugar, was prepared in a two-step enzymic method from [U-^{14}C]-inosine,[29] and ribo-, 2-deoxyribo- and arabinofuranosyl nucleosides of the purines azathioprine and thiamiprene have been prepared enzymically by glycosyl-transfer procedures from uracil or thymine nucleosides.[30]

6-Amino-5-azacytidine (18) has been prepared by a process of building up the heterocyclic ring on a protected ribosyl isocyanate,[31] and some 2-substituted 5-amino-ribofuranosyl imidazoles have been synthesized by Shaw's methods from the ribofuranosylamine.[32]

Both chemical and microbiological methods have been used for the



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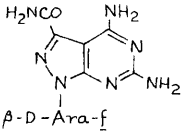

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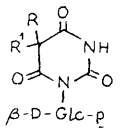

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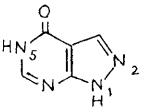

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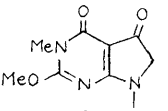


(22)

synthesis of 1-(β-D-arabinofuranosyl)thymine,[33] and the pyrazolopyrimidine (19) has been synthesized by oxidation-reduction of a 3',5'-TIPDS-derivative.[34] Solid-liquid phase transfer glycosylation has been used for preparation of 1-(β-D-arabinofuranosyl)pyrrolo[3,2-*c*]pyridines (and some related 2'-deoxy- and 2',3'-dideoxy systems; see also Vol. 21, p.206).[35]

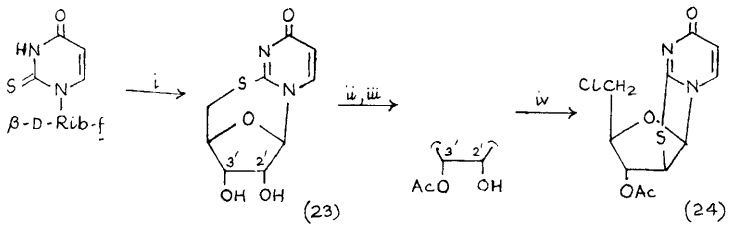
9-(β-D-Xylofuranosyl)adenine has been prepared by regiospecific opening of the 2',3'-*ribo*-epoxide with KCNO in acetonitrile containing BF_3 and a crown ether,[36] and also by an oxidation-reduction sequence at C-3' of a suitably-protected adenosine derivative.[37] Triflate displacement at C-2' of a suitable derivative of xylofuranosyladenine was used in a new high yielding synthesis of 9-(β-D-lyxofuranosyl)adenine.[38]

The β-D-glucopyranosyl conjugates (20) of some common barbiturates have been synthesized conventionally,[39] and N^1-α-, N^2-β-, N^5-β-, and N^1, N^5-bis-D-glucopyranosides of allopurinol (21) have been reported.[40] A number of β-D-glycopyranosyl pyrrolo[2,3-*d*]pyrimidines such as (22) have been prepared by annulating the pyrrole ring onto a (glycopyranosylamino) pyrimidine;[41,42] a sequence of nitrosation-reduction-diazotization of these intermediates gave rise to β-D-glycopyranosyl *vic*-triazolo[4,5-*d*]pyrimidines.[41]

A further report has appeared dealing with 'glycosyl-O-N' analogues of nucleosides (see Vol. 22, p. 207).[43]

2 Anhydro- and Cyclonucleosides

2,5'-Anhydro-2-thiouridine (23) has been prepared by Mitsunobu reaction as indicated in Scheme 2. It had been hoped that, after selective acylation at O-3', nucleophilic displacements might be possible at C-2', but the rearranged 2,2'-cyclonucleoside (24) resulted during reaction with triflyl chloride; similar findings have been observed earlier for the oxygen-bridged analogues (Vol.21, p.203).[44]

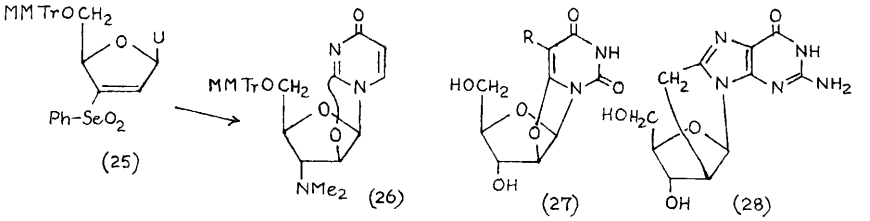


Reagents: i, Ph_3P, DEAD; ii, Bu_2SnO, MeOH; iii, Ac_2O; iv, TfCl, Py, Et_3N, DMAP

Scheme 2

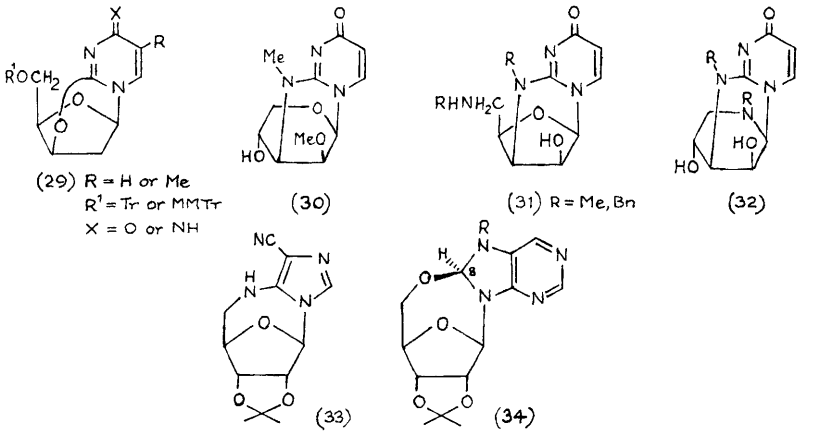
Treatment of the 3'-phenylselenoyl -2'- ene (25) (see Sect. 6) with dimethylamine gave the 2,2'-anhydrouridine derivative (26); by analogy with reactions of (25) with primary amines (Sect. 5), a 2',3'-aziridinium

intermediate is most likely involved.[45] Some 6,2'-anhydrouridines of type (27) have been prepared from their parent barbiturates and 1-*O*-acetyl -2,3,5-tri-*O*-benzoyl β-D-ribofuranose,[46] and 2'-deoxy-8,2'-methanoguanosine (28) has been synthesized by the same method as was used (Vol.20, p.206) for the adenosine analogue.[47]



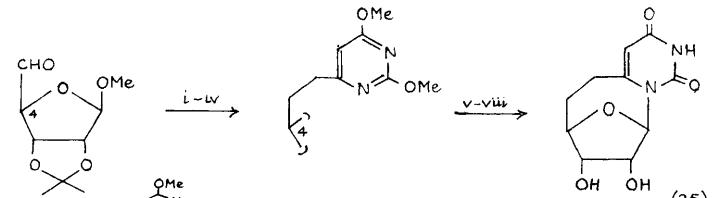
Various 2,3'-anhydro-2'-deoxypyrimidine nucleosides (29) have been prepared by cyclization of the 5'-*O*-protected deoxynucleosides with DAST or related reagents;[48,49] some further references to the synthesis and use of 2,3'-anhydrothymidine derivatives are mentioned in Sections 4 and 5. The 2,3'-iminopyranosyl nucleoside (30) was produced by base-catalysed ring expansion of the furanosyl analogue,[50] and a similar process occurred when 5'-alkylamino compounds (31), made from uridine in three steps, were treated with alkali to give the piperidine nucleosides of type (32).[51]

A number of 2,5'-anhydro- derivatives of AZT and similar compounds with other substituents at C-5 have been prepared by base-catalysed cyclization of 5'-*O*-tosylates.[52] When the 5'-*O*-tosyl derivative of 2',3'-*O*-isopropylidene adenosine was treated with Me_2CuLi, the product was unexpectedly the

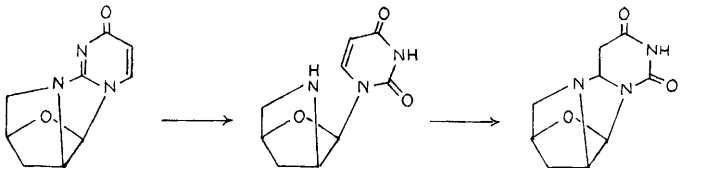


imidazole cyclonucleoside (33). Also, when isopropylidene nebularine was treated with acetyl chloride in pyridine, the cyclic product (34, R=Ac), confirmed by X-ray, was obtained as the only isolable product; use of TsCl led to the formation of (34, R=Ts), together with the 8-epimer and the expected 5'-*O*-tosyl derivative.[53] The 6,5'-methano-linked uridine (35) has been prepared as indicated in Scheme 3.[54]

The strained, doubly-bridged compound (36) (Scheme 4) underwent ready hydrolysis under acidic or basic conditions to give the 2',5'-imino system (37), which under further basic conditions gave the Michael adduct (38).[55]



Scheme 3



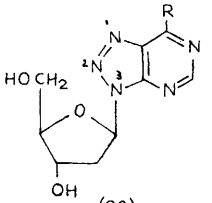
Scheme 4

3 Deoxynucleosides

Solid-liquid phase-transfer glycosylation has been used to prepare 2'-deoxyribonucleosides of pyrrolo[2,3-*b*]pyridines and indoles,[56] further pyrrolo[2,3-*d*]pyrimidines,[57] and nitrobenzimidazoles,[58] with a further report appearing on this route to 2-deoxyribonucleosides of pyrazolo[3,4-*d*] pyrimidines (see Vol.22, p. 209).[59] A study has been made of the regio- and stereoselectivity of the reaction between 2-deoxy- 3,5-di-*O*-toluoyl-α-D-*erythro*-pentofuranosyl chloride and the ambident bases 2-pyridone, 4-pyridone, and 2-pyrimidinone; kinetically-controlled reactions gave mainly *O*-glycosides, which could be isomerized in acid to the *N*-linked products.[60] The same pentosyl chloride was used to prepare 2-deoxyribofuranosides of some triazolo[4,5-*d*] pyrimidines (39) via the sodium salts; the process was β-selective, but also gave N^1-and N^2-regioisomers.[61] Two procedures have been reported to effect condensation between adenine and furanosyl chlorides so as to give

stereoselectively the β-isomer of 2'-deoxyadenosine, but only in moderate yields.[62,63] In the pyrimidine series, condensation of silylated uracils and 6-azauracils with 2-deoxy-3,5-di-*O*-toluoyl-α-D-*erythro* pentofuranosyl chloride gave high proportions and high yields of the β-isomer when carried out in chloroform in the presence of CuI,[64] whilst the reaction of (40) with bis(trimethylsilyl)thymine and TMSOTf was also highly β-selective; the bulky 3'-*O*-blocking group could be removed by base treatment.[65]

Transglycosylation of 2'-deoxy-2'-^{3}H-uridine with 5-halouracils, catalysed by pyrimidine nucleoside phosphorylase, was used to prepare the labelled 2'-deoxy-5-halouridines,[66] and ^{15}N-enriched 2-aminopurine-2'-deoxyribonucleoside has been prepared enzymically from the labelled base.[67] The imidazole deoxynucleoside (41) was prepared by biotransformation from the base and 2'-deoxyuridine, along with about half as much of the N^3-regioisomer; chemical synthesis gave a mixture of regio- and stereoisomers.[68]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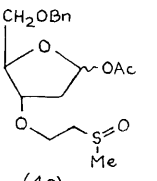
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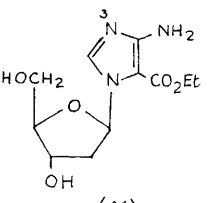
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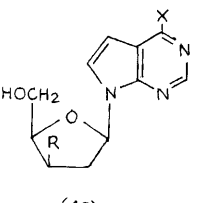
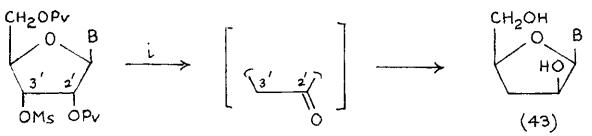

(42)

Swern oxidation and subsequent reduction was used in an improved route to [5'-^{2}H]-labelled thymidine.[69]

A study of the reaction of 1,3,4-tri-*O*-benzoyl-2-deoxy-β-D-ribopyranose with bis(trimethylsilyl)thymine has confirmed that the stereo- and regioselectivity are catalyst-dependent.[70]

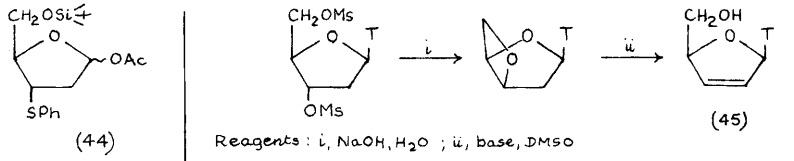
An oxidation-reduction sequence was used to invert stereochemistry at C-3' in a preparation of some 2'-deoxy-β-D-*threo*-pentofuranosyl pyrrolo-pyrimidines (42, R=OH).[71] A hydride shift process (Scheme 5) was used to make 3'-deoxy-β-D-*threo*-pentofuranosyl nucleosides of type (43),[72] whilst a similar process is involved in the formation of (43, B=Ad) by treatment of 2',3'-*di*-*O*-tosyladenosine with $LiEt_3BH$; the same product (43, B=Ad) was also obtained, in higher yields, by the same reduction of the analogous D-*arabino*- and D-*lyxo*-systems.[38]



Reagents: i, NaOMe, $NaBH_4$

Scheme 5

The synthesis of 2',3'-dideoxynucleosides continues to attract attention. The synthon (44) has been used to give β-selective condensation with silylated bases; reductive desulphurization then gave 2',3'-dideoxy systems.[73] Deoxygenation procedures have been used to prepare 2',3'-dideoxy- and 2',3'-dideoxydidehydro nucleosides of 2-substituted adenines,[74,75] pyrrolo[2,3-*d*] pyrimidines (42, R=H),[56,71] and further pyrazolo[3,4-*d*]pyrimidines.[59] Enzymic



Scheme 6

transglycosylation with the broad-specificity transglycosidase from *Lactobacillus helviticus* has been used to make diverse purine and pyrimidine 2',3'-dideoxynucleosides.[76] The potent anti-HIV agent 2',3'-didehydro-2',3'-dideoxythymidine (d4T, 45) has been prepared in a high-yielding way as indicated in Scheme 6,[77] whilst the 5'-*O*-trityl derivative of (45) has been made by treatment of the 2,3'-anhydronucleoside (29, R=Me, R'=Tr, X=O) with CsF in DMSO.[78] A range of 2',3'-didehydrodideoxy nucleosides, and the corresponding saturated hydrogenation products, have been made by Bu_3SnH reduction of 2',3'-bisxanthates or cyclic thionocarbonates,[79] and 2',3'-didehydrodideoxyuridine is accessible via Corey-Winter reaction on a 5'-*O*-protected uridine thionocarbonate.[80] A reference to such derivatives of the pyrrolopyrimidine nucleoside antibiotics is discussed in Chapter 19, and various truncated analogues of type (46) have been reported.[81]

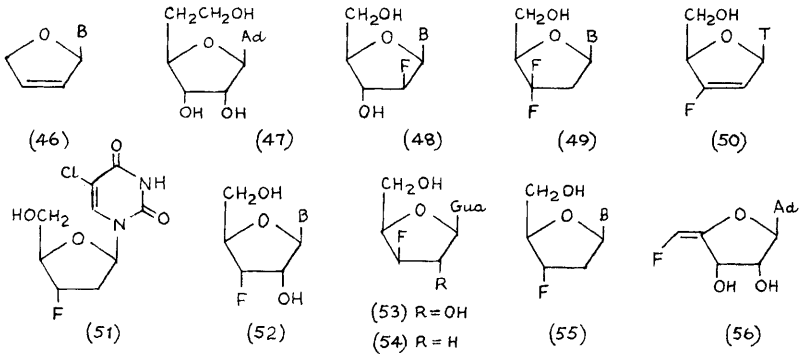
A new convenient synthesis of 5'-deoxy-β-D-*ribo*-hexofuranosyladenine('homoadenosine', 47) involves the preparation of an appropriate deoxyhexose derivative from D-glucose, and conventional nucleoside synthesis.[82] Some 2'.6'-dideoxyhexose nucleosides of thymine have been prepared by hydride reduction of chloroderivatives.[83]

Methods have been reported to differentiate between isomeric 2', 3'-, and 5'-deoxynucleosides using E.I. and C.I.-linked scanning mass spectrometry.[84]

4 Halogenonucleosides

A rapid synthesis of 2'-deoxy-2'-fluoroadenosine involves the use of DAST on a suitably protected ara-A derivative.[85] A number of purine nucleosides containing the 2'-deoxy-2'-fluoro-β-D-arabinofuranosyl moiety (48) have been prepared from glycosyl bromide and purine bases; the guanosine analogue (48,

B=Gua) shows promising antileukaemic activity.[86] The 2',2'-difluoro- analogues of 2'-deoxyadenosine and -guanosine have been made by methods similar to those used previously for pyrimidine analogues (Vol. 22, p. 210),[87] and, by introducing a conventional deoxygenation, this chemistry could be adapted for the synthesis of 2',3'-dideoxy-2',2'-difluorocytosine.[88] Treatment of a



3-ketosugar with DAST was used during a synthesis of 2',3'-dideoxy-3',3'-difluorocytosine and -uridine (49, B=U or C).[88] Other workers have reported the corresponding thymidine analogue (49, B=T), and its conversion by methoxide to the unsaturated fluoronucleoside (50). This paper also reports a variety of 2'- and 3'-fluorinated 2',3'-dideoxynucleosides, with the uridine derivative (51) displaying good anti-HIV activity.[89] The Leiden group have also reviewed earlier methods for the introduction of fluorine into nucleosides,[90] and given further examples of the use of DAST to produce 3'-deoxy-3'-fluoronucleosides (52) from *xylo*-compounds.[90,91] Other workers have also reported the synthesis of the guanosine analogue (52, B=Gua), by a similar halogenation with inversion using DAST,[92] whilst a number of compounds of type (52) have been made by conventional nucleoside synthesis from a 3-deoxy-3-fluoro-ribose derivative.[93,94] The D-*xylo*- analogue (53) has also been synthesized by base-sugar coupling, and a deoxygenation step gave the 2'-deoxy compound (54).[95] 3'-Deoxy-3'-fluorothymidine (55, B=T) has also been made by a DAST reaction,[96] and both it and the uridine analogue (55, B=U) can be prepared by fluoride-ion opening of a cyclonucleoside of type (29).[96,97]

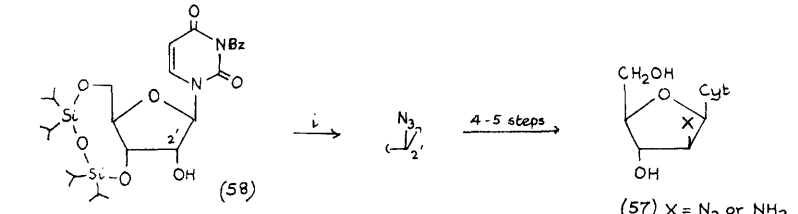
When a series of 8-substituted adenosines was treated with thionyl chloride in HMPA, the corresponding 5'-chloro- 5'-deoxy compounds were obtained in moderate to good yields.[98] When 2'-deoxyuridine was treated with benzoyl chloride in DMF, 5'-chloro-2',5'-dideoxyuridine was formed slowly, whereas the same reagents in the presence of MCPBA gave rapid chlorination of the heterocycle to give 5-chloro-2'-deoxyuridine. Several other similar cases were also reported.[99] The unsaturated compound (56), and its (*Z*)-isomer,

have been synthesized and shown to be powerful inhibitors of *S*-adenosylhomocysteine hydrolase.[100]

β-D-Glucopyranosyltheophylline has been converted into its 6'-deoxy-6'-fluoro- analogue, and fluorine was also introduced using DAST into the same starting material at C-3' and C-4', with inversion of configuration, to give β-D-*allo*- and -D-*galacto*- products, respectively.[101]

5 Nucleosides with Nitrogen-substituted Sugars

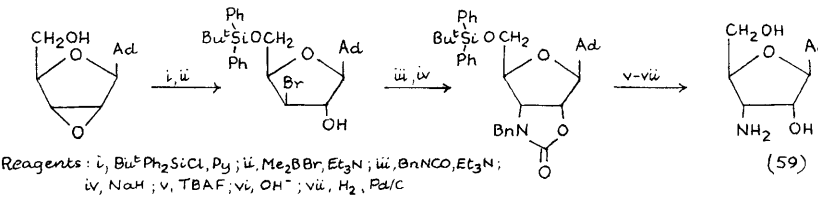
A new route to the antineoplastic nucleosides 2'-azido- and 2'-amino-2'-deoxy-β-D-arabinofuranosylcytosine (57) involves the reaction of the uridine derivative (58) as indicated in Scheme 7; the *N*-benzoyl group prevents intramolecular



Scheme 7

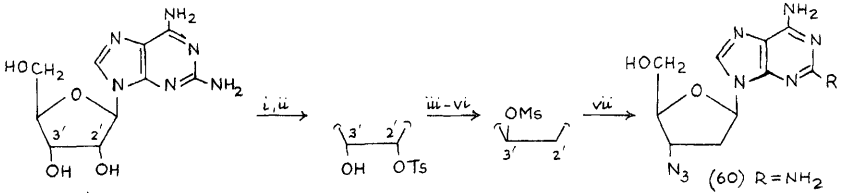
participation of *O*-2 during the Mitsunobu reaction.[102] A similar displacement was used to prepare the analogues in the 2-alkylpurine series; in this case the inversion at C-2' was carried out on a protected imidazole nucleoside, and the pyrimidine was annulated at a late stage.[103] A paper describing the synthesis of 2'-azido-2'-deoxy-β-D-xylofuranosyluracil (Vol. 21, Chapter 20, ref.68) has been reprinted with two previously-omitted pages now present.[104] A range of mono- and diaminoderivatives of 2'-deoxyadenosine, cordycepin (3'-deoxyadenosine), and their β-D-*threo*-analogues have been prepared, using standard hydroxyl → azide conversions with inversion of configuration.[105]

An efficient synthesis of 3'-amino-3'-deoxyadenosine (59) proceeds from the *ribo*-epoxide as indicated in Scheme 8.[106] A route to 3'-acetamido-3'-deoxy-β-D-arabinofuranosyladenine involves opening of the D-lyxo-epoxide at



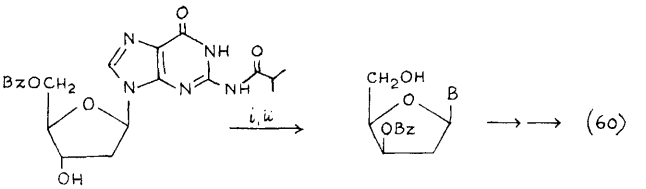
Scheme 8

C-3' by potassium isocyanate.[36] The diaminopurine analogue (60) of AZT, which displays good anti-HIV activity, has been made as indicated in Scheme 9 using a 1,2-hydride shift.[107] The same sort of approach has been used by other workers to prepare the corresponding adenosine analogue (61), and this paper also gives a full account of the use of such chemistry to make 2'-azido-2',3'-dideoxyadenosine (see Vol. 21, p.208).[108] Diamino analogue (60) has also been prepared from a 2'-deoxyguanosine precursor, where inversion of configuration at C-3' was accomplished by intramolecular participation of a 5'-O-benzoyl group (Scheme 10).[109] This approach can similarly be used to make (61).[110]



Reagents: i, Bu_2SnO, MeOH ; ii, TsCl, Et_3N ; iii, $LiEt_3BH$, THF, DMSO; iv, TrCl, Py ; v, MsCl, Py ; vi, HOAc, H_2O ; vii, LiN_3, DMF

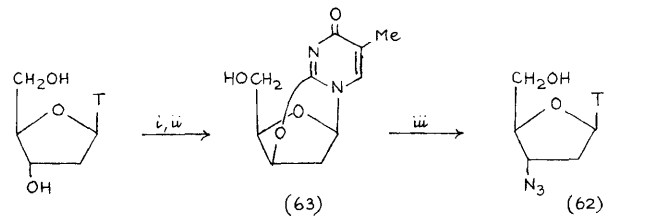
Scheme 9



Reagents : i, Tf_2O, Py ; ii, H_2O

Scheme 10

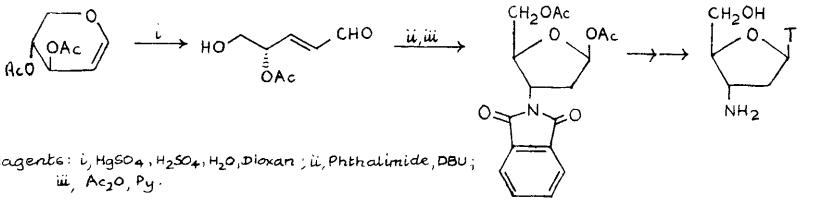
A new direct route to AZT (62) via the anhydroderivative (63) is shown in Scheme 11,[111] and other workers have used compounds of type (63)/(29) to prepare AZT, 3'-amino-3'-deoxythymidine, and related systems.[112,113] Dehydration of *N*-formyl derivatives of 3'-amino-3'-deoxythymidine has been



Reagents: i, $(PhO)_2SO$, Me_2NAc, NMe (cat) (156°); ii, Et_3N, H_2O ; iii, LiN_3, Me_2NAc

Scheme 11

used to make the 3'-isocyanocompound.[113,114] An alternative approach to 3'-amino-3'-deoxythymidine is indicated in Scheme 12;[115] this work has also been carried out in the enantiomeric series starting from L-arabinal[116] and extended to the synthesis of 3'-aminohexofuranosyl nucleosides.[117] The



Reagents: i, $HgSO_4$, H_2SO_4, H_2O, Dioxan; ii, Phthalimide, DBU; iii, Ac_2O, Py.

Scheme 12

3'-azido/amino-3'-deoxy-(64) and 5'-azido/amino-5'-deoxyanalogues (65) of 5-methoxymethyl-2'-deoxyuridine have been prepared by sulphonate displacement; their conformations were studied, and the 5'-aminocompound was found to have a considerable proportion of the *syn*-rotamer.[118] Two papers on the phosphonate analogue of AZT monophosphate are mentioned in Section 11.

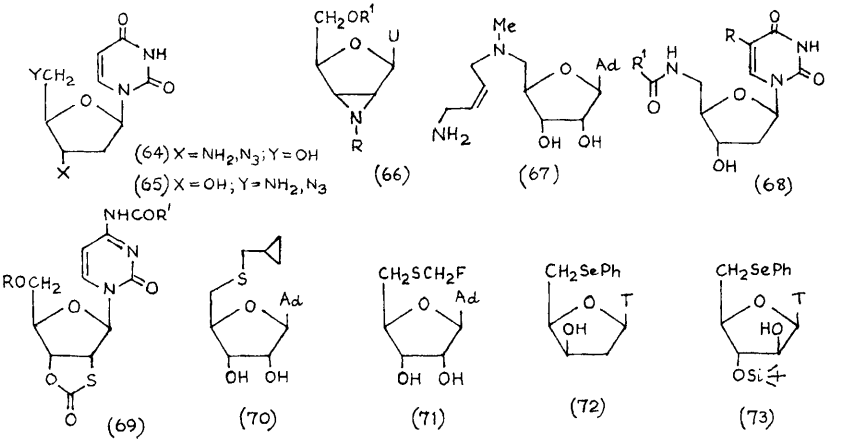
Treatment of the selenoylalkene (25) with various primary amines has led to a range of 2',3'-epiminocompounds (66);[45] this result may be compared with the analogous sulphonyl case reported last year (Vol. 22, p. 210-211).

The 5'-alkylaminoadenosine (67) has been synthesised from adenosine, and found to be a potent irreversible inhibitor of *S*-adenosyl-L-methionine decarboxylase.[119] A range of *N*-acyl derivatives (68), and corresponding *N*-sulphonyl compounds, have been prepared as viral thymidine kinase inhibitors.[120]

6 Thio- and Seleno-nucleosides

In contrast to the case of uridine derivatives noted above,[80] attempts to carry out a Corey-Winter fragmentation of N^4,5'- protected cytidine 2',3'-thionocarbonates caused isomerisation to 2'-deoxy-2'-thiocytidine-2',3'-carbonates (69).[121] The 3'-thiomethyl-, methylsulphinyl-, and methylsulphonyl derivatives of 3'-deoxythymidine have been prepared by treatment of the 5'-*O*-trityl derivative of (63) with methanethiolate ion, followed by oxidation at sulphur and deprotection as appropriate.[122]

5'-Deoxy-5'-(cyclopropylmethylthio)adenosine (70) has been prepared from 5'-chloroadenosine,[123] and there has been a further report on the synthesis of 5'-(fluoromethylthio)adenosine (71), formed with the 5'-fluoro-5'-methylthio compound discussed last year (see Vol.22, p. 212) from reaction of the 5'-methylsulphinyl derivative with DAST. Thioether (71) is a potent inhibitor of methylthioadenosine phosphorylase.[124] An oxidation-reduction



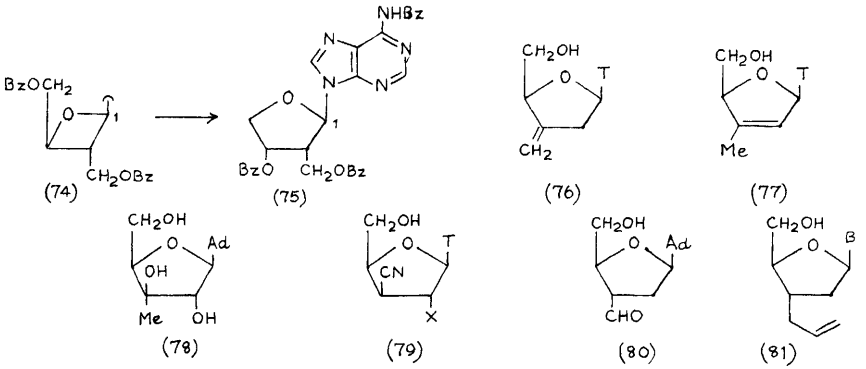
sequence has been used to convert 5'-deoxy-5'-methylthioadenosine into its 3'-epimer, a natural product (Vol.21, p.209).[125]

The 3'-phenylselenoyl-2',3'-ene (25) has been prepared by ring-opening of a 2',3'-*lyxo*-epoxide with PhSeLi, followed by elimination and oxidation at selenium.[45] The applications of (25) in synthesis are mentioned in Sections 2, 5, and 7. The 5'-deoxy-5'-phenylselenonucleosides (72) and (73) have been obtained by ring-opening of an oxetan and an oxolane, respectively.[126]

7 Nucleosides with Branched-chain Sugars

An interesting ring expansion has been observed when tribenzoyl-oxetanocin (74) is treated with Lewis acids, giving (75).[127] A similar process also occurred when the *N*-benzoyl-*O,O*-diacetyl analogue of (74) was treated with stannic chloride and bis(trimethylsilyl)uracil, giving a mixture of the *O,O*-diacetyl analogue of (75) and the equivalent compound in which transglycosidation had occurred to give the uracil nucleoside.[128]

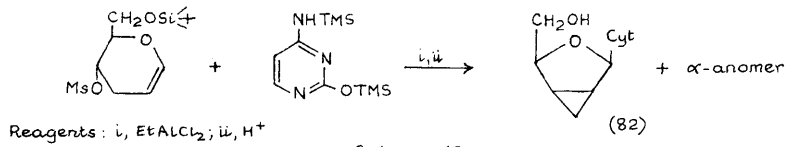
In an account of a review lecture, Ueda has covered the work of his group on 2'-*C*-methyl and -methylidene derivatives of cytosine and thymidine (see Vol.22, p.213, and earlier volumes).[129] The same group has also reported the synthesis of 2',3'-dideoxy -3'-methylidene thymidine (76) and the isomeric 2',3'-didehydro-2',3'-dideoxy-3'-methylthymidine (77), both of which were obtained by deoxygenation of the allylic alcohol system in 3'-deoxy-3'-methylidene-S-methyluridine.[130] When MeMgI reacted with a protected 3'-ketonucleoside, subsequent deprotection gave (3'-*C*-methyl-β-D-*xylo* furanosyl)adenine (78) as the major product, along with lesser amounts of the epimer, 3'-*C*-methyladenosine. The orientation of the methyl group affected the sugar conformation (n.m.r.); (78) had a predominant $^3T_2$ shape, whilst the



epimer adopted a $^2T_3$ arrangement.[131]

The Madrid group has given further details of their work on the synthesis of 3'-cyano-3'-deoxythymidine and related compounds (Vol. 22, p. 214), with extensions to similar analogues containing the other nucleoside bases,[132] and another synthesis of 3'-cyano-3'-deoxythymidine itself has been reported, in which bis-TMS-thymine was coupled with a preformed *C*-cyano sugar unit; the product was again found to be inactive against HIV, in contrast to the initial reports.[133] Products of type (79, X = -NHMe, morpholino-, $-CH_2NO_2$) have been obtained by Michael additions to a 3'-cyano-5'-protected -2',3'-ene; the D-*xylo* isomers shown predominated, except in the case of addition of ammonia, where the cis-(D-*ribo*)- product was the major.[134] Deoxyadenosine has been converted into 3'-cyano- 2',3'-dideoxyadenosine and its 3'-epimer, and these were converted via DIBAL reduction into the branched-chain aldehyde (80) and its epimer,[135] whilst two groups have synthesized *C*-allyl compounds of type (81, B = U,T,C) by coupling of C-3' free radicals with alkyltributyl stannane;[136,137] the free radicals could also be added to methyl acrylate and acrylonitrile to give the expected α-adducts.[137]

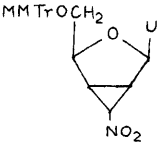
An interesting 'homo-Ferrier' reaction has been used to prepare the cyclopropacytosine analogue (82), as outlined in Scheme 13.[138] When the selenoyl alkene (25) was treated with the potassium salt of nitromethane, the cyclopropyl system (83) was formed, whilst reaction of (25) with the anion of ethyl acetoacetate gave the product (84).[45]



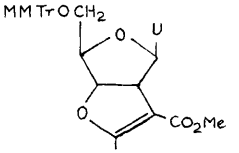
Scheme 13

8 Nucleosides of Unsaturated Sugars, Ketosugars, and Uronic Acids

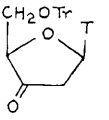
An improved procedure for the preparation of 3'-keto-5'-*O*-tritylthymidine (85) has been reported, using PDC oxidation in the presence of molecular sieves.[139]



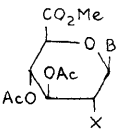
(83)



(84)



(85)

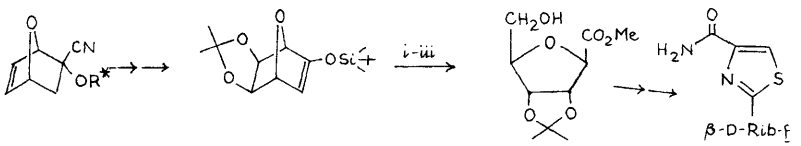


(86) X = NHCOCF$_3$
(87) X = OAc

Derivatives of 2-amino-2-deoxy-D-glucopyranuronic acid nucleosides (86) have been prepared by conventional coupling procedures,[140] and uronic ester nucleosides of type (87) give the 4',5'-ene on treatment with DBU.[141]

9 C-Nucleosides

The asymmetric synthesis of *C*-nucleosides by Diels-Alder reaction between furan and di(*l*-menthyl)(acetoxymethylene)malonate has been briefly reviewed.[142] In rather similar work, Vogel has used his 'naked sugar' approach to prepare thiazofurin (88) from the homochiral adduct of furan and cyanovinyl (*S*)-camphanate, as indicated briefly in Scheme 14,[143] and similar chemistry



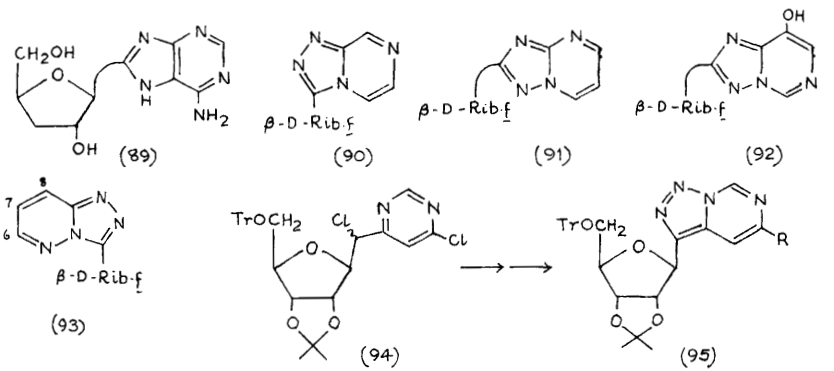
Reagents: i, O_3, MeOH, CH_2Cl_2; ii, $NaBH_4$; iii, CH_2N_2

(88)

Scheme 14

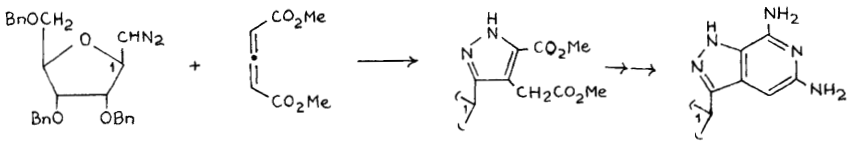
was also used by the same group to prepare 2,5-anhydro-4-deoxy-D-*ribo*-hexonic acid, and hence the *C*-nucleoside analogue (89) of cordycepin.[144]

A number of papers have discussed the use of derivatives of 2,5-anhydroallonic acid to prepare *C*-nucleosides. Condensation of the ethyl dithioate with 2-hydrazinopyrazine gave the 1,2,4-triazolo[4,3-*a*]pyrazine (90), whilst a similar reaction with 2-hydrazinopyrimidine gave the 1,2,4-triazolo[1,5-*a*]pyrimidine (91), the product of Dimroth rearrangement.[145] Reaction of a protected *S*-benzylthioimidate with 5-benzyloxy-4-hydrazinopyrimidine gave a mixture of two protected systems, both of which gave the same rearranged triazolo[1,5-*c*]pyrimidine (92) on base-catalysed deprotection.[146] Use of various 3-hydrazinopyridazines gave triazolo[4,3-*b*]



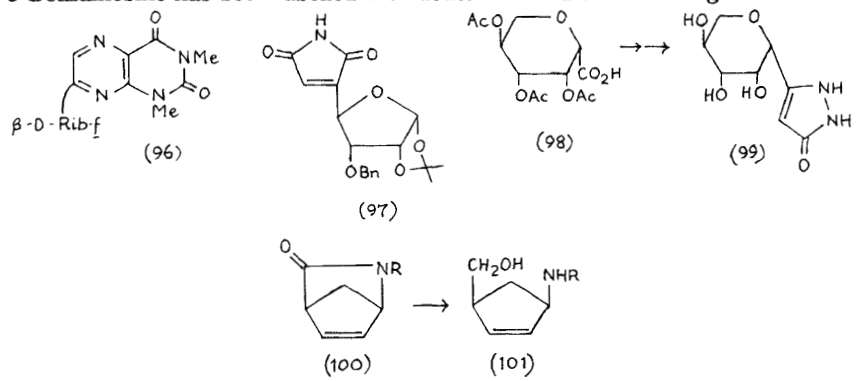
pyridazines (93) with an amino group at position 6,7, or 8.[147]

The pyrimidine 'homo-*C*-nucleoside' (94) has been made by a Wittig reaction followed by Michael-type cyclization, and this could be converted into the 1,2,3-triazolo[1,5-c]pyrimidine systems (95).[148] Pyrazolo[3,4-c]pyridine *C*-nucleosides have been prepared via the [3+2] cycloaddition shown in Scheme 15,[149] and the lumazine *C*-nucleoside (96) has been prepared from an intermediate reported last year (Vol.22, p.216)[150]



Scheme 15

The 2'-deoxy-derivatives of formycin B and oxoformycin have been prepared by fairly standard methods,[151] and the 2',3'-didehydro-2',3'-dideoxy- and 2',3'-deoxyderivatives of 9-deazaadenosine have been prepared from 9-deazaadenosine itself via the reaction with 2-acetoxyisobutyryl bromide.[152] 9-Deazainosine has been labelled with deuterium and tritium using reduction of



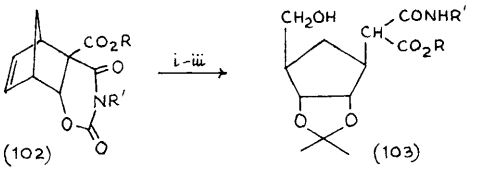
a C-5'- aldehyde.[153]

In the area of pyridine *C*-nucleosides, a full account has been given of the synthesis of 3-chloro-4-(β-D-ribofuranosyl)pyridine and 3-(β-D-ribofuranosyl) pyridone (Vol.21, p.211),[154] and both α- and β- isomers of 2-carbamoyl-5-D-ribofuranosyl pyridine have been prepared by a similar approach.[155]

Some 'pseudo-*C*-nucleosides' such as (97) have been prepared from diisopropylidene glucose.[156] Tri-*O*-acetyl-2,6-anhydro-L-galactonic acid (98) is available from D-galacturonic acid in three steps, and has been used to prepare some β-L-lyxopyranosyl *C*-nucleosides such as (99).[157]

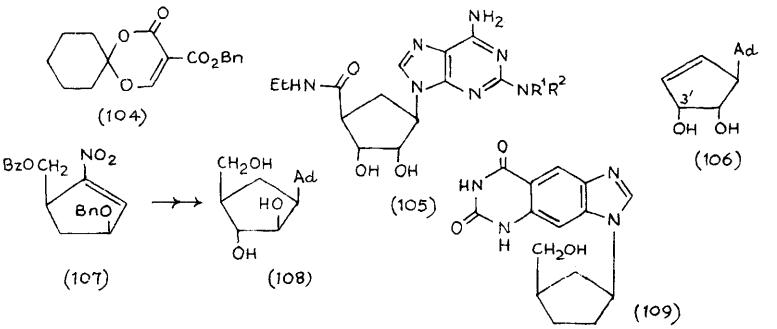
10 Carbocyclic Nucleoside Analogues

Racemic bicycles of type (100), where R is electron-withdrawing, undergo reductive cleavage with sodium borohydride to give (101); where R = CONHMe, reduction and heterocycle formation gave rise to 2',3'-dideoxy-N^3-methyl uridine.[158] In an extension of earlier work (see Vol.21, p.213-4) on the synthesis of carbocyclic *C*-nucleosides, Diels-Alder adducts (102) could be transformed into synthons (103) (Scheme 16) by hydroxylation and reductive retroaldol cleavage. By use of a chiral auxiliary, R = *l*-menthyl, good asymmetric inductions could be obtained in favour of the 'natural' absolute configuration.[159] Similar work has also been reported using the (racemic) Diels-Alder adduct of cyclopentadiene and (104).[160]



Reagents: i, OsO_4, NMMO; ii, $Me_2C(OMe)_2$, H^+; iii, K_2CO_3, $NaBH_4$, MeOH

Scheme 16



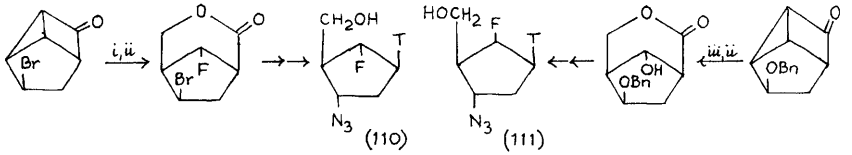
The carbocyclic analogue of 3-deazaadenosine is a promising antiviral agent, and a number of 5'-substituted analogues of it have been prepared.[161] Carbocyclic uronamides of type (105) have also been reported; these incorporate features which give hypotensive effects in adenosine analogues.[162]

The neplanocin analogue (106) (see Vol.21, p.194) is a powerful inhibitor of *S*-adenosyl homocysteine hydrolase; it has been shown that it is oxidized by the enzyme to the 3'-ketone, which can also be made chemically using MnO_2, and that this ketone binds tightly to the NADH form of the enzyme.[163] Some other references to neplanocin and aristeromycin analogues are given in Chapter 19, along with papers on carbocyclic analogues of oxetanocin.

Michael addition of N^6-benzoyladenine to nitroalkene (107), and reductive denitration, were key steps in a synthesis of cyclaridine (108).[164] The thymine analogue of (108) has been prepared by building up the pyrimidine ring around the amino group of an aminocyclopentane,[165] and some 2-arylaminoderivatives of (108) were similarly synthesized.[166]

Griengl and coworkers have used the same synthon as in previous work (Vol.22, p.217; Vol.21, p.213-4) to prepare carbaanalogues of BVDU and 5-iodo-2'-deoxyuridine in optically-pure forms,[167] and the 2',3'-dideoxycarbanucleoside (109) has been reported.[168]

The CHF analogues (110) and (111) of AZT have been prepared from the previously-known strained tricyclic ketones shown in Scheme 17.[169] Treatment of carbocyclic 5'-*O*-trityl-3'-*epi*-thymidine with DAST led not only to the expected carba-3'-deoxy-3'-fluorothymidine, but also to the 4'-fluoro-3'-deoxy isomer and the 3',4'-alkene.[170]



Reagents : i, $Et_3N.HF$; ii, MCPBA ; iii H_2O, THF

Scheme 17

The same type of chemistry as was used for the synthesis of (108) has also been applied to the synthesis of the carbocyclic analogue of (β-D-glucopyranosyl)adenine.[171]

11 Nucleoside Phosphates and Phosphonates

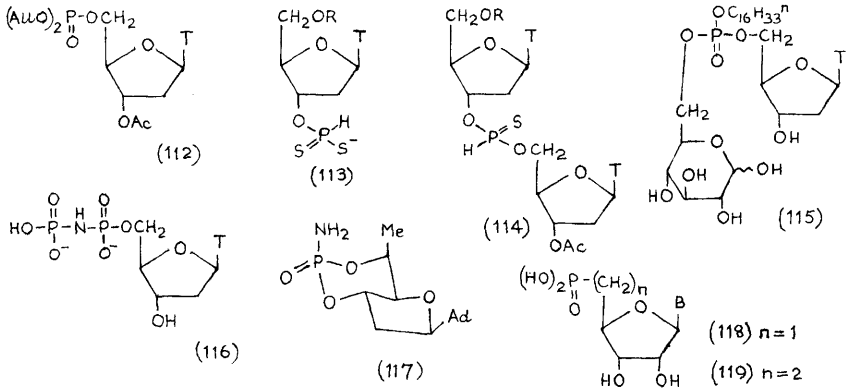
A review on gene synthesis includes a discussion of methods for the preparation of oligonucleotides.[172] Bis(allyloxy)(diisopropylamino)phosphine has been developed as a new reagent for phosphorylation; intermediates such

as (112), obtained after oxidation of the initial phosphite, can be deprotected at the phosphate by use of $Pd(PPh_3)_4$.[173] Pfleiderer's group have described preparative-scale syntheses of protected di-2'-deoxynucleotide phosphotriesters and thiophosphotriesters via the phosphoramidite approach,[174] and the 2-(4-pyridyl)ethyl protecting group has been used for phosphite/phosphate protection during such syntheses.[175]

A 2-5A analogue which is deoxygenated at C-3' in both end units has been synthesised (see also Vol.21, p.215),[176] and 2'-5'-linked oligoadenylates with a nucleotide branch at the 3'-position have also been reported.[177] Four different strategies for synthesis of related branched-chain ('lariat') structures have been reviewed.[178]

Di-deoxynucleoside methylphosphonates, with the *Rp* isomer predominating, can be obtained by sequential reaction of a 3'-hydroxyl group and a 5'-hydroxyl group with $MePCl_2$, followed by oxidation with *t*-butylhydroperoxide,[179] and a somewhat similar sequence was used to prepare dithymidine phosphomorpholidate.[180] The (*Rp*, *Rp*) and (*Sp*, *Sp*) -isomers of TpTpT diphosphorothioate have been prepared.[181] Di(deoxynucleoside) phosphorodithioates have been synthesized using deoxynucleoside thiophosphoramidites as intermediates,[182] or from deoxynucleoside 3'-hydrogenphosphonodithioates (113), either directly[183] or using di(deoxynucleoside)hydrogen phosphonothioates (114) as intermediates.[183,184]

The cytidine diphosphate of D-quinovose has been prepared by coupling the sugar 1-phosphate and CMP.[185]



In an investigation of a possible way of delivering nucleoside drugs across cell membranes, the glucosyl phospholipid (115) of thymidine was prepared. This was found to interact with large unilamellar vesicles so as to place the nucleotide derivative inside the vesicles, suggesting transport across the lipid bilayer.[186] Similar mannose phosphate derivatives of AZT, ddT and FDU were

also synthesized as membrane-soluble prodrugs towards cells with mannosyl receptors,[187] and other workers have linked mannose with 5-iodo-2'-deoxyuridine and 2-5A via a diphosphate, with a similar aim in mind.[188]

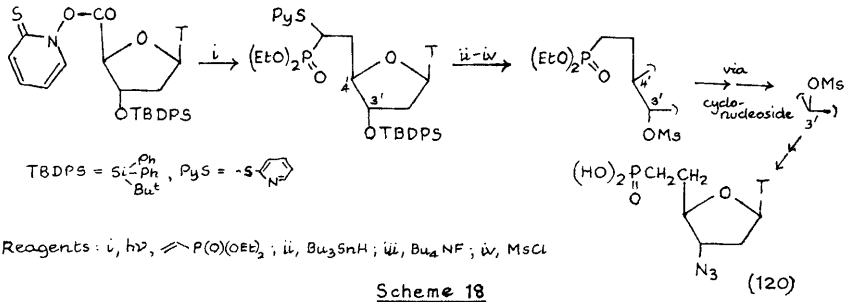
The α,β-imido analogue (116) of thymidine diphosphate has been prepared[189] and 5'-*O*-(α-thio)triphosphates of some 2',3'-dideoxynucleosides have been synthesized.[190] A cyclic dimer of FDU monophosphate has been shown to have *in vivo* antitumour activity as does FDU itself, and with less toxicity.[191]

The interaction of cyanogen bromide and imidazole gives rise to *N*-cyanoimidazole and diimidazole imine, both of which can be used to make 2',3'-cyclic AMP from 3'-AMP.[192] There have been further reports on the cyclodextrin-catalyzed cleavage of 2',3'-cyclic nucleoside phosphates (see vol.22, p.218); use of α-cyclodextrin cleaves 2',3'-cUMP to the 3'-phosphate in 94% yield,[193] whilst a fuller account has been given of the hydrolysis of 2'.3'-cAMP and -GMP to the 2'-phosphates by β- and γ-cyclodextrins,[194] and the same selectivity can be achieved using 6-*O*-α-D-glucopyranosyl-β-cyclodextrin.[195] The rate and selectivity of the β-cyclodextrin-induced cleavage of 2',3'-cAMP are considerably increased by the presence of alkali-metal cations.[196]

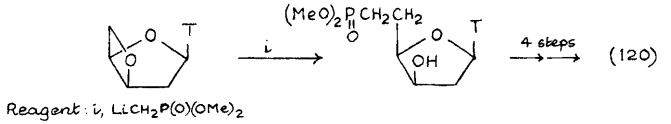
A method has been developed for the direct synthesis of 3',5'-cyclic phosphates from unprotected nucleosides,[197] and the 2',5'-cyclic phosphate of ara-A has been prepared.[198] The 3',5'-cyclic phosphoramidate (117), of *Rp* chirality, undergoes acid hydrolysis (with P-N cleavage) more rapidly than does the analogue without the axial methyl group, whilst there is no such effect for the *Sp* isomer, results which can be rationalised on stereoelectronic grounds.[199] A comparable study was carried out on both P-chiral isomers of the corresponding compound with an equatorial methyl group.[200] An n.m.r. study of the demethyl analogue of (117), its *Sp* isomer, and N-methylated derivatives, (see vol.22, p.217) has been reported.[201] An efficient route to 3',5'-cyclic phosphoramidates of 5-substituted-2'-deoxyuridines involves the formation and oxidation of the cyclic phosphoramidites.[202]

In the area of phosphonates, analogues of type (118) have been prepared by coupling of silylated bases with a 1-*O*-acetyl derivative of the phosphonosugar;[203] in the case of (118, B = Gua), the base unit (14) was used to ensure good N^9-selectivity in the coupling.[24] A similar method was used to prepare the higher homologues (119), and here the hexose unit required for coupling was elaborated from diisopropylidene glucose.[204] The Gif group have applied some of their free-radical methods to the synthesis of the isosteric phosphonate of UMP (119, B = U),[205] and to the phosphonate analogue (120) of AZT monophosphate; as applied to the latter target, the process is indicated

in Scheme 18.[206] Other workers have also made (120), using as the key step the opening of a 3',5'-oxetan (Scheme 19).[207] Isosteric phosphonate analogues



Scheme 18



Scheme 19

of 2',3'-dideoxynucleoside monophosphates have been prepared by Wittig extension of the 5'-aldehydes.[208] The phosphonate (121), devised as a potential precursor to a transition-state analogue of purine nucleoside phosphorylase, has been prepared from fructose in a multistep process.[209]

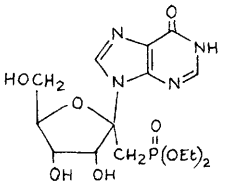
12 Ethers, esters and acetals of nucleosides

In a study on oligoribonucleotide synthesis by the phosphoramidite approach, the chemical properties of various 2'-*O*-protecting groups (e.g. THP, TBDMS) have been investigated.[210] Other workers have similarly evaluated the stability and resistance to migration of the 2'-*O*-TBDMS group during ribonucleotide formation, and found it to be satisfactory for most methods.[211] The *p*-cyanophenylethylsulphonyl(CPES) and carbomethoxyethylsulphonyl (CMES) groups have been developed for 2'-OH protection during ribonucleotide formation. The former is more stable than the previously-used *p*-nitrophenylethylsulphonyl group, but can be removed with fluoride ion, whilst the CMES group seems more labile, and thus less generally useful.[212]

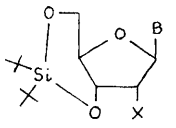
Studies on the methylation of 1-β-D-ribofuranosyl derivatives of 2-pyridone, 4-pyridone and 3-methyluracil using trimethylsulphonium hydroxide suggested that the reactivity of the 2'-OH is enhanced by hydrogen bonding to *O*-2.[213] Syntheses of 3'-*O*-propargyl thymidine (an AZT analogue)[214] and 3'-*O*-benzyltrifluridine[215] have been reported.

Reaction of deoxyadenosine and deoxythymidine with dialkyldichlorosilanes gives 3',5'-*O*-dialkylsilanediyl derivatives of which the di-*t*-butyl species (122, B = Ad or T) are the most useful (see also Vol.19, p.207).[216] Similar derivatives (123) can be obtained for ribonucleosides.[217] Acidic hydrolysis of (122, B = T) gives mainly the 3'-*O*-hydroxysilyl ether,[218] whilst base treatment gives a mixture of 3'- and 5'-*O*-isomers, these being stable to further hydrolysis under mild acidic or basic conditions.[219] Complete removal of the di-*t*-butylsilanediyl group is best done with tributylamine hydrofluoride in THF.[220] The sugar conformations of compounds (122) have been studied.[221]

N^6,N^6-Dimethyladenosine has been converted into a series of mono-,di- and triesters with fatty acids, using conventional protection-deprotection procedures. The 2'-monoesters could not be isolated due to facile ester migration, but 3'- and 5'-monoesters with C_{10}-C_{13} acids were obtained and were potent antitumour agents.[222] Various 5'-*O*-acyl derivatives of 5-iodo-2'-deoxyuridine[223] and 5-fluorouridine have been prepared; the 5'-*O*-heptanoyl derivative of 5-fluorouridine showed good antitumour activity.[224] Enzymic synthesis of 5'-*O*-acyl derivatives of some 2'-deoxy-5-substituted uridines can be carried out efficiently by use of the acid anhydride and *Pseudomonas fluorescens* lipase (PFL) in an organic solvent.[225] Alternatively, the 3',5'-di-*O*-acyl derivatives can be selectively hydrolysed to the 5'-*O*-acyl deoxynucleosides using PFL in DMF; hydrolysis by subtilisin gives the 3'-*O*-acyl derivatives instead, but in only moderate yield.[226] Cytosine nucleosides can be selectively acylated on nitrogen, avoiding *O*-acylation, by the use of acetic or benzoic anhydride in DMF at room temperature.[227]

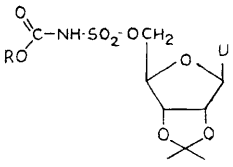


(121)

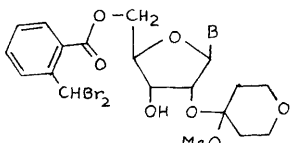


(122) X = H

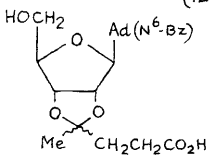
(123) X = OH



(124)



(125)



(126)

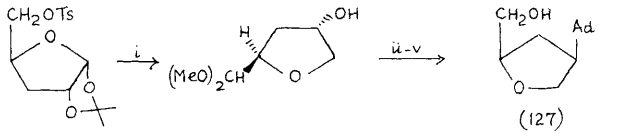
Further analogues of UDPG (see Vol.22, p.221, and earlier) of type (124), and also simpler *N*-alkyl sulphamoyl derivatives, have been reported.[228]

A set of selectively-protected nucleosides such as (125) have been prepared for use in phosphotriester syntheses of oligonucleotides,[229] and the

acetal (126) has been coupled to 6-aminohexyl sepharose 4B, for use in affinity chromatography.[230]

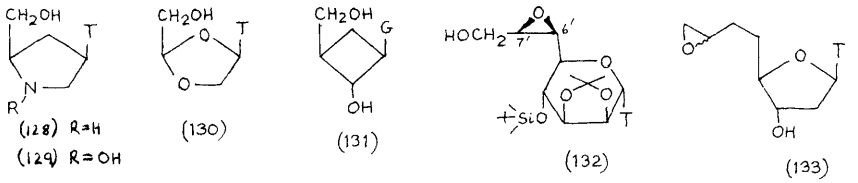
13 Miscellaneous nucleoside analogues

A number of unusual and interesting furanose analogues have been reported. 'Iso-ddA'(127) has been prepared as indicated in Scheme 20, and shown to have anti-HIV activity.[231] The anti-tumour pyrrolidine analogues (128) and (129) have been made from 4-hydroxy-proline,[232] and the racemic dioxolane (130) shows anti-HIV properties.[233] The carbocyclic analogue (131), prepared as its racemate by reaction of the anion of 2-amino-6-benzyloxypurine with an epoxide, has antiviral activity similar to acyclovir.[234] Related carbocyclic analogues of oxetanocin are mentioned in Chapter 19.



Reagents: i, 1% HOAc, MeOH; ii, TsCl; iii, Adenine, K_2CO_3, 18-crown-6; iv, H_3O^+; v, H_2, PtO_2

Scheme 20

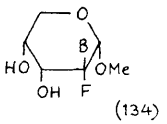


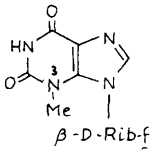
The epoxide (132), and its 6',7'-epimer, have been prepared as potential precursors of nucleosides of higher-carbon sugars.[235] Pentofuranosyl nucleosides have been chain-extended at C-5' by Wittig reactions[236] and reactions of 5'-halides with stabilized carbanions.[237] The epoxide (133), a possible trap for monophosphate binding sites of enzymes utilising nucleotides, has been produced using Wittig chemistry.[238]

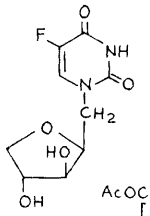
Abnormal nucleoside/nucleotide-like compounds of type (134),[239] (135),[240] and (136)[241] have been prepared.

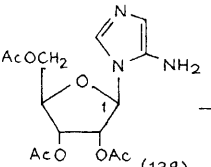
14 Reactions

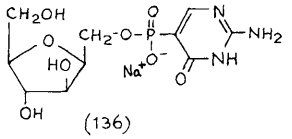
A review has been published on the acidic hydrolysis of nucleosides and nucleotides, particularly with regard to the influence of sugar and base substitutions on the stability of the *N*-glycosidic bond.[243] First-order rate


(134)


(137)


(135)


(138)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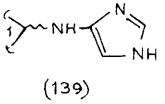
(139)

constants have been determined for the acidic hydrolysis and for acidic and acid-buffer catalysed deamination of cytidine and a number of methylated derivatives.[243] A study of the influence of metal ions on the acidic hydrolysis of 2'-deoxyguanosine and 2'-deoxyadenosine has shown that certain metals can be used to protect 2'-deoxyguanosine selectively against acidic depurination, with the metals binding to N^7 of the deoxyguanosine.[244] The mechanism for acid-catalysed hydrolysis of benzimidazole nucleosides has been shown to involve cleavage of an N^3-protonated substrate to give the free base and a carbocation.[245] The *N*-glycosidic bond in N^3-methylxanthosine (137) has been shown to undergo acidic cleavage 10^3 times faster than that of xanthosine,[246] and a review of the minor components of t-RNA discusses the rates of hydrolysis of the unusually labile glycosidic bonds in these nucleosides.[247] The enzymic and chemical stabilities of 2',3'-dideoxy-2',3'-didehydropyrimidine nucleosides have been assessed. While showing enzymic stability, they are less stable chemically, to either acid or base, than araC; for example, the cytosine analogue degrades rapidly ($t_{1/2}$ 20 min) at pH3.[248] A study has been reported of the kinetics and mechanism of phosphate migration, phosphate hydrolysis, and purine hydrolysis for adenosine 2'- and 3'-phosphates in aqueous solution at different pH values.[249]

The aminoimidazole nucleoside derivative (138) has been shown to undergo rearrangement in aqueous buffer at pH7 to give the glycosylamines (139), with the β-anomer predominating; this observation may well be relevant to the previously-noted lability of the corresponding nucleoside and nucleotide.[250]

A study has been made of the reactions of hydroxyl radicals and the sulphate anion radical with uridine, 2'-deoxyuridine, and related nucleosides under anoxic conditions. With HO• the e.s.r. spectra observed were mainly those of species formed by addition to the double bonds. With $SO_4^{-\bullet}$, radicals were derived from the bases of the deoxynucleosides, whereas the

ribonucleosides gave radicals derived from the sugar. Radicals formed at C-3' underwent ring opening by cleavage of the C(4')-O ring bond.[251] The reactions of hydroxyl radicals with purine nucleosides and deoxynucleosides have also been investigated. In all cases, H-abstraction from C-5' was observed, and for dAMP and dGMP, also from C-4'.[251] On γ- irradiation of adenine and guanine nucleotides in dilute aqueous solution, the degree of cleavage of the *N*-glycosidic bond is greater for ribonucleotides than for 2'-deoxy systems, or where the 2'-OH is protected as a cyclic acetal. The experimental data support the formation of ortho- and metaphosphate ions during irradiation.[253]

In further studies of the cleavage of oligonucleotides by bleomycin- metal systems, the balance between the oxygen-dependent pathway for breakdown of the C-4'-radical and the O_2-independent pathway has been investigated with various deoxy-tetranucleotides. In certain cases an unusual selective hydroxylation at C-4' of a terminal cytidine unit was observed.[254]

15 Spectroscopic and Conformational Studies

The anomeric configurations of D-ribo-, D-arabino-, 2'-deoxyribo-, and 2',3'-dideoxyribonucleosides have been determined unambiguously by NOEDS methods. The 1'-H signals were saturated and the n.O.e. factors for 4'-H, 3'-H and 2'-H were measured.[255]

Conformational analyses have been carried out on 2',3'-*O*-alkylideneuridines by n.m.r. methods,[256] and on 8-substituted-2',3'-*O*-isopropylideneadenosine 5'-carboxylic acids, using n.m.r. and c.d. measurements, where stabilisation by an N^3 to carboxyl group interaction was demonstrated.[257]

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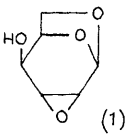
21
N.M.R. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

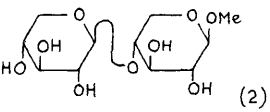
Reviews have appeared on the use of high resolution n.m.r. spectroscopy in the structural determination of complex carbohydrates[1] and of some 3-O-, 4-O-, and 3,4-di-O-glycopyranosyl-substituted methyl D-glycopyranosides. The latter publication includes complete assignments of ^{1}H- and ^{13}C-n.m.r. resonances as well as conformational studies using HSEA effect theory.[2] The application of various n.m.r. techniques (multi-relayed correlation, ^{1}H-^{1}H-correlated, triple quantum field ^{1}H-^{1}H-correlated and ^{1}H-^{1}H homonuclear Hartmann Hahn spectroscopy) to carbohydrate analysis has been reviewed in Japanese,[3] and in a further Japanese review the interactions of metal ions with uronic acids and amino sugars as observed by the lanthanide-probe n.m.r. method are discussed.[4]

A symposium report deals with the use of n.m.r. spectroscopy for piecing together fragments of oligosaccharides, inter alia, isolated from liverworts (Hepaticae).[5]

As part of a paper on the analysis of components of complex sugar mixtures by two-dimensional mass- and n.m.r.-spectroscopy, the 2D J-coupled COSY spectra of six sugars (arabinose, xylose, sorbose, cellobiose, lactose and melibiose) in D_2O have been presented.[6] A modified version of the 2D semi-selective INEPT technique for the determination of three-bonded heteronuclear coupling constants ($^{3}J_{H\text{-}C\text{-}O\text{-}C}$) has been developed, its potency being demonstrated by application to compounds (1) and (2) as examples of rigid and flexible carbohydrate derivatives, respectively.[7] For the magnitude of $^{3}J_{H\text{-}C\text{-}O\text{-}C}$ and the corresponding dihedral angle a Karplus-like relationship has been proposed.[8]



(1)



(2)

The kinetics of anomerisation of D-talose have been investigated by ^{1}H-n.m.r. spectroscopy, and by ^{13}C-n.m.r. spectroscopy using ^{13}C-labelled substrate. Six tautomeric forms (α- and β-pyranose, α- and β-furanose, aldehydo and hydrated aldehydo) were observed in D_2O.[9] A ^{13}C-n.m.r. spin - lattice relaxation study of the effect of solvent on the rotational dynamics of methyl α- and β-glucopyranosides has been published. For both anomers the rate of overall motion increases on going from D_2O, MeOH or DMF to pyridine to DMSO, this trend reflecting, apparently, the increasing viscosities and increasing molecular weights of solvated entities.[10]

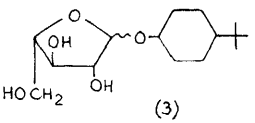
2 Acyclic Systems

In a first application of pattern recognition to n.m.r. spectroscopy by a neural network, the ^{1}H-n.m.r. spectra of six alditols have been assigned.[11] Analysis of the preferred conformations of partially acetylated alditols in $CDCl_3$ showed that they are mainly determined by intramolecular hydrogen-bonding between the free hydroxy groups.[12]

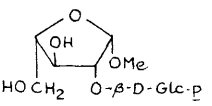
3 Furanose Systems

In a simulation study of the pseudorotation of methyl 2-deoxy-β-D-erythro-pentofuranoside, use was made of several model compounds of increasing complexity (cyclopentane, tetrahydrofuran, 3-hydroxy-, and 2,3-dihydroxy-tetrahydrofuran) to examine in detail the conformation of the furanose ring.[13] An interesting new analysis of the anomeric effect in furanoses indicated that in these systems the axial orientation of electronegative groups at the anomeric centre is particularly favoured which implies an sp^2 hybridised ring-oxygen with non-equivalent lone pairs.[14]

The ^{13}C-n.m.r. spectra of various glycosides of α- and β-L-arabinofuranose [e.g. monosaccharides (3) and glucosylated derivatives such as disaccharide (4)] have been assigned, and chemical shift patterns characteristic of certain types of



(3)

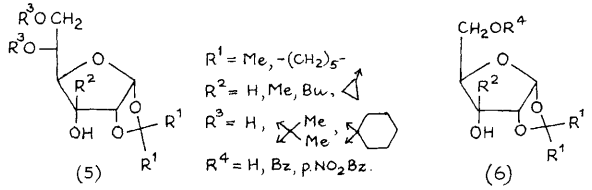


(4)

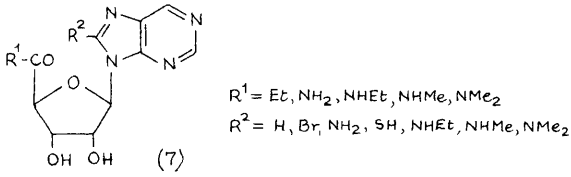
glycosides have been established.[15] The ^{13}C-n.m.r. spectra of a large number of branched α-D-allofuranose acetals (5) and α-D-ribofuranose acetals (6) have been

described with special attention to the effect of substitution on the ring carbon atom chemical shifts.[16]

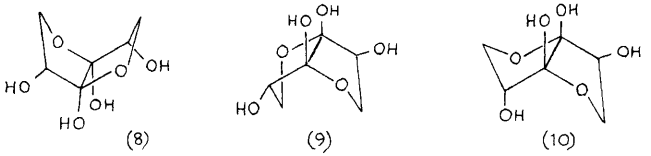
^{1}H-n.m.r. and CD data have been reported for seventeen 8-substituted adenosine 5'-carboxylic acid derivatives (7). The magnitudes of the spin - spin coupling constants for the protons of the ribose moieties were consistent with preference for the proposed $_3$E conformations, and the orientations of the



heterocycles relative to the furanose rings appeared to depend on the size of the substituent R^2 at C-8.[17] A number of antiviral nucleosides such as 3'-azido-3'-deoxythymidine and the 2',3'-dideoxy analogues of adenosine, cytidine and inosine have been examined by ^{13}C-n.m.r. spectroscopy. Assignments were made on the basis of twenty 2D INADEQUATE experiments to determine carbon - carbon connectivities.[18]



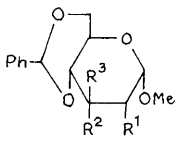
It has been established by ^{1}H-n.m.r. spectroscopy that D-threo-3,4-hexodiulose exists in solution (D_2O) as a 2:1 mixture of the bicyclic α,α- and β,β-forms (8) and (9), respectively, both with endo-endo geometry, whereas in the solid state it is present as the endo-exo-β,β-conformer (10) (see also Chapter 22).[19]

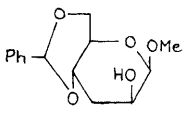


4 Pyranose Systems

A quantitative investigation of the ^{1}H-n.m.r. line shifts induced by Eu(fod)$_3$ in the spectra of the methyl 4,6-O-benzylidene-2- or 3-deoxy-D-hexopyranosides (11)-(15) has been undertaken. In addition, the ^{13}C-n.m.r. spectra of these compounds have been completely assigned by use of selective ^{1}H-spin decoupling and off-resonance experiments.[20]

A comparative evaluation of the ^{13}C-n.m.r. data of ten 1-C-aryl-D-glucopyranoses including four pairs of anomers showed that, with the exception of C-4, the carbon atoms of the β-pyranose rings resonate at lower fields than do the corresponding carbon atoms of the α-anomers.[21] The configurations at the acetal centres of hexopyranoside 4,6-O-pyruvate acetals [compounds (20)-(25) in





(15)

(11) R^1 = OH, R^2 = R^3 = H
(12) R^1 = OTs, R^2 = R^3 = H
(13) R^1 = H, R^2 = OH, R^3 = H
(14) R^1 = R^2 = H, R^3 = OH

Chapter 6] have been assigned on the basis of the finding that the ^{13}C-n.m.r. signals of axially disposed methyl groups appear at higher fields than do those of equatorial ones.[22]

The ^{1}H- and ^{13}C-n.m.r. spectra of the pseudo-2-acetamido-2-deoxy-DL-hexopyranoses with α- and β-gluco-, -manno- and -galacto-configurations have been compared with those of the corresponding true sugar analogues. No major conformational differences were observed between the pyranose- and pseudo-pyranose-rings, but a somewhat different rotamer distribution about the exocyclic C-5 – C-6 bond (carbohydrate numbering) seemed indicated by the chemical shifts of H-6 and H-6' and the $J_{5,6}$ values.[23] The solution conformation (in DMSO-d_6) of methyl 6-deoxy-α-D-idopyranoside has been studied by ^{1}H-n.m.r. spectroscopy;[24] the solid state conformation of this compound is referred to in Chapter 22. The conformations of the 7-, 8- and 9-deoxy- and the 4,7-dideoxy-analogues of N-acetylneuraminic acid have been investigated by ^{1}H-n.m.r. spectroscopy and hard sphere calculations, with emphasis on the shapes adopted by the side-chains, as these play a major role in enzyme-binding.

The differences in ($\Delta\delta/\Delta T$), the temperature-dependence of the n.m.r. chemical shift, of the amide protons in anomeric pairs of alkyl 2-acetamido-2-deoxy-D-glucopyranosides have been measured in a number of solvents together with the rates of exchange of the amide protons with solvent protons.[26]

5 Di- and Oligo-Saccharides and Related Compounds

Structural parameters for the modelling of complete ^{13}C-n.m.r. spectra of disaccharides have been derived from forty experimental spectra by use of molecular mechanics techniques. The average difference between simulated and experimentally determined chemical shift values was ±0.45 ppm.[27]

The ^{13}C chemical shifts of glycosides with chiral cyclohexane-type aglycons and of disaccharides with pyranosyl aglycons are affected by the anomeric configuration of the glycosylating sugar residue, by the relative absolute configurations of glycon and aglycon and by stereochemical factors such as, for example, the orientation of the proton(s) on the carbon atoms adjacent to the glycosylated centre of the aglycon. Simple rules have been formulated for predicting the magnitude of these glycosylation effects, which can be used for determining unknown structural features in glycosides and disaccharides, in particular the absolute configuration of one of the constituent sugars.[28]

Complete ^{1}H- and ^{13}C-n.m.r. spectral assignments, by application of combined 1D- and 2D-correlation experiments, have been reported for two sulphated oligosaccharide alditols derived from hen ovomucin,[29] for eight oligosaccharides of the lacto-N-tetraose- and the neotetraose-series,[30] for some xylose-containing oligosaccharides derived from the carbohydrate chains of N-glycoproteins,[31] and for the new, hexuronic acid-containing disaccharide (16), isolated after mild hydrolysis from the red alga Rhodella reticulata.[32]

Improved 2D n.m.r. methods (RECSY, COSY-LR) allowed the accurate measurement of the chemical shifts of most protons of A-pentasaccharide (17) and of some other tri-, tetra- and penta-saccharides containing the sequence β-D-Galp-(1→4)-D-Glc, without the need for a variety of solvents, derivatisation, or end group reduction. The results provided extended data sets for a chemical shift library.[33]

α-D-Glc$_p$UA-(1→3)-L-Gal

(16)

α-D-Gal$_p$NAc-(1→3)-β-D-Galp-(1→4)-D-Glc

(17)

3 3

↑ ↑

1 1

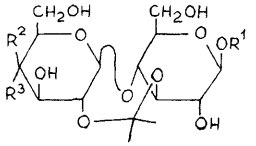
α-L-Fucp α-L-Fucp

Complete ^{1}H-n.m.r. spectral data have also been recorded for lactosyl ceramide, globotriasyl-Z-, and isoglobotriasyl-E-ceramides, special attention being given to glycosylation- induced shifts and to shielding by the Z- and E-ceramide residues. Some reassignments in related structures have been suggested.[34]

α-D-Galp-(1→4)-β-D-Galp-OR (18) R=Me
(19) R=Et

A conformational analysis of furanoid - pyranoid non-reducing disaccharides, based on crystallographic data, has been published,[35] and the conformation of trehalose incorporated in a micelle has been studied by ^{1}H-n.m.r. spectroscopy.[36]

Conformational analysis by use of various ^{1}H- and ^{13}C-n.m.r. techniques in combination with theoretical calculations has been achieved for the two galactobiosides (18) and (19),[37] for the eight-membered 3,2'-O-isopropylidene acetals (20) and (21) of methyl β-cellobioside and benzyl β-D-lactoside, respectively,



(20) R^1 = Me, R^2 = H, R^3 = OH
(21) R^1 = Bn, R^2 = OH, R^3 = H

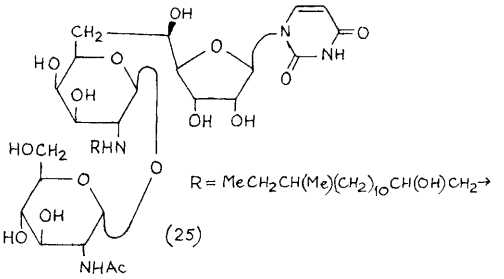
and that of β-methyl maltoside,[38] for the disaccharide moiety of avermectin B_{1a} which contains two oleandrose units,[39] for the G_{M4} ganglioside (22) in DMSO-d_6 and its component disaccharide in D_2O,[40] for several branched trisaccharide methyl glycosides with a 2,3- or 3,4-disubstituted D-galactose residue, e.g. compounds (23) and (24),[41,42] and for four branched, (1→6)-linked trisaccharides. In the last case chiral deuteration at C-6 allowed the signals for H-6R and H-6S to be distinguished.[43]

α-Neu5Ac-(2→3)-β-D-Galp-(1→1)-Cer (22)

α-D-Glcp-(1→n)-β-D-Galp-OMe (23) n=2
3
↑ (24) n=4
1
α-D-Manp

The stereochemistry of the glycosidic linkages of Corynetoxin 17a (25), an antibiotic in the tunicamycin group, have been unambiguously determined with the help of 1D and 2D n.m.r. methods,[44] and in a powerful illustration of the potency of n.m.r. spectral analysis the structure of a new bisdesmosidic triterpene saponin

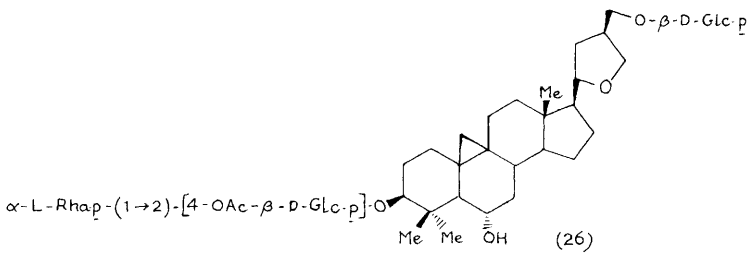
containing ten sugar residues has been solved almost entirely by n.m.r. techniques, especially by use of selective excitation by Gauss-shaped pulses in combination with coherence transfer experiments.[45]



(25)

Some antihistaminic and analgesic agents have become amenable to chiral analysis by ^{1}H-nmr spectroscopy after formation of cyclodextrin inclusion complexes. In many cases equivalent protons of enantiomeric pairs showed different chemical shifts after inclusion.[46]

Negative NOE's have been observed between H-3 and the anomeric proton of the 3-O-sugar moieties in a number of soponins such as compound (26).[47]



(26)

6 N.m.r. of Nuclei other than ^{1}H and ^{13}C

A multi-nuclear n.m.r. study (^{1}H, ^{13}C, ^{51}V) of the interaction of vanadate with monosaccharides has been published. Aldoses give rise to mono-, bi- and/or tri-dentate vanadate complexes depending on the number of consecutive cis-disposed hydroxy groups available in their various tautomeric forms.[48]

The ^{1}H, ^{31}P relayed spin-echo difference spectra of maltose 1-phosphate and D-glucose 1-phosphate have been reported. Use of this technique allowed observation of the total sub-spectrum of the phosphorylated glucose residue of the disaccharide.[49]

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22
Other Physical Methods

1 I.r. Spectroscopy

F.t.i.r. spectra of both anomers of a variety of peracetylated 2,4-dinitrophenyl D-gluco- and galacto-pyranosides[1] and peracetylated aryl 1-thioglycosides[2] have been recorded. The anomers give characteristic absorptions. F.t.i.r. spectra of adducts formed between D-glucose and zinc(II), cadmium(II) and mercury(II) halides in the solid (KBr pellets) and in 'solution' (film cast) have been discussed in detail.[3]

2 Mass Spectrometry

Reviews have appeared on stereochemical and other applications of m.s. techniques in carbohydrates and other oxygen heterocycles (365 refs)[4], and on the application of c.i.-m.s. for determining carbohydrate structure and reactivity.[5]

The fast atom bombardment (FAB)-m.s.-m.s. fragmentation patterns of heptaacetate daughter ions formed from disaccharide octaacetate primary ions have been used to identify the interglycosidic linkages and sugar constituents of disaccharides and their methyl glycosides.[6] FAB-m.s. spectra of the α- and β-anomers of 1-C-D-glucopyranosylbenzene have been studied; the fragmentation patterns were established by FAB-collisional activation - MIKES methods, but no differences were observed between the anomers.[7] The intensity of the $[M+H_3NCH_2CO_2Et]^+$ ion in the FAB-m.s. of permethylated monosaccharides in the presence of glycine ethyl ester hydrochloride was shown to be dependent upon the sugar configuration.[8] Acyl-linked glucuronides have been characterised by e.i.-m.s. and both positive and negative ion FAB-m.s.[9] Hydrolysable tannins based on galloylated glucose gave [M-H]- and diagnostic fragment ions upon negative ion FAB-m.s. from an HMPA-glycerol matrix.[10] While the positive and negative ion FAB-mass spectra could not be used to differentiate methyl α-D-galactopyranoside 2-, 3-, 4- and 6-(sodium sulphate), the metastable ion and collisional activation spectra of the $[M+Na]^+$ and $[M-Na]^-$ ions could be used for this purpose.[11] FAB-m.s. has been used to determine the structures of butaneboronate esters formed with monosaccharides,[12a] galactosides and glucosides.[12b]

The mechanism of the cationisation of sucrose by sodium during laser desorption m.s. has been studied using a split probe on which the sucrose and sodium chloride were spatially separated.[13] ERIAD-m.s. has been used to identify the products of periodate oxidation of sucrose.[14]

The four cyclic and one acyclic isomers of each of the four pertrimethylsilylated ketohexoses (sorbose, fructose, tagatose, and psicose) were separated and identified by capillary g.c.-e.i.-m.s.[15] The e.i.-m.s. fragmentation patterns of pertrimethylsilylated aldononitriles have also been detailed.[16]

Further applications of coupled h.p.l.c.-m.s. systems have been detailed; a review on biomedical applications included a section on the analysis of carbohydrates.[17] Capillary h.p.l.c. with gradient elution on a 0.22 mm i.d. column using a 1 μl.min^{-1} liquid flow (which is equivalent to a 1 ml.min^{-1} gas flow), has been coupled to an e.i.- m.s. system with an improved ion source interface, and applied to glucose, sucrose, myo-inositol, and the cyanogenic glucoside dhurrin. The glucose spectrum compared with those obtained by e.i., field ionization, field desorption and c.i. techniques.[18] Thermospray h.p.l.c.-m.s. and -m.s.-m.s. have been used for the identification and determination of desulphoglucosinolates derived from plant material.[19] The post-column addition of a reverse gradient to a salt gradient eluant avoided interface clogging and permitted the use of up to 0.8 M ammonium acetate buffer needed for the ion-exchange h.p.l.c.-thermospray m.s. analysis of an inositol phosphate mixture.[20] A preparative reversed-phase h.p.l.c. system, which employed detection by thermospray-m.s. on a split effluent flow in which 75-93% of the eluant is collected, has been used for the isolation from a crude reaction mixture containing three isomeric di-O-cyclohexylidene-1,2,3,4,5,6-[$^2H_6$]-myo-inositols of the 1,2:4,5-isomer.[21] The trimethylsilyl ether and ester derivative of inositol triphosphate, which is not suitable for g.c. analysis, can be employed in capillary CO_2 supercritical-fluid chromatography-m.s.; chemical ionization (iso-C_4H_{10}) gave an MH^+ base peak, but e.i. - like spectra could also be obtained.[22] A capillary h.p.l.c. - coaxial continuous flow FAB-m.s.-m.s. system in which capillaries independently deliver eluant and FAB matrix to the ion source, has been used to obtain an MH^+ ion peak on 230 pmol of the aminoglycoside antibiotic dihydrostreptomycin.[23] H.p.l.c.-thermospray m.s. has been used for the analysis of nucleosides derived from DNA chemically modified by the action of the anticancer drugs mitomycin C and porfiromycin.[24]

3 X-ray and Neutron Diffraction Crystallography

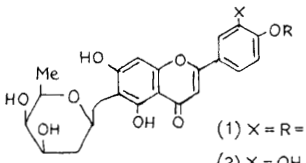
Flip-flop hydrogen bonding (i.e., O-H$\bullet\bullet\bullet\bullet$O-H $\rightharpoonup$ H-O$\bullet\bullet\bullet\bullet$H-O) in which the directionality is inverted dynamically even in the crystalline state, has been detected

by neutron diffraction in crystaline β-cyclodextrin undecahydrate by comparison of data at 120 and 293K.[25]

Specific x-ray crystal structures have been reported as follows:

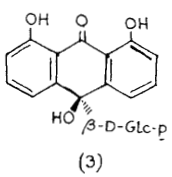
Free Sugars and Simple Derivatives Thereof.- The inclusion complex of (R)-phenylethylamine with 2,3,4,6-tetra-O-acetyl-D-glucose.[26]

Glycosides and Derivatives Thereof.- 2,6-Dimethoxy-p-hydroquinone 1-O-β-D-glucopyranoside,[27] methyl 6-deoxy-α-D-idopyranoside,[28] heptyl 1-thio-α-D-glucopyranoside,[29] sucrose.NaBr.2H2O (a redetermination),[30] $(sucrose)_2.(NaI)_3.3H_2O$,[31] methyl 2-O-(α-D-mannopyranosyl)-α-D-mannopyranoside,[32] methyl 4,6-O-ethylidene-2,3-di-O-nitro-α- and β-D-glucopyranoside,[33] 3-O-benzoyl-4,5-O-isopropylidene- and 2,3:4,5-di-O-isopropylidene-derivatives of methyl β-D-glucoseptanoside,[34] flavanoid C-β-D-oliosides (1) and (2),[35] and the C-glucoside aloin B (3).[36]



(1) X = R = H

(2) X = OH, R = Me



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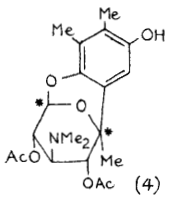
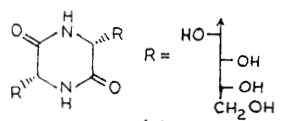


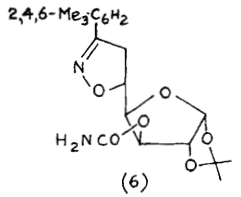
(4)

Anhydro-sugars.- Methyl 2,3-anhydro-4-deoxy-β-D-lyxo-hexopyranoside,[37] and the anhydro-sugar-like material (4) and its stereoisomer epimeric at the asterisked carbon atoms.[38]

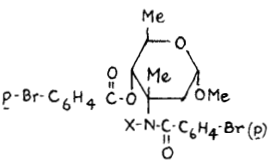
Nitrogen- and Sulphur-containing Compounds.- The dioxopiperazine derivative (5) (from base treatment of methyl 2-amino-2-deoxy-D-gluconate),[39] the



(5)



(6)

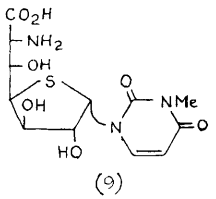


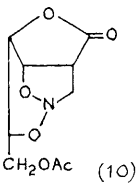
(7) X = H

(8) X = OH

dehydroisoxazole derivative (6),[40] 2,6-anhydro-1-deoxy-1-nitro-D-glycero-D-gulo- and D-glycero-L-manno-heptitol and their 3,4,5,7-tetra-O-acetates, 2,6-anhydro-1-deoxy-1-nitro-L-manno- and D-galacto-hexitol, and 3,4,5-tri-O-acetyl-2,6-anhydro-1-deoxy-1-nitro-L-manno- and D-altro-hexitol,[41] 6-benzylamino-6-deoxy-1,2:3,4-di-O-isopropylidene-L-glycero-α-D-galacto-heptopyranurononitrile,[42] the branched-chain

amino- and hydroxylamino-sugar derivatives, (7) and (8), respectively,[43] 6-thio-β-D-fructopyranose,[44] and the thiosugar derivative (9) (an enzymic hydroxylation product from the antibiotic albomycin).[45]


(9)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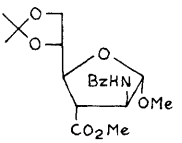
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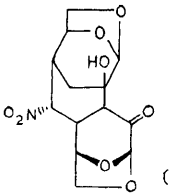
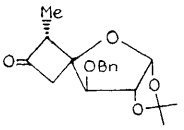
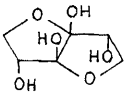

(12)

Branched-chain Sugars.- Methyl 6-deoxy-3-C-methyl-α-L-mannopyranoside,[46] the tricyclic lactone (10),[47] the 3-carboxymethyl-3-deoxy-sugar (11),[48] the adduct (12) from levoglucosenone and nitromethane,[49] and the cyclobutanone derivative (13).[50]


(13)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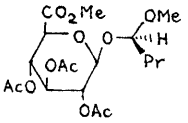
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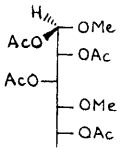
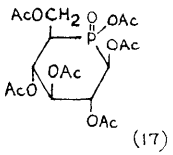
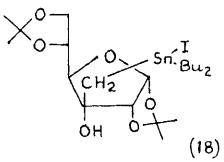
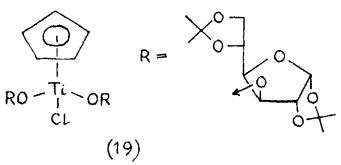

(16)

Diuloses, Sugar Acids, and their Derivatives.- The cyclic β,β-isomeric form (14) of D-threo-3,4-hexodiulose,[51] methyl 3,5-O-benzylidene-1,2-O-isopropylidene-β-L-threo-D-gluco-octofuranuronate,[52] the acetal glucuronide derivative (15),[53] the acyclic glucronate derivative (16),[54] calcium galactarate,[55] magnesium galactarate,[56] and 6-bromo-6-deoxy-L-ascorbic acid.[57]

Inorganic Derivatives.- The 5-deoxy-5-phosphinyl-D-glucose derivative (17),[58] the branched-chain tin-containing sugar (18),[59] (methyl 5-deoxy-β-D-ribofuranos-5-yl)(pyridine) cobaloxime,[60] and the bis(glucos-3-O-ylated)titanate (19).[61]

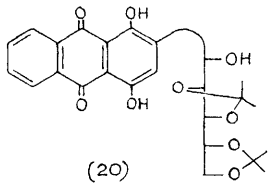

(17)


(18)

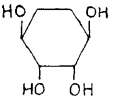

(19)

Alditols, Cyclitols and Derivatives Thereof.- 4-(D-arabino-Tetritol-1-yl)-4-imidazolin-2-ylideneammonium chloride,[62] (4R, 5R)-4-(D-arabino-1,2,3,4-tetraacetoxybutyl)-1,2-dimethyl-5-nitro-1-cyclohexene,[63] the D-gluco-pentitol-1-ylated anthraquinone derivative (20),[64] 1-(3,5-dimethyl-3-nitro-1-pyrazolin-4-yl)-penta-O-

acetyl-D-galacto-pentitol,[65] 1,2:3,4:5,6-tris-O-[(diethylamido)thionophosphate] galactitol,[66] toxocarol (21),[67] and the 2-deoxy-myo-inositol camphanate derivative (22).[68]



(20)



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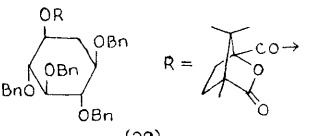
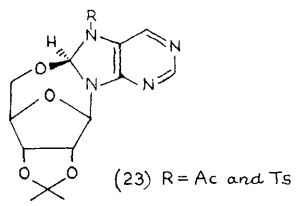
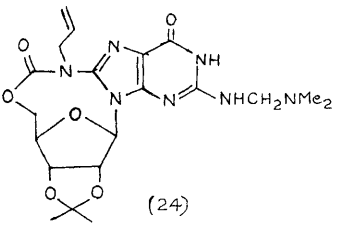


(22)

Nucleosides and their Analogues and Derivatives.- 3-Methyladenosine p-toluenesulphonic acid salt,[69] 4-amino-6-chloro-1-β-D-ribofuranosyl-pyrrolo[2,3-d]-pyrimidine,[70] 8-amino-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-b]pyridazine,[71] 5-(trifluoromethyl)-2'-deoxyuridine,[72, 73] 5-methyl-2'-deoxycytidine 5'-phosphate,[74] 1-(2-deoxy-β-D-ribofuranosyl)-5-[(1S)-2,2-dibromocyclopropyl]uracil,[75] 2,'3,'5'-tri-O-acetyl-4-(1,2,4-triazol-1-yl)uridine,[76] 2',3'-O-isopropylidene-guanosine,[77] 6,5'-cyclo-5'-deoxy-4-thiouridine, 6,5'-cyclo-5'-deoxy-2',3'-O-isopropylideneuridine, and 6,6'-cyclo-5',6'-dideoxy-D-ribo-hexofuranosyluracil,[78] the 8,5'-O-cyclonebularine derivatives (23),[79] the urethane bridged cyclonucleoside (24),[80] ethyl hydrogen

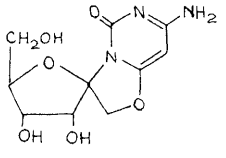


(23) R = Ac and Ts

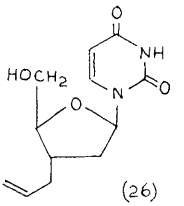


(24)

P(R),5'-anhydro-2',3'-O-isopropylideneadenosine-8-phosphonate hemi(ethyl acetate) solvate,[81] 6,1'-anhydro-6-hydroxy-1-(2-β-D-psicofuranosyl)cytosine (25)[82] and the analogous 8,1'-anhydro-8-hydroxy-9-(2-β-D-psicofuranosyl) adenine,[83] 3'-amino-2',3'-dideoxythymidine hydrochloride,[84] 3'-azido-2',3'-dideoxy-1-β-D-erythro- and threo-pentofuranosyluracil,[85] 2,4,6-trichloro- and 4-amino-6-chloro-8-(2,3-O-isopropylidene-β-D-ribofuranosylamino)pyrimido[5,4d]- pyrimidine,[86] 3'-deoxythymidine,[87] 2',3'-dideoxyadenosine,[88] 1-(6-deoxy-β-D-allo- and 6-deoxy-α-L-talofuranosyl)-cytosine,[89] 2',3'-dideoxyformycin A,[90] 2',3'-dideoxy-2',3'-



(25)



(26)

didehydrocytidine,[91] 1-(2-C-methyl-β-D-ribofuranosyl)uracil,[92] the 3-C-allyl nucleoside (26),[93] and 1-(6-amino-9H-purin-9-yl)-1-deoxy-N-ethyl-β-D-ribofuranuronamide.[94]

4 E.s.r. Spectroscopy

Differences were observed in the e.s.r. spectra of the epimeric methyl 2,3,6-tri-O-benzoyl-4-deoxy-4-hydroxylamino-α-D-gluco- and -galacto-pyranosides.[95] A one step synthesis of water-soluble spin-labelled glycosylamine derivatives involved condensation of amino-substituted N-oxides with free sugars (see Chapter 10); e.s.r. spectra were recorded.[96]

5 Polarimetry, Circular Dichroism and Related Studies

A method to determine the absolute and relative stereochemistry of 1,2,3-triols of general formula $RCHOH.CHOH.CH_2OH$ has been reported. Derivatisation with 9-anthroyl chloride gives the primary anthroate ester, then treatment with p-methoxycinnamoyl chloride gives the dicinnamate. The c.d. spectra of such derivatives are diagnostic.[97] O.r.d., c.d. and u.v. data for nine acylated glucose, 1-thioglucose, and 2-amino-2-deoxy-D-glucose derivatives have been reported, and spectral variations correlated with structure.[98] The chiroptical properties of thiazolidines derived from aldoses have been reported.[99]

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23
Separatory and Analytical Methods

1 Chromatographic Methods

Gas-Liquid Chromatography.- Unless otherwise stated, all analyses were performed on capillary g.c. columns.

The separation on several columns of the isomeric forms of several aldohexoses[1] and the four ketohexoses (fructose, psicose, sorbose and tagatose)[2] as their pertrimethylsilyl ether derivatives has been reported, and a mathematic approach used in an attempt to relate retention times to structures. Monosaccharides can be identified by Curie-point pyrolysis (358°) and g.c. analysis (packed column) of the volatile products since fragments characteristic of the sugar class (e.g. hexose, pentose, deoxy-sugar, uronic acid, alditol and amino-sugar) were obtained.[3] Sugars and polyols in biological fluids have been determined quantitatively by g.c. of their pertrimethylsilyl ether derivatives.[4]

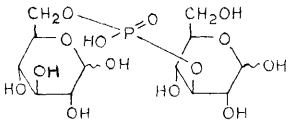
D-Arabinitol is a Candida metabolite, and can be used as a diagnostic marker of infection. Levels of D- and L-arabinitol, with ribitol as internal standard, have been determined by dual column g.c. of their heptafluorobutyrate derivatives, the mixture of alditol derivatives being collected from the first column by cold trapping and separated on the second bonded chiral phase column.[5] Mannitol, galactitol, glucitol and myo-inositol have been determined in biological samples by g.c.-m.s. as their tris(butylboronate) derivatives in runs of 4 minute duration. The application of flame ionisation, flame photometric and c.i.-m.s. detection, and the use of packed columns were also investigated.[6]

A series of aldoses has been reductively aminated ($NaBH_3CN$) with octadecylamine to give hydrophobic conjugates as model compounds in the g.c.-m.s. analysis (as the N-acetylated O-trimethylsilyl ether derivatives) of reductively aminated oligosaccharides from the Streptococcus pneumoniae capsular polysaccharide.[7] Isosorbide dinitrate and its metabolites have been assayed in plasma by g.c. with electron-capture detection.[8]

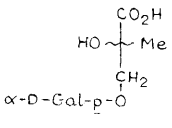
Methods have been developed to reveal the presence and the position of phosphate ester moieties on sugars. Phosphorylated sugar constituents, e.g. KDO, heptoses and glucosamine, in bacterial polysaccharides were detected by comparison

of the results obtained by methanolysis - pertrifluoroacetylation - g.c. analysis before and after reaction with conc. hydrogen fluoride (48% w/w in H_2O) at room temperature. This treatment dephosphorylates without cleaving glycosidic linkages. Without this treatment, the phosphorylated residues are not detected.[9] A methylation analysis procedure for synthetic disaccharides composed of reducing sugars linked non-glycosidicaly by phosphate ester groups, as in compound (1), has been devised. A five step reduction sequence (i, $NaBD_4$; ii, CH_2N_2-Et_2O; iii, NaOH-MeI-DMSO; iv, $LiAlH_4$; v, Ac_2O-py) provides partially methylated alditol acetate derivatives for g.c.-m.s. analysis.[10]

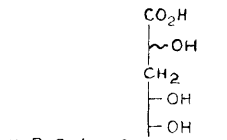
O-α-D-Galactopyranosyl-saccharinic acids such as compounds (2) and (3) have been identified by g.c.-m.s. of their pertrimethylsilyl ether derivatives.[11]



(1)



(2)



(3)

The relative merits of a variety of derivatisation procedures in the g.c. analysis of monosaccharides have been examined in detail. While pertrimethylsilylated O-methyloxime derivatives were concluded to be the best for the separation of simple mixtures, two new procedures were developed to enable the separation of more complex mixtures. Sequential O-benzyloximation-pertrifluoroacetylation permitted the best resolution to date of the C_3-C_6 aldoses and the corresponding alditols, but complications interfered with the quantitative analysis of ketoses. Pertrimethylsilylated O-benzyloximes were particularly useful for C_5 sugars, ketohexoses and mixtures of sugars, alditols, and lactones.[12] A procedure for g.c. analysis of aldoses as their peracetylated O-pentafluoro-benzyloxime derivatives (Vol. 23, p.245) has been modified to permit amino-sugars (GlcNAc and GalNAc) to be determined as well. The method, using a shorter column (6 m cf. 15 m) and helium carrier gas of increased purity, was applied to the analysis of sugars in known glycoproteins.[13]

A procedure has been defined for the rapid quantitative analysis of free sugars (tetroses to disaccharides) and related compounds (43 in total) in plants at the 1% level. After extraction with cold ethanol, the sugars are converted to peracetylated aldononitriles, ketoximes, alditols and non-reducing sugars for g.c. analysis.[14] The analysis of aldoses by g.c. and g.c.-m.s. as their pertrimethylsilylated aldono-nitriles has been reported, using a new derivatisation procedure [i, H_2NOSO_3H-Et_3N; ii, N,O-bis(trimethylsilyl)-trifluoroacetamide] which is claimed to give a single product peak for each saccharide.[15]

Thin-Layer Chromatography.- A review of the current status of planar chromatographic techniques, essentially t.l.c., in biomedicine has included sections on carbohydrates, gangliosides and cerebrosides.[16] High performance t.l.c. of mono- to oligo-saccharide mixtures on silica using the forced-flow technique has been reported.[17] α- and β-C-glycosides with aromatic substituents,[18] and the dansylhydrazone derivatives of unsaturated disaccharides produced enzymically from chondroitin sulphates,[19] have been separated on silica plates.

High-Pressure Liquid Chromatography.- Reviews on the biomedical applications of h.p.l.c.-m.s.,[20] and immobilised enzyme reactors in h.p.l.c. detector systems,[21] have included carbohydrate applications.

A new detector with considerable promise for use with underivatised carbohydrates eluted from microbore h.p.l.c. columns (1.0 mm id), a refractive index gradient detector, has been demonstrated with the separation of fructose and sucrose on a normal phase column. The apparatus is relatively simple and relies upon angular deflection of a 780 nm laser beam onto a position-sensitive detector. Good linearity and reproducibility were attained, and detection limits (ca. 1 ng) were three orders of magnitude lower than with commercial refractive index detectors.[22] The use of an evaporative light scattering detector in sugar analysis has been described, in which a silica-based diol phase was preferred to aminopropyl-silica because it permitted gradient elution with good sensitivity of detection (30-50 ng).[23]

α- and β-Cyclodextrin silica-bonded phase columns are an interesting new development. When used in the separation of 50 mono- to tetra-saccharides, deoxysugars, and alditols with water-organic solvent eluant combinations, they proved more efficient and selective than bonded-phase alkylamine and ion-exchange columns. Retention was related to molecular size and number of available hydroxy-groups in the solute.[24] Additionally, anomeric pairs of 16 free sugars and of 18 glycosides were separated on such columns.[25]

New developments in the separation of mono- and di-saccharides on anion-exchange columns using alkaline eluants and pulsed amperometric detection have been reported.[26] The major monosaccharides (Glc, Gal, Man, Ara and Xyl) in soil hydrolysates have been determined by h.p.l.c. on a polystyrene-based Pb^{2+}-form cation-exchange column. Minor sugars (Rha and Fuc) co-eluted with major components.[27]

Enantiomers of diginose (2,6-dideoxy-3-O-methyl-lyxo-hexose) and cymarose, oleandrose and digitoxose (all 2,6-dideoxyhexoses) have been resolved by h.p.l.c. as their methyl glycoside O-3,5-dinitrophenylcarbamate derivatives on chiral amine-

bonded silica columns.[28, 29] Enantiomers of digitoxose,[30] rhamnose and lyxose were similarly separated as carbamate derivatives of their acetonides.[29]

H.p.l.c. on a pellicular anion-exchange resin (Dionex HPIC-AS6, a 10 μm substrate coated with a monolayer of anion-exchange latex) with a strongly alkaline eluant and pulsed amperometric detection, has given extraordinarily good separations of homologous series of (1→2)-, (1→3)-, (1→4)- and (1→6)-linked α- or β-D-gluco-oligosaccharides up to DP≥ 50,[31] and of cyclodextrins, branched cyclodextrins and cyclo-sophoraoses with DP's in the 6-25 range.[32] The drug carrier '2-hydroxypropyl-β-cyclodextrin' of DS 0.4, which is a mixture of variously alkylated derivatives, has been determined in plasma by reversed-phase extraction followed by h.p.l.c. on a size exclusion column (diol bonded-silica) with indirect colorimetric detection using the ability of the derivatives to bind phenolphthalein.[33]

The specific detections of the galactose-containing oligosaccharides stachyose, raffinose and melibiose, along with galactose, in the aqueous h.p.l.c. eluant from a cation exchange resin, have been achieved with a post-column enzyme reactor with co-immobilised galactose oxidase/peroxidase coupled to a fluorimetric detection system for the H_2O_2 generated.[34]

Homologous series of α-(1→6)-D-gluco-oligosaccharides (DP 1-13 and 6-20), chito-oligosaccharides (DP 1-5), and oligosaccharides released from ovomucoid by hydrazinolysis, have been reductively aminated ($NaBH_3CN$) with 2-aminopyridine and fractionated by size on a Na^+-form cation exchange resin eluted with aqueous acetonitrile containing NaOAc or Et_3N•HOAc to suppress protonation of the derivatives.[35] Lactosamine and 34 mixed-type and oligo-mannoside-type oligosaccharides from glycoproteins and glycopeptides have been converted to N-(4-methylcoumarin-7-yl)glycamines by reductive amination and separated by h.p.l.c. on reversed-phase and size exclusion columns.[36] Oligosaccharides released from Klebsiella pneumoniae O_1K_1 lipopolysaccharide on mild hydrolysis have been separated on a silica-based anion exchange column.[37]

Modified procedures have been detailed for the direct cleavage of perbenzoylated (especially per-bromobenzoylated) oligosaccharides convenient for microscale analysis of the derived monomers by h.p.l.c. separation and u.v., c.d. and m.s. characterisation. Reaction with bromoacetyl bromide and water (which generates HBr-$BrCH_2CO_2H$) yielded glycosyl bromides and bromoacetates of the liberated alcohols without benzoyl migration. The glycosyl bromides were converted to methyl glycosides, the bromoacetate groups removed with thiourea, and the liberated hydroxy-groups cinnamoylated to yield the desired monomers.[38] A systematic study on the elution profiles of structurally related isomeric benzyl and nitrophenyl glycosides of mono- to tetra-saccharides on a Waters Carbohydrate Analysis column has been reported.[39]

The h.p.l.c. analysis of naturally occurring monoterpene, cyanogenic, and coumarin glycosides and saponins on a recently developed hydroxyapatite column revealed a correlation of elution behaviour with that obtained on silica gel t.l.c.[40] Reversed-phase analyses of maysin [6-O-(2-O-α-L-rhamnosyl-6-deoxy-L-xylo-hexos-4-ulosyl)luteolin], the flavonoid glycoside in corn silks that is toxic to corn earworm,[41] monolignols and their glucosides,[42] and secondary cardiac glycosides in Digitalis purpurea leaves[43] have been reported.

Narrow-bore h.p.l.c.(0.22 mm id, 3 or 5 μm silica particles)-e.i.-m.s. with gradient elution has been applied to glucose, sucrose, myo-inositol, and the cyanogenic glucoside dhurrin.[44] Reversed-phase h.p.l.c.-thermospray m.s. and m.s.-m.s. has been used to identify and determine desulphogluco-sinolates derived from plant material.[45]

The phenolic constituents, including galloylglucoses and acyl-glucoses, in rhubarb (Rhei Rhizoma) have been determined by reversed-phase h.p.l.c.,[46] and the stevia food sweeteners, diterpene oligosaccharide glycoside/glycosyl esters such as stevioside, by h.p.l.c. on a primary amine bonded silica column.[47]

Galactosamine, glucosamine and 26 amino-acids have been analysed by h.p.l.c. as their N-phenylthiocarbamate derivatives.[48] Unsaturated disaccharides generated by enzymic cleavage of heparin sulphates have been separated on a polystyrene-based cation exchange resin,[49] while unsaturated disaccharides with 0-3 sulphate moieties similarly released from chondroitin sulphate, have been separated on a primary amine gel, with post-column reaction with 2-cyanoacetamide and fluorimetric detection.[50] The reversed-phase analysis of 1-N-(β-D-glucopyranosyl)amobarbital diastereomers in urine has also been reported.[51]

Low molecular weight organic solutes in marine algae, including altritol, mannitol and volemitol, have been assayed on silica modified with amine in the eluant.[52] Inositol phosphate mixtures have been separated and analysed on an ion-exchange h.p.l.c.-thermospray m.s. system that permitted post-column addition of a reverse gradient so that a high salt gradient eluant could be used.[53] The trimethylsilyl ether/ester derivative of an inositol triphosphate has been analysed by capillary SFC (supercritical CO_2 - fluid chromatography)-c.i.-m.s.[54] Preparative reversed-phase h.p.l.c. of three di-O-cyclohexylidene-1,2,3,4,5,6-[$^2H_6$]-myo-inositol isomers was conducted on a system that employs detection by thermospray-m.s. on a split effluent flow such that 75-93% of the eluant is collected.[55] A 'solid injection technique' for applying relatively insoluble samples to preparative h.p.l.c. columns, which involved packing a powdered sample mixed with silica into a pre-column, has been demonstrated using the purification of N-butyl-1-deoxynojirimycin as an example.[56]

A variety of h.p.l.c. methods have been used to analyse sugar acids and their conjugates. A versatile, rapid ion-pair reversed-phase method using cethexonium bromide, has been described for the separation of alcohols, phenols, steroids and carboxylic acids and their glucuronic acid conjugates in biological systems, and used to monitor in vivo glucuronidation of clofibric acid.[57] The mixed saponins in Gypsophila extracts have been quantified by conversion to the single acid-stable gypsogenin 3-O-glucuronide by acid hydrolysis and ion-pair reversed-phase h.p.l.c.[58] The triterpene glucuronic acid disaccharide glycyrrhizin and its aglycon have been determined in plasma on a reversed-phase column,[59] phenols and their glucuronic acid and sulphate conjugates on a strong anion-exchange column,[60] and carbohydrate substrates and metabolites (Glc, GalA, gluconic acid and galactonic acid), along with other compounds in mammalian cell cultures, on a strongly-acidic cation-exchange resin in the H^+-form.[61] The h.p.l.c. analysis of KDN (3-deoxy-D-glycero-D-galacto-2-nonulopyranosonic acid) and N-acetyl-D-neuraminic acid on a strongly-basic anion-exchange resin has been applied to their determination in fertilized eggs of Chum salmon.[62] Sialo-oligosaccharides released from gangliosides have been chromatographed on tryptamine- or serotonin-bonded silica, while N-acetyl- and N-glycolyl-neuraminic acids have been separated on a novel silica-bound wheat germ agglutinin stationary phase.[63]

Ascorbic and dehydroascorbic acids in plasma and cerebrospinal fluids,[64] and common water-soluble antioxidants including ascorbic acid in biological samples,[65] have been determined by reversed-phase h.p.l.c. with electrochemical detection. In a study of chromium toxiciy, ascorbic acid and chromium(VI) in biological samples have been simultaneously analysed on an anion-exchange column.[66] The principal anionic components in wine and soft drinks, including ascorbate, have been determined using ion-interaction reversed-phase chromatography, using C_7 or C_8 alkylamines with salicylic acid as ion-interaction reagents.[67]

The aminoglycoside sisomicin and its 1-N-ethyl derivative, netilmicin, have been determined in blood and dried blood by precolumn derivatization with σ-phthalaldehyde and β-mercaptopropanoic acid and reversed-phases analysis.[68, 69] Dihydrostreptomycin has been used in the exemplification of capillary h.p.l.c.-coaxial continuous flow FAB-m.s.-m.s. in which capillaries independently deliver eluant and FAB matrix to the m.s. source.[70]

A number of papers on the reversed-phase h.p.l.c. analysis of nucleosides and related compounds have appeared. The analysis of both the major and modified ribonucleosides present in nucleic acids and biological fluids using photodiode array detection has been critically reviewed. Retention times under standardised chromatographic conditions and u.v.-data, along with the preparation of samples from various RNA's, are dealt with in detail.[71] Useful increases in the retention of

nucleotides was achieved by addition of metal ions (K^+, Mg^{2+}, Mn^{2+}, Ni^{2+}, Zn^{2+}) to the eluant, while nucleoside retention was unaffected.[72] The advantages of microcolumn h.p.l.c. using 50 and 250 μm id fused silica columns with 70-100 x 10^3 theoretical plates and miniaturized u.v. detection have been exemplified by the simultaneous analysis of nucleosides, bases, and nucleotides.[73] Other applications have been to the determination in biological samples of the ratio of deoxyguanosine to deoxythymidine in complex mixtures of ribo- and deoxyribo-nucleosides,[74] cytosine arabinoside and uracil arabinoside,[75] 2',3'-dideoxycytidine,[76] adenosine and its cyclic 3',5'-monophosphate,[77] 5-bromo-2'-deoxyuridine and its free base,[78] 5-bromo-5-deoxyuridine,[79] and trace levels of AZT (3'-azido-2',3'-dideoxythymidine) using on-line preconcentration on a Ag(I)-thiol stationary phase.[80] Modified nucleosides formed from the action of the anticancer drugs mitomycin C and porfiromycin on DNA have been analysed by h.p.l.c.-thermospray m.s.[81]

The h.p.l.c. separation of 2'- and 3'-O-acyl derivatives of uridine and their 5'-O-monomethoxytrityl derivatives has been used in a study of acyl migration.[82]

Ion-pair reversed-phase h.p.l.c. separations of purine nucleosides, bases and nucleotides in cells, employing various ion-pairing agents,[83] and of pseudouridine and creatinine in urine for monitoring patients with cancer,[84] have been reported. A vinyl alcohol copolymer column (Asahipak GS-320H), which works by both adsorption and gel permeation mechanisms, proved best for the h.p.l.c. analysis of adenine compounds including nucleosides and nucleotides following derivatisation with chloroacetaldehyde. Detection limits of 0.17-0.5 pmol/10 μl injection were attained using fluorescence detection.[85] 2',3'-Dideoxycytidine and AZT have been analysed in plasma by preconcentration on a glycine-phenylalanine-phenylalanine silica column then chromatography on two β-cyclodextrin-bonded silica columns in series.[86] The immunosuppresive imidazole-nucleoside mizoribine in human serum has been chromatographed on primary amine bonded silica,[87] and ^3H-labelled cytosine arabinoside and eight metabolites in cell extracts have been analysed on a silica-based ion-exchange column with u.v. and scintillation counter detection.[88]

Column Chromatography.- An anion-exchange resin chromatographic procedure for the analysis of sugars in polysaccharide hydrolysates has been described. Using a boric acid-containing eluant (pH 8.4-8.8) and post-column colorimetric derivatisation the analysis was complete inside 4 h. The main advantages over previous systems were that no regeneration of the column was required between analyses, and no special pretreatment of the hydrolysate was required.[89] The sorption and diffusion characteristics of glucose, maltose and maltotriose in silica gels, required for the design of large scale gel permeation chromatographic separations, have been

evaluated using chromatographic responses.[90] The Stokes radii of hyaluronate oligosaccharides have been calculated from the chromatographic behaviour of even-numbered di- to hexadeca-saccharides on size-exclusion meia (Sephadex G-25, -50 and -75).[91]

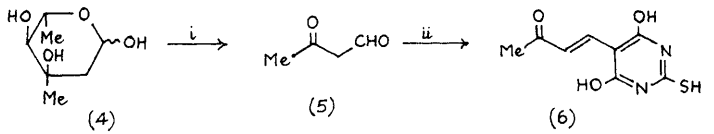
Partition Chromatography.- A dual-flow countercurrent extraction procedure for the continuous separation of glucosides has been applied to phenyl β-D-glucopyranoside and esculin.[92] Further applications of centrifugal partition chromatography to the separation of labile oligomeric hydrolysable tannins (cf., Vol. 20, p.254) have been reported.[93]

2 Other Analytical Methods

Amino-sugars, alditols and acidic sugars have been detected by electrocatalytic oxidation on a copper-containing electrode produced by deposition of a CuCl-containing crystalline species on to glassy carbon. This electrode is readily adapted for use in flow-injection analysis and h.p.l.c., giving detection limits in the nano- to pico-gram range.[94] A maltose-specific amperometric enzyme electrode based on an oligosaccharide dehydrogenase-modified carbon paste electrode containing p-benzoquinone, has been described.[95]

Reducing carbohydrates produced fluorescence when heated with eight 1,2-diarylethylenediamines in meso- or DL-form. The most favourable reagent, meso-1,2-bis(4-methoxyphenyl)-ethylenediamine permitted sensitive fluorimetic detection of reducing sugars including 2-deoxy-sugars, amino-sugars, and sialic acids at concentrations as low as 0.2-0.9 nmol.ml^{-1}.[96]

A new colormetric method has been proposed for estimating 2-deoxy-3-C-methyl branched-chain sugars, such as (4) (Scheme 1). Thus treatment with periodate affords acetylacetaldehyde (5) which is condensed with 2-thiobarbituric acid to give the chromophore (6) with an absorption maximum at 372 nm.[97]



(4) (5) (6)

Reagents: i, $NaIO_4$; ii, 2-Thiobarbituric acid

Scheme 1

Sugar solutions have been desalted by electrodialysis using an ion-exchange membrane.[98]

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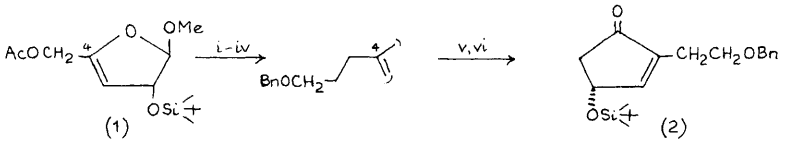
24
Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

A review on the synthesis of optically-active pheromones includes a section on the use of carbohydrates as chiral starting materials.[1]

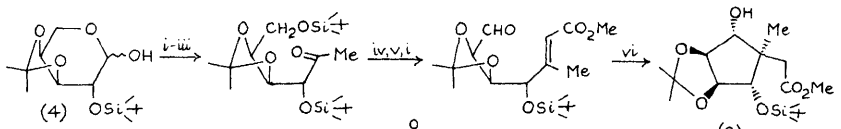
1 Carbocyclic Compounds

The glucose-derived alkene (1) has been converted into the prostaglandin-related hydroxycyclopentenone (2), using an aldol condensation, as indicated in Scheme 1.[2] Reductive cyclization using SmI_2 was employed in a route to the chiral cyclopentane (3) from the L-arabinose derivative (4) (Scheme 2); the functionality and chirality of (3) corresponds with that of the C-ring of the trichothecene-type sesquiterpene anguidine.[3]



Reagents: i, $CH_2(CO_2Me)_2$, $Pd(PPh_3)_4$ (cat); ii, KOH; iii, LAH; iv, NaH, BnBr; v, H^+; vi, $Ba(OH)_2$, MeOH

Scheme 1

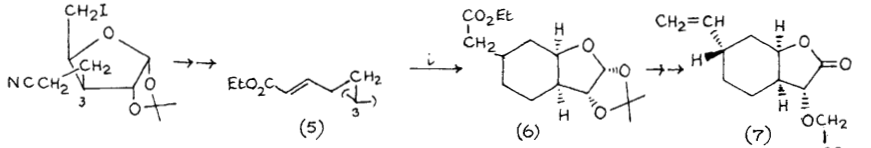


Reagents: i, PDC; ii, MeLi; iii, $\rightarrow$SiCl; iv, $(EtO)_2P(O)CH_2CO_2Me$, NaH; v, H^+; vi, SmI_2

Scheme 2

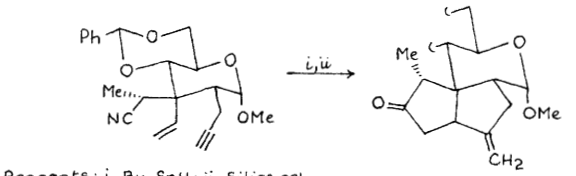
A review has appeared from Fraser-Reid's group describing some of their work on the annulation of carbocyclic rings onto carbohydrate templates.[4] This group has reported the free-radical cyclization of unsaturated ester (5) (Scheme 3) into carbocycle (6), which was converted in seven steps into the intermediate (7) in Collum's synthesis of phyllanthocin.[5] The same team have given a full account of their routes to pyranoside diquinanes by serial radical cyclization (see Vol. 21, p.148-9),[6] and some more sophisticated examples, designed to

yield diquinanes with additional functionality present in natural products, have also been described; the transformation shown in Scheme 4 is typical.[7]



Reagents: i, Bu_3SnH, AIBN, C_6H_6

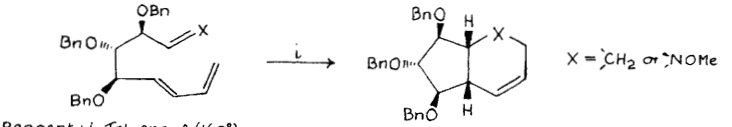
Scheme 3



Reagents: i, Bu_3SnH; ii, Silica gel

Scheme 4

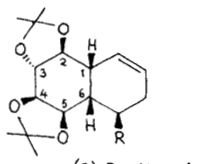
The intramolecular Diels-Alder cyclizations shown in Scheme 5 gave just one cycloadduct in each case even though the starting dienes, made from 2,3,4-tri-*O*-benzyl-D-xylose, were *E*/*Z* mixtures; the yield was not good in the case of the



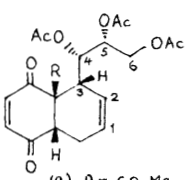
Reagent: i, Toluene, Δ(160°)

Scheme 5

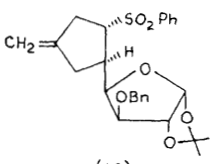
oxime, however.[8] Similar cyclizations of glucose-derived 1,7,9-trienes gave the 6,6-ring system (8) (sugar carbons numbered),[9] and an intermolecular Diels-Alder reaction between a diene derived from triacetyl-D-glucal (carbons numbered) and a quinone generated *in situ* gave cycloadduct (9) stereo- and regiospecifically.[10] Trost's trimethylenemethane-palladium complex has been shown to undergo [3+2] cycloadditions to α,β-unsaturated sulphones; cyclopentane derivative (10) was obtained from the glucose-derived *trans*-α,β-



(8) R = H or Ac



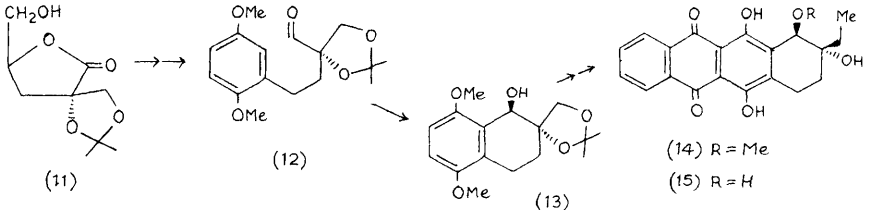
(9) R = CO_2Me



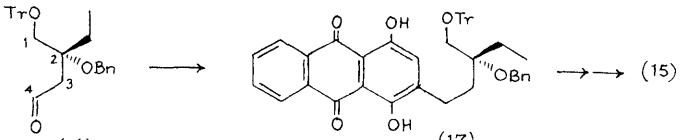
(10)

unsaturated sulphone as the major diastereomer (7.5:1). Ozonolysis and elimination of phenylsulphinic acid gave the corresponding chiral cyclopentenone.[11]

α-D-Isosaccharinolactone (11) can be converted (*J. Org. Chem.*, 1987, 52, 1057) into aldehyde (12) (Scheme 6). This can undergo stereoselective intramolecular cyclization to tetralin (13) in the presence of $SnCl_4$, giving a route to a precursor (14) of 4-deoxy-γ-rhodomycinone (15).[12] In somewhat similar work, the synthon (16), derived from D-glucose (carbons numbered), was transformed (Scheme 7) by Marschalk reaction with leucoquinizarin into

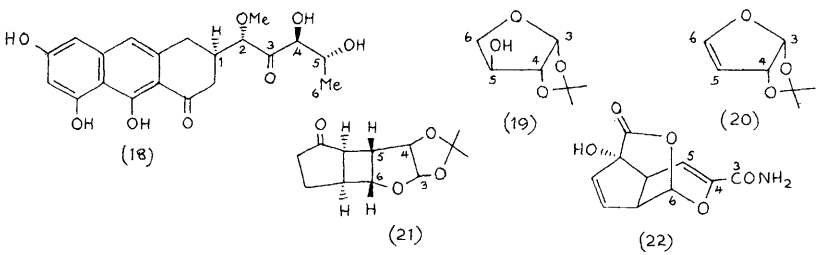


Scheme 6



Scheme 7

anthraquinone (17), which could be converted, again with stereocontrol in the cyclization, into 4-deoxy-γ-rhodomycinone (15).[13] In a total synthesis of (+)-olivin (18), the side-chain chirality could be constructed from D-galactose (sugar carbons numbered), although an alternative approach in which the side-chain was built up by stereoselective reactions of a threonine derivative proved more efficient.[14]



Methyl 3,4-*O*-isopropylidene-L-threonate, available from L-ascorbic acid in three steps, can be converted into L-threose derivative (19), and the dihydrofuran (20). This latter compound underwent photocycloaddition to

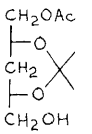
cyclopentenone to give (21), as the first key step in the synthesis of (-)-echinosporin (22); the carbons of L-ascorbate are numbered in the formulae.[15] A route to a cyclopropyl aminoacid is discussed in Section 4.

2 γ- and δ-Lactones

The new chiral building block (23) has been obtained by lipase-catalysed hydrolysis of the corresponding *meso*-diacetate, which was itself prepared from ribitol; monoester (23) was converted in three steps into the lactone (24), which has been reported to have hunger-modulating properties.[16]

Full details have been given of the synthesis of the marine metabolite leptosphaerin (see Vol. 20, p.260-1),[17] and also of the synthesis of the antitumour pyrone (+)-altholactone and its enantiomer (see Vol. 21, p.259).[18]

The lactone (25) is a degradation product of the macrolide nyastatin A, and to confirm its absolute configuration, it has been synthesized from D-glucal (sugar carbons numbered); the key reaction involved the formation of the α-cuprate (26) and its reaction with an epoxide.[19] The chiron (27), suitable for synthesis of the δ-lactone moiety of the mevinic acids, has been prepared from levoglucosan.[20] The β,γ-unsaturated lactone (28) is a potential precursor for polyhydroxylated α-aminoacids; it has been made from di-*O*-acetyl-D-xylal, the key step being the [3,3]-sigmatropic rearrangement of the allylic trichloroacetimidate (29).[21]



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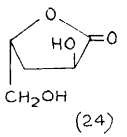

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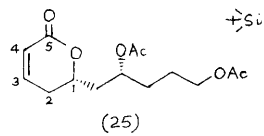

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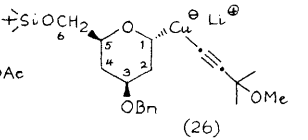

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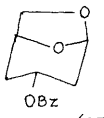

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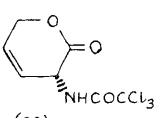

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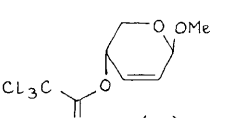


(29)

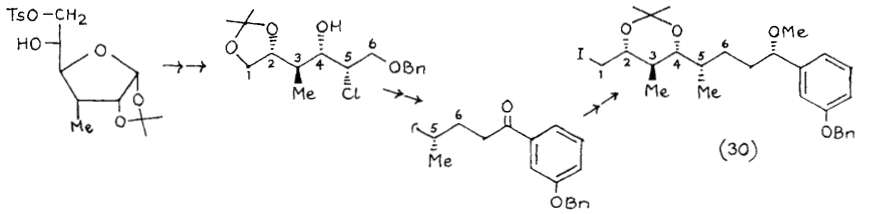
3 Macrolides, Macrocyclic Lactams, and their Constituent Segments

A full account has been given of Danishefsky's carbohydrate-based synthesis of avermectin A_{1a} (see Vol. 21, p.262-3).[22]

In the erythromycin area, Kochetkov's group has described in full their route to erythronolides A and B by linking C(1) - C(6) and C(9) - C(13) units derived from laevoglucosan (see Vol. 21, p.261),[23] and Yonemitsu's group has given a full account, with some improvements,[24] of their synthesis of (9S)-9-dihydroerythronolide A (Vol. 21 p.261; Vol. 19, p.263-4).[25] Other Japanese

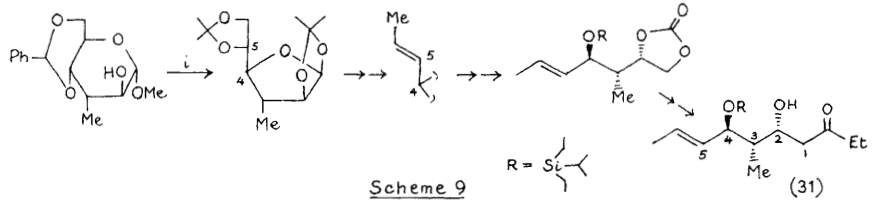
workers have described fully their alternative route to erythronolide A from sugar precursors (see Vol. 20, p.263).[26]

A segment of the marine toxin debromoaplysiatoxin has been prepared from D-glucose as outlined in Scheme 8;[27] carbons 1 and 2 (glucose numbers) and O-2 of intermediate (30) were then incorporated into the complete macrodiolide of 3-deoxydebromoaplysiatoxin by combination with two other tartrate-derived fragments.[28]



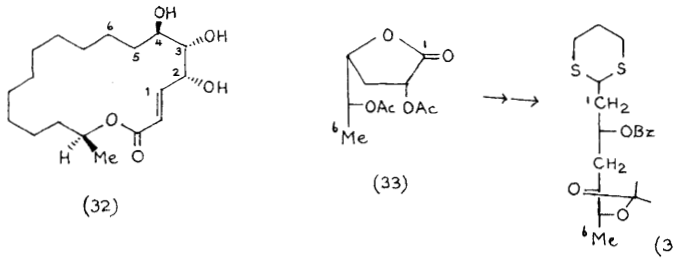
Scheme 8

The 18-ring macrolide concanamycin contains a stereochemically-complex side-chain unit. Much of this chirality is incorporated in the synthon (31) prepared from D-glucose (Scheme 9), the sugar carbons being indicated. A 2,6-dideoxy-D-glucose unit, also present in the antibiotic, was attached to O-2 of (31) with moderate β-selectivity.[29]

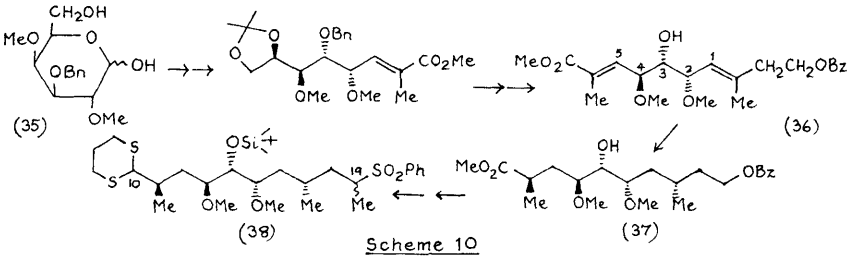


Scheme 9

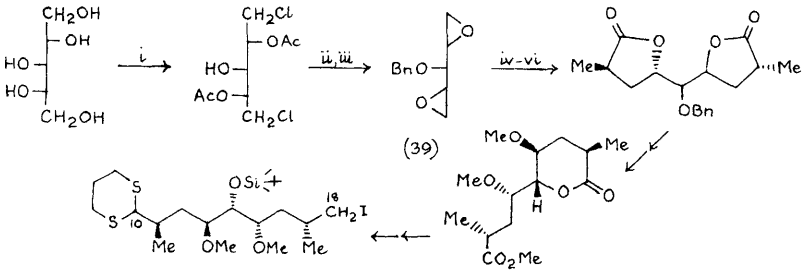
Chirality from D-mannose was used to establish most of the chiral centres in a synthesis of the lichen metabolite (+)-aspicillin (32; sugar carbons numbered).[30] The known lactone (33), accessible in two steps from D-galactono-γ-lactone, was used to prepare the fragment (34) containing the chirality of C(21) - C(27) of the antineoplastic bryostatins.[31]



The powerful immunosuppressant FK-506 has attracted much synthetic activity, and the viability of carbohydrate-based approaches to segments of this molecule has been demonstrated by several groups. In one approach to a C(10) C(19) fragment, the D-galactose derivative (35) was converted as indicated briefly in Scheme 10 to diene (36) (galactose carbons indicated); hydroxyl-directed homogeneous hydrogenation of this gave, with high stereoselectivity, reduction product (37), extendable to the chiron (38).[32] In another approach, which also recognizes the hidden symmetry of this segment, L-arabinitol was



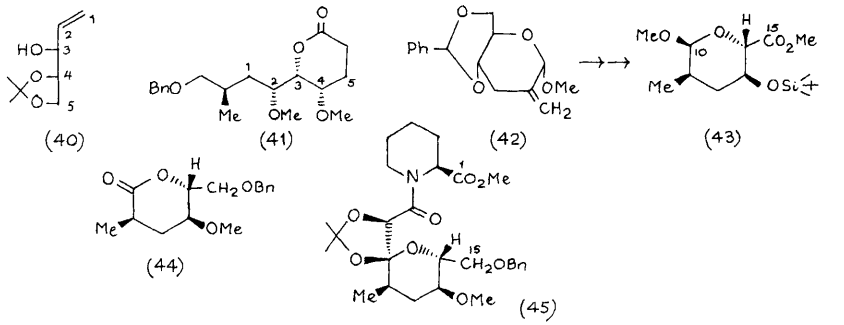
Scheme 10



Reagents: i, $AcOC(Me)_2COCl$; ii, NaOMe; iii, BnBr, NaH; iv, $HC{\equiv}C{\cdot}OEt$, BF_3; v, HCl, MeOH; vi, LDA, MeI

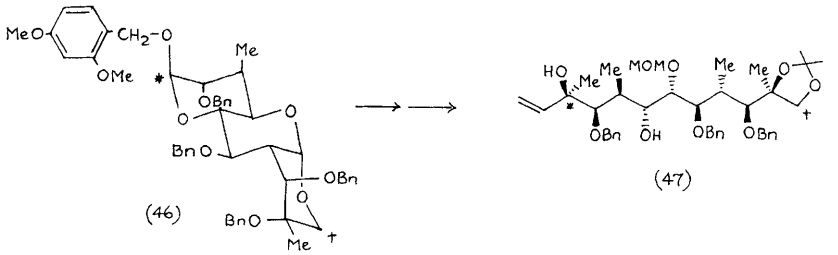
Scheme 11

converted into diepoxide (39) (Scheme 11), which was further manipulated as indicated to give a C(10) - C(18) unit.[33] In another approach, L-arabinose was



converted in seven steps (60% overall with no chromatography) into the allylic alcohol (40), and hence into lactone (41) (sugar carbons indicated) in a number of steps, the first being an Ireland-Claisen rearrangement with the usual chirality transfer. Intermediate (41) was then built up into a C(10) - C(24) unit of FK-506.[34] Other workers have converted the known alkene (42) into the uronic ester (43), representing C(10) - C(15) of FK-506, and then extended this unit to prepare a C(10) - C(23) structure.[35] In an approach to the C(1) - C(15) 'left-hand' segment of FK-506, lactone (44) was prepared from methyl α-D-glucopyranoside, and then elaborated into (45), the key step being the reaction of (44) with the lithium enolate of ethyl α-tetrahydropyranyloxy-acetate.[36]

A report of a review lecture describes progress by Fraser-Reid's group on the synthesis of the ansa-chain of streptovaricin A using the concept of pyranosidic homologation,[37] and the same team has successfully converted the known tripyranoside (46) into the advanced precursor (47) of streptovaricin A.[38]



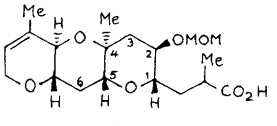
4 Other Oxygen Heterocycles

The synthesis of muscarine analogues from hexitols has been reviewed.[39]

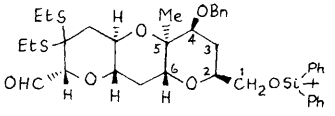
A major landmark in synthetic organic chemistry is the completion of Kishi's synthesis of palytoxin carboxylic acid and amide by linking together eight chiral building blocks and subsequent removal of the 42 protecting groups.[40] Full reports have been given of the synthesis of building blocks of the polyether antibiotic salinomycin (see Vol. 21, p.263)[41,42] and the linking of these units to complete the synthesis of salinomycin itself.[43]

The tricyclic structure (48), constituting the ABC ring framework of brevetoxin B has been prepared in chiral form from tri-*O*-acetyl-D-glucal,[44] and the IJK substructure (49) of the same major target has been synthesized from penta-*O*-acetyl-D-mannopyranose.[45] In both sequences, the first step involved formation of a *C*-glycoside by reaction with allyl-trimethylsilane; sugar carbons are numbered.

A homochiral unit corresponding with the H-ring of the halichondrin class of antitumour polyethers has been synthesized from the 3-deoxy-3-C-methyl-D-glucose derivative (50) as indicated in Scheme 12.[46]



(48)



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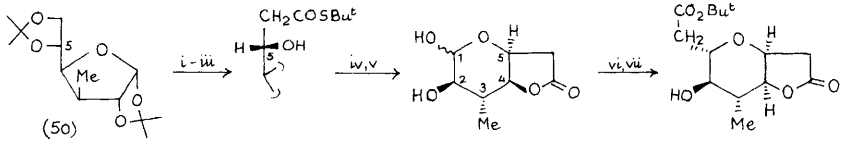


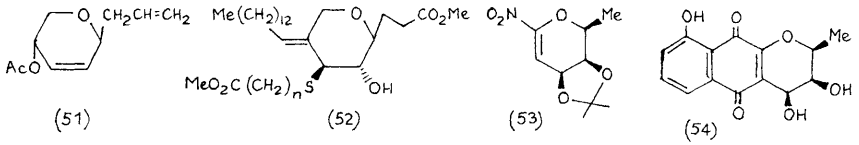
(50)

Reagents: i, H_3O^+; ii, $NaIO_4$; iii, $CH_2=C(SBu^t)(OTBDMS)$, $TiCl_4$; iv, NaOH; v, TFA; vi, $Ph_3P=CHCO_2Bu^t$; vii, Na, THF

Scheme 12

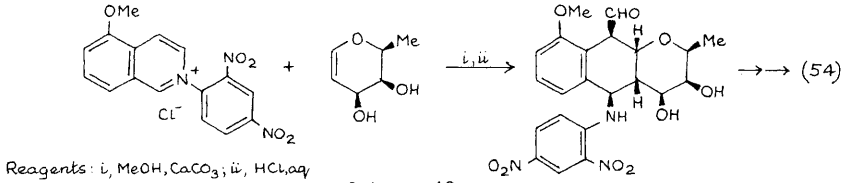
The total synthesis of pseudomonic acids has been reviewed,[47] and Keck has streamlined his earlier synthesis (Vol. 18, p.247; Vol. 19, p.257) of pseudomonic acid C by direct linkage of an L-lyxose derivative with a chiral side-chain, using free-radical methods.[48]

Alkene (51) can be prepared by reaction of allyl-trimethylsilane with diacetyl-D-xylal, the stereoselectivity in this reaction being opposite to that observed with triacetyl-D-glucal (Vol. 16, p.40); further manipulation of (51) led to the conformationally-restricted analogue (52) of leukotriene D_4.[49]



(51) (52) (53) (54)

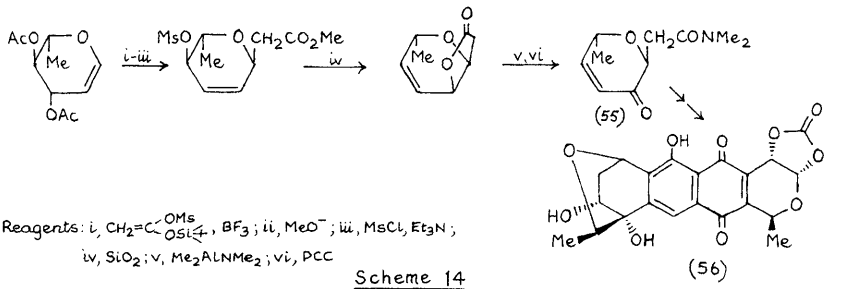
The unsaturated nitrocompound (53) could be converted in two steps into (-)-cryptosporin (54), the enantiomer of the natural product.[50] Other workers have prepared the same compound by use of the Bradsher cycloaddition shown in Scheme 13,[51] and a number of similar cycloadditions to glycals have also



Reagents: i, MeOH, $CaCO_3$; ii, HCl, aq

Scheme 13

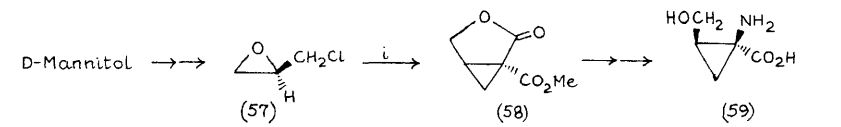
been reported.[52] The enone (55), derived from L-rhamnal (Scheme 14), could be converted to granaticin (56) via reaction with a phthalide.[53]



Reagents: i, $CH_2{=}C(OMs)OSiR_3$, BF_3; ii, MeO^-; iii, MsCl, Et_3N; iv, SiO_2; v, Me_2AlNMe_2; vi, PCC

Scheme 14

A route has been described for the preparation of anhydrous (*R*)-epichlorohydrin (57) from D-mannitol; this epoxide could be converted (Scheme 15) into the lactone (58) by initial attack at the epoxide, and hence into (-)-(1*S*,2*R*)-1-amino-2-(hydroxymethyl)cyclopropane carboxylic acid (59) through Hoffmann reaction.[54]



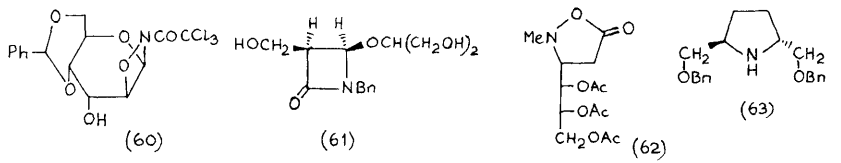
Reagents: i, $CH_2(CO_2Me)_2$, Na, MeOH

Scheme 15

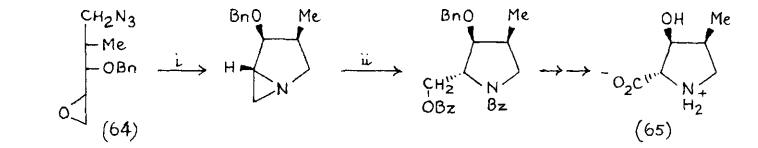
5 Nitrogen Heterocycles

Full details[55] and further examples[55,56] have been reported of the [2+2] cycloadditions of glycal derivatives and isocyanates to give β-lactams. In such reactions, the major direction of attack on the glycal is *trans* to the oxygen substituent at C-3. Use of the D-allal derivative and trichloroacetyl isocyanate gave adduct (60), convertible to the β-lactam synthon (61),[56] the enantiomer of which is accessible from D-galactal.[55] Various chiral isoxazolidin-5-ones such as (62) are accessible by Michael addition of *N*-alkylhydroxylamines to α,β-unsaturated glycono-1,5-lactones.[57]

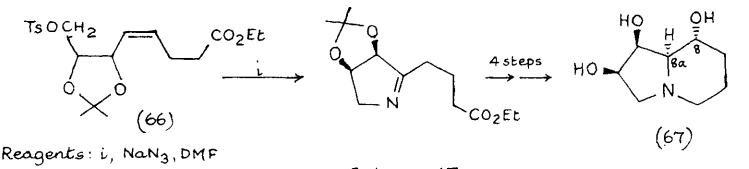
The chiral pyrrolidine (63) has been prepared from 1,2:5,6-di-*O*-isopropyl-



idene-D-mannitol by free-radical deoxygenation at the central carbons, and cyclization of the 1,6-di-O-benzyl derivative.[58] In a new and interesting approach to functionalized pyrrolidines, the epoxide (64), accessible from D-mannitol via 2,3-*O*-isopropylidene-D-glyceraldehyde, was converted into the aminoacid (65) as indicated in Scheme 16. Similarly, starting from mannose-derived 1,2-anhydro-5-azido-5-deoxypentitols, 1,4-dideoxy-1,4-iminopentitols could be produced, but in certain cases the bicyclic intermediates underwent ring opening to piperidine derivatives instead.[59] Alkene tosylate (66), derived from 2,3-*O*-isopropylidene-D-erythrose, has been used in a new chiral synthesis of the mannosidase inhibitor swainsonine (67), as indicated in Scheme 17.[60]



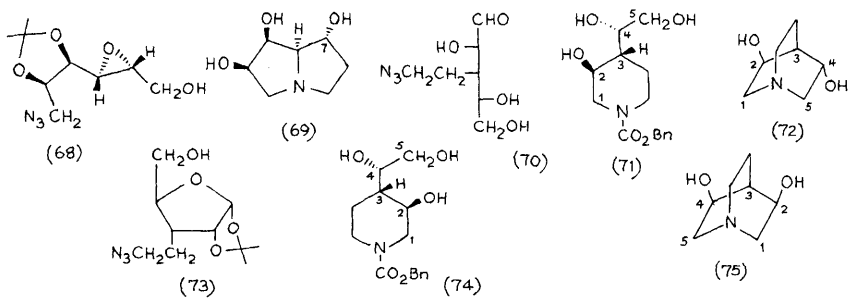
Scheme 16



Scheme 17

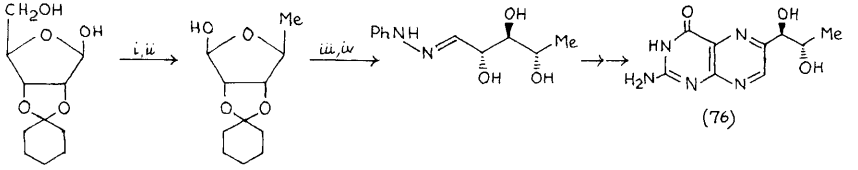
The same group has reported routes to 8-*epi*-, 8a-*epi*-, and 8,8a-di-*epi*-stereomers of swainsonine (see 67), using 2,3-*O*-isopropylidene-L-erythrose as precursor, and epoxide intermediates.[61] In somewhat similar work by others, the D-mannose-derived azidoepoxide (68) was converted into swainsonine (67), its ring-contracted analogue (69), and the 7-epimer of (69).[62]

D-Arabinose has been converted via intermediates (70) and (71) into the chiral quinuclidine diol (72),[63] whilst D-glucose, via (73) and (74), gave the *meso*-isomer (75);[64] sugar carbons are numbered, but in each case the



symmetry of the target is such that alternative initial cyclizations of the azidoethyl chains onto C-5 also led to the same products (72) and (75).[63,64]

The side-chain chirality of (-)-biopterin (76) has been assembled from 2,3-*O*-cyclohexylidene-D-ribose as indicated in Scheme 18.[65]



(76)

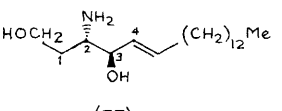
Reagents: i, MeMgI; ii, $NaIO_4$; iii, H^+/H_2O; iv, $PhNHNH_2$

Scheme 18

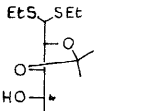
6 Acyclic Compounds

Earlier work on the synthesis of chiral α-hydroxyaldehydes (see Vol. 21, p.174 and Vol. 20, p.270) from D-mannitol-derived diepoxides has been extended to the synthesis of methyl (*R*)- and (*S*)-9-hydroxyeicosatetraenoates (methyl 9*R*- and 9*S*-HETE),[66,67] and to coriolic acid [13(*S*)-hydroxy-9*Z*,11*E*-octadecadienoic acid] and its 13(*S*)-*N*-tosylamino-analogue, made from a bis-aziridine (Vol. 20, p.271).[68]

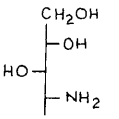
D-Sphingosine (77) and some related compounds have been prepared from 2-amino-2-deoxy-D-glucose (sugar carbons numbered) in a multistep process involving inversion of configuration of the sugar at C-3.[69] A full account has been given of the synthesis of the marine sulpholipid D-*erythro*-1-deoxydihydroceramide-1-sulphonic acid from D-galactose (see Vol. 22, p. 267), together with the synthesis of a phosphonocerebroside.[70]



(77)

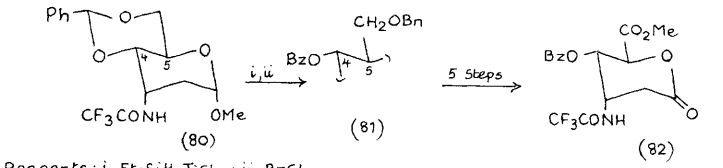


(78)



(79)

A number of papers have described routes from carbohydrates to hydroxylated aminoacids. The azide (78), derived from L-arabinose, was converted, via the 4,5-aziridine, into polyoxamic acid (79), a constituent of the polyoxin class of antibiotics.[71] The aminosugar derivative (80), an intermediate in Horton's daunosamine synthesis, can be transformed (Scheme 19) into (81), and hence into the lactone (82), which is a protected form of the hydroxylated β-amino-acid found in the antiulcerogenic compound AI-77-B; the regiochemistry in the reductive opening of the acetal is unexpected.[72] D-Glucose has been converted

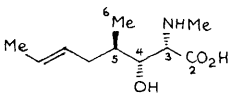


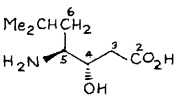
Scheme 19

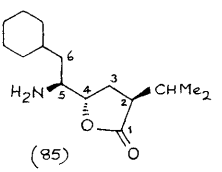
in a multistep process into MeBmt (83), a constituent of cyclosporin (sugar carbons indicated),[73] and glucose was also used in a synthesis of statine (84) and some analogues.[74] The related lactone (85), corresponding to a hydroxyethylene dipeptide isostere, has been prepared from triacetyl glucal.[75] The lactone (28), a potential precursor for hydroxylated α-aminoacids, was mentioned earlier.[21]

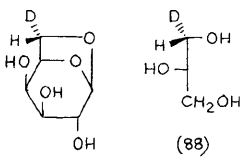
A route has beendetailed for the preparation of (*R*)-*O*-isopropylidene-glyceraldehyde from D-glucono-1,5-lactone.[76] A good route has been worked out for the conversion of (*S*)-*O*-isopropylidene-glycerol (from D-mannitol) into (*S*)-(+)-glycerol monotosylate (86), and the (*R*)-isomer is also accessible starting from L-ascorbic acid.[77] An alternative preparation of (86) proceeds from D-ribonolactone via the 2,3-*O*-benzylidene-5-*O*-tosyl derivative.[78] The stereospecifically deuteriated derivative (87) of 1,6-anhydro-β-D-galactopyranose can be made by the known photobromination-reductive dehalogenation of its triester derivatives; degradation of (87) has provided a route to (1*S*)-(1-^{2}H)-*sn*-glycerol (88), and, by a longer sequence involving inversion at C-1, the (1*R*)-diastereomer can also be obtained.[79]

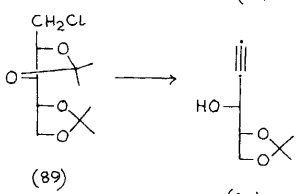
Some chiral polyhydroxyalkynes have been prepared by treating 2-alkoxy-1-chlorosugar derivatives with strong bases ($LiNH_2/NH_3$ or LDA); the conversion of (89), derived from D-xylose, into alkyne (90) is typical.[80] Periodate cleavage of 3,4-*O*-isopropylidene-D-mannitol, followed by Wadsworth-Emmons reaction, gave diene diester (91).[81]





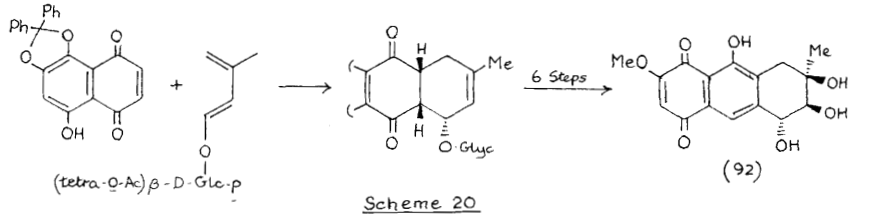




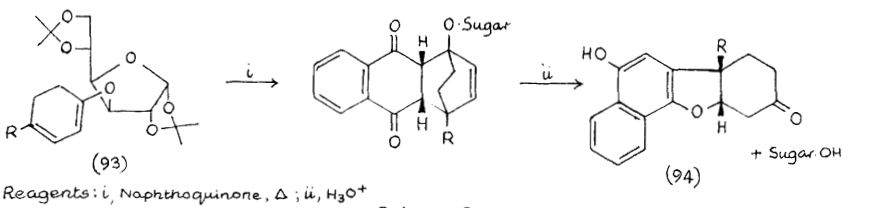


7 Carbohydrates as Chiral Auxiliaries

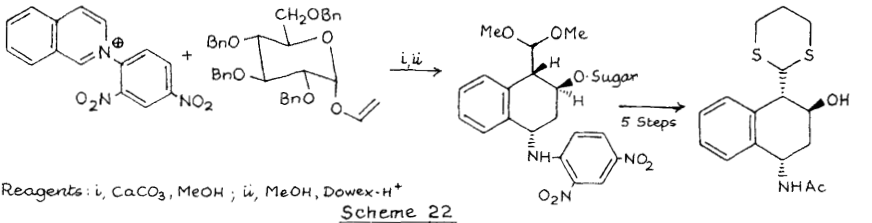
The stereostructure of (-)-bostricin has been revised following the asymmetric synthesis of its enantiomer (92) using Stoodley's glycosyloxydiene approach (Scheme 20).[82] The chiral alkoxydienes (93, R=H, Me) have also been shown to undergo highly diastereoselective Diels-Alder reactions with naphthoquinone (Scheme 21); the hydrolysis products (94) were estimated as being 97.5% enantiomerically pure.[83] Vinyl glycosides can be used in the Bradsher cycloaddition to give chiral tetralins with high enantiomeric excess (e.e.) (Scheme 22).[52]



Scheme 20



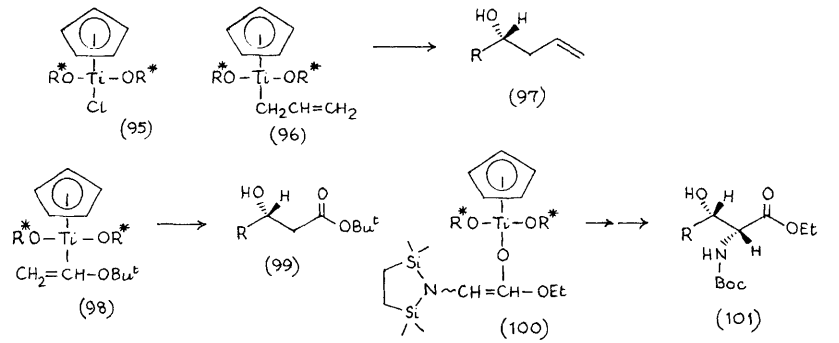
Scheme 21



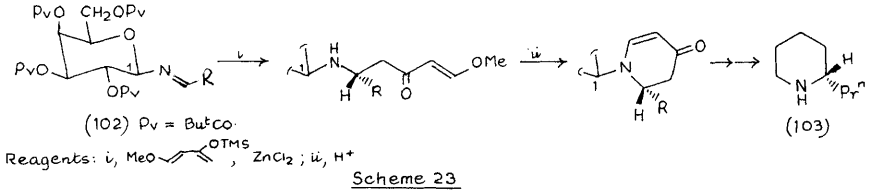
Scheme 22

A group of papers have described elegant work with chiral units derived from the titanium(IV) species (95), where R* is the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl unit. The allyl titanate (96) reacts with aldehydes to give adducts (97) of >85% e.e.,[84] whilst the chiral enolate (98) gives β-hydroxyesters (99) with >90% e.e. in high yields.[85] The nitrogen-substituted enolate (100) reacted with aldehydes to give, after hydrolysis and conversion to *N*-BOC derivatives, α-amino-β-hydroxy acids with high e.e. and high diastereomeric excess in favour of the *syn*-adducts (101).[86]

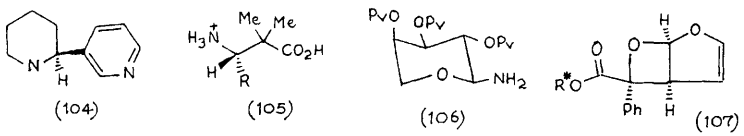
Kunz's group have extended their work on the use of galactosylamine



derivatives (102) as chiral auxiliaries (see Vol. 21, p.101) to the reactions of Scheme 23. In most cases studied, the major diastereomers formed in high excess were those indicated, leading, in the case of R= *n*-Pr, to a synthesis of (+)-coniine (103),[87] but in the case of R= 3-pyridyl, the major diastereomer had *opposite* chirality (96:4 ratio), leading to a synthesis of (S)-anabasine (104);[87,88] transition-state models were proposed to account for the difference.[87] Reaction of imines of type (102) with the TMS-ketene acetal derived from methyl isobutyrate, followed by hydrolysis, gave β-aminoacids (105) with high e.e.[89] The stereoselective Ugi synthesis of α-aminoacids using D-galactosylamine auxiliaries (Vol. 22, p. 110-111) has been employed using the D-arabinopyranosylamine derivative (106); since the D-arabinose derivative is enantiomeric with a D-galactose system, except for loss of C-6, the α-aminoacids are now produced with (S)-chirality.[90]

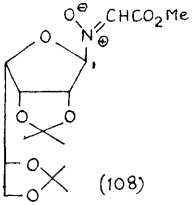


Scheme 23

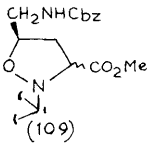


When phenylglyoxylate esters derived from various carbohydrate alcohols are employed in the Paterno-Buchi reaction with furan, the products (107) can show up to 80% diastereomeric excess.[91] The nitrone (108) underwent facially-selective addition to the appropriate alkene to give adduct (109);

hydrolytic removal of the auxiliary and further manipulation was used to make the aminoacid (+)-negamycin and its C-3 epimer.[92]

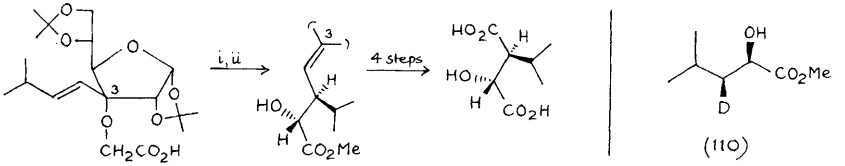


(108)



(109)

A [2,3]- Wittig rearrangement carried out on a carbohydrate template has been used in a route to 3-alkyl malic acids, as indicated in Scheme 24. The product of opposite chirality at C-3 could be obtained from the *cis*-alkene, and transition-state models were proposed to rationalize the results.[93] Somewhat similar intermediates were used in a synthesis of the stereospecifically-deuteriated ester (110), required as a standard in a study of enzyme stereospecificity; in this case C-3 of D-glucose became C-1 of the carboxylic acid by oxidative cleavage.[94]



Reagents: i, 3 LDA ; ii, CH_2N_2

Scheme 24

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ISBN 0-85186-172-5

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