SPECIALIST PERIODICAL REPORTS

Carbohydrate Chemistry

VOLUME 24

Monosaccharides, Disaccharides, and Specific Oligosaccharides

A Review of the Literature
Published in 1990

ROYAL SOCIETY OF CHEMISTRY

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A Review of the Recent Literature Published during 1990

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Preface

Once again I am indebted to the reviewing team for their painstaking labours in covering an increasingly complex literature, and although complaints have been few, there are worrying signs that the magnitude of our task is increasing both rapidly and surreptitiously. Neil Williams, in particular, has to be thanked for his handling of all of the drawings.

Although the advance of the subject is not uniform, the approach we have adopted is largely that of recent volumes.

The Royal Society of Chemistry has again been helpful in all possible ways; Dr P.G. Gardam and Mr A.G. Cubitt, in particular, have been understanding of our needs and restrictions.

R.J. Ferrier
April 1992

Contents

REPRINTS

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 renaissance being enjoyed by carbohydrate chemistry is reflected in the world-wide strength of the 1990 literature of the subject, biology and improved methodologies stretching research further and faster.

While the evolved format of these Reports largely allows for the handling of new material, some adaptation is desirable and (after some debate) treatment of chain-extended sugar derivatives is now included in Chapter 2. Carbohydrates as chiral auxiliaries is another aspect that the normal format does not accommodate too readily; it is treated in Chapter 24, and Chapter 4 now includes brief reference to chemical aspects of the cyclodextrins.

A monograph on carbohydrate chemistry has appeared in Topics in Current Chemistry,[1] the history of the subject from its origins has been surveyed in a Chinese language publication[2] and a data bank of the structures of all complex carbohydrates larger than disaccharides has been set up.[3] Reports of papers given at an American Chemical Society Symposium on computer modelling of carbohydrate compounds have appeared in a collected volume.[4]

The nomenclature committee of the International Union of Biochemistry has recommended that the early method used to number the atoms of *myo*-inositol be relaxed. According to the proposal substituents need not necessarily be numbered so that the smallest possible locant is used; authors may use alternative designations to bring out structural relationships.[5]

An extensive review has appeared on the anomeric and exo-anomeric effects in carbohydrate chemistry.[6] A further review of the anomeric effect asserts that $n \rightarrow \sigma^*$ contributions to the former effect are small relative to those of $n \rightarrow n^*$ destabilising components.[7] Further consideration has been given to the effect following analysis of 529 crystal structures of carbohydrates, in particular the C-O bond lengths and C-O-C and O-C-O bond angles as they depend on dihedral angles in the sequence C-O-C-O-C. The work is an extension of an earlier study (Vol. 18, p.2, ref. 4).[8]

Reviews have also been published on the following chemical aspects of carbohydrates: thermal decomposition,[9] DMSO-dependent oxidation of hydroxyl groups,[10] and reactions in liquid hydrofluoric acid.[11]

Thermodynamic data on aqueous solutions of mono- and oligo-saccharides have been surveyed; new hypotheses on the state of water in the hydration shells of sugars were considered in the light of interactions with third species.[12]

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2

Free Sugars

Reviews have been published on the chemistry of sucrose and its derivatives (90 refs.),[1] on the synthesis of stable isotope enriched D-glucose (61 refs.),[2] and on the interaction between saccharides, metal ions and polyamines (44 refs.).[3]

1 Theoretical Aspects

Earlier reports of unusually large parity-violating energy differences between enantiomers of sugar precursors (see Vol. 20, p. 2, ref. 4 and Vol. 22, p. 4, ref. 8) have now been shown to be wrong.[4]

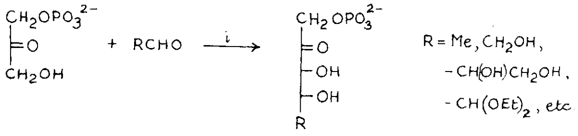
Correlated variations of bond lengths in pseudorotating furanose rings have been estimated by a theoretical method,[5] and the quantisation of hydrogen bond lengths in carbohydrate crystals has been investigated by use of a 1-dimensional anharmonic oscillator model.[6]

The kinetic effects of various aldohexoses, ketohexoses, and aldopentoses as solutes on the hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole, a reaction which is catalysed by water, have been studied. All the sugars tested caused retardation of the hydrolysis. The results were evaluated in terms of stereochemical features and hydration of the monosaccharides.[7]

2 Synthesis

A summary has been presented on the 2-(trimethysilyl)thiazole method of ascent in the aldose series (see Vol. 23, p. 4, ref. 15 and p. 11, ref. 48).[8] A review on the synthesis of stable isotope enriched D-glucose is referred to above (ref. 2).

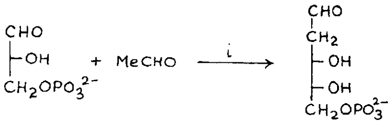
The autocatalytic synthesis of carbohydrates from formaldehyde was found to



Reagent : i, Fuculose 1-phosphate aldolase

Scheme 1

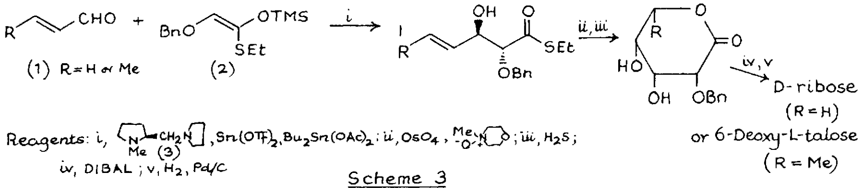
require the presence of trace amounts of acetaldehyde. It was assumed that the initial condensation of formaldehyde with acetaldehyde, followed by retroaldol splitting of the condensation products, furnishes glycolaldehyde and low molecular carbohydrates which further condense with formaldehyde.[9] The self-condensation of glycolaldehyde phosphate in aqueous NaOH is covered in Chapter 7.



Reagent: i, 2-Deoxyribose 5-phosphate aldolase (DERA)

Scheme 2

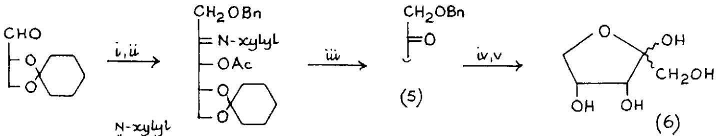
2.1 Pentoses and Hexoses. - The transketolase-catalysed synthesis of D-*threo*-pentulose from L-serine reported in Vol. 21, p. 6, ref. 31, has now been carried out with doubly ^{13}C-labelled starting material to give D[1,2-$^{13}C_2$] *threo*-pentulose.[10] In a preliminary publication, the cloning and overproduction of bacterial fuculose 1-phosphate aldolase (EC 4.1.2.17) has been described. This enzyme catalyses the aldol reaction between dihydroxyacetone phosphate and various aldehydes to give, as shown in Scheme 1, products with 3*R*, 4*R* stereochemistry. The commonly used rabbit muscle fructose 1,6-diphosphate aldolase (RAMA) furnishes 3*R*, 4*S*-configurated products.[11] The synthetic utility of a bacterial 2-deoxyribose 5-phosphate aldolase (DERA, EC 4.1.2.4) has been assessed. DERA catalyses the reversible aldol condensation between acetaldehyde and D-glyceraldehyde 3-phosphate, Scheme 2, *i.e.*, between two aldehydes, which is unusual. Many alternative aldehydes, including sugars and their phosphates are accepted as substrates.[12]



Scheme 3

High yielding and highly stereoselective aldol condensations involving simple α,β-unsaturated aldehydes (1), the silylenol ether (2), and the chiral catalyst (3), have been employed to prepare free sugars *via* aldonolactones. As illustrations, the syntheses of D-ribose and 6-deoxy-L-talose are given in Scheme 3.[13]

The reaction of 2,3-*O*-cyclohexylidene-D-glyceraldehyde with the α-hydroxyacetyl anion equivalent (4), prepared from benzyl chloromethyl ether, 2,6-xylyl isocyanide and

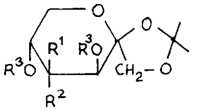


Reagents: i, $BnOCH_2\text{-}\overset{\text{N-xylyl}}{\overset{\|}{C}}\text{-}SmI_2$ (4); ii, Ac_2O, Py; iii, H^+; iv, K_2CO_3, MeOH; v, CF_3CO_2H, H_2O; vi, H_2, Pd/C

Scheme 4

SmI_2, proceeded with excellent stereoselectivity to furnish, after acetylation and imine hydrolysis, the D-*erythro*-pentulose derivative (5). Deprotection gave the free sugar (6) as shown in Scheme 4.[14]

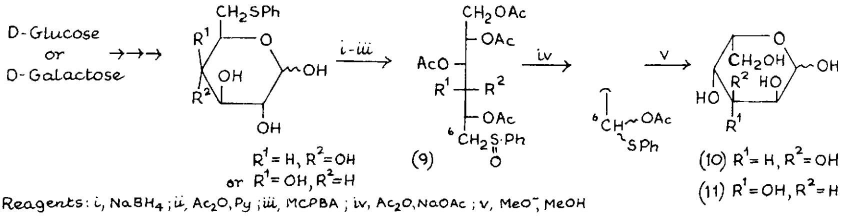
Full experimental details have been published for the synthesis of all eight L-hexoses from 2-butene-1,4-diol by a reiterative two-carbon extension cycle consisting of four key steps (asymmetric epoxidation, epoxide opening with benzenethiol accompanied by epoxide migration, Pummerer rearrangement, and Wittig olefination) which was outlined in



(7) $R^1 = H, R^2 = OH, R^3 = Bz$
(8) $R^1 = OH, R^2 = R^3 = H$

Vol. 17, p. 4, Scheme 4.[15] A ten step synthesis of the β-D-tagatopyranose 1,2-acetonide (8) from D-fructose involved epimerisation at C-4 of an appropriately protected intermediate (7) by an oxidation - reduction sequence,[16] and the key step in the preparation of L-gulose (10) and L-galactose (11) from D-glucose and D-galactose, respectively, shown in Scheme 5, was the Pummerer rearrangement of the peracetylated 6-deoxy-6-phenylsulphinyl-D-hexitols (9).[17]

The release of free sugars by selective deprotection at C-1 of perbenzylated and peracetylated hexopyranoses is referred to in Chapters 5 and 7, respectively.

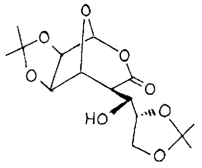


Reagents: i, $NaBH_4$; ii, Ac_2O, Py; iii, MCPBA; iv, Ac_2O, NaOAc; v, MeO^-, MeOH

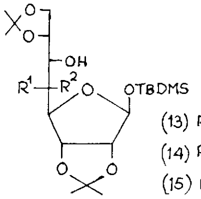
Scheme 5

2.2 Chain-extended Compounds. - De Las Heras *et al.* have presented a summary of their contributions to the synthesis of branched-chain and higher sugars and nucleosides.[18]

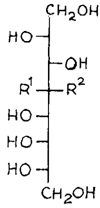
The lactone (12) (see Vol. 23, p. 8, ref. 31) has been converted to the 5-*C*-hydroxymethyl-D-*threo*-D-*allo*-octose derivative (14) and its D-*threo*-L-*talo* isomer (15) by



(12)



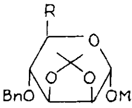
(13) $R^1, R^2 = {>}CH_2$
(14) $R^1 = OH, R^2 = CH_2OH$
(15) $R^1 = CH_2OH, R^2 = OH$



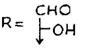
(16) $R^1 = OH, R^2 = CH_2OH$
(17) $R^1 = CH_2OH, R^2 = OH$
(18) $R^1 = H, R^2 = CH_2OH$

dihydroxylation of the known methylidene intermediate (13). Deprotection and reduction gave the 4-*C*-hydroxymethyl octitols (16) and (17), respectively. The 4-deoxy analogue (18) was available by direct reduction of the lactone (12) with $LiBH_4$ and subsequent acetal hydrolysis.[19]

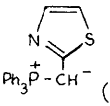
The synthesis of KDO and related structures from monoepoxides of divinylcarbinols, which proceeds *via* tetra-*O*-benzyl-*aldehydo*-D-ribose is covered in Chapters 16 and 18, and the preparation of a 2-deoxy-L-*galacto*-heptose derivative from ascorbic acid *via* methyl L-threonate in Chapter 12.



(19) R = CHO



(20) R =

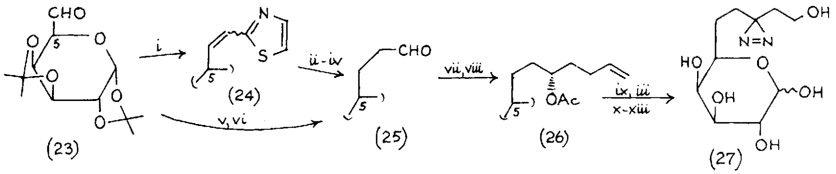


(21)

$Ph_3P{=}CHCHO$

(22)

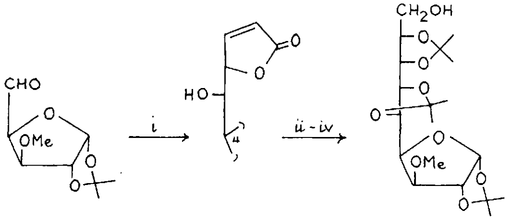
A variety of methods have been used to prepare higher sugars from suitably protected dialdehydo-pentoses and -hexoses: the synthesis of the L-*glycero*-D-*manno*-heptose derivative (20) involved a one-carbon extension at C-6 of the hexodialdehydo precurson (19) by stereoselective reaction with vinyl magnesium bromide and ozonolysis of the terminal alkene thus formed, followed by reductive work-up.[20] Two-carbon homologation was achieved by use of either 2-thiazolymethylene triphenylphosphorane (21)[21] or the more traditional Wittig reagent (22)[22]. As an illustration, the preparation of the di-*O*-isopropylidene dideoxyoctose (25) from diacetone D-*galacto*-dialdose (23) is shown in Scheme 6. With the former method an E/Z mixture of alkenes (24) was first obtained, the double bond being reduced during the subsequent thiazole unmasking procedure.

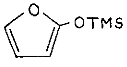


Reagents: i, Cpd (21); ii, MeI; iii, $NaBH_4$; iv, $HgCl_2.H_2O$; v, Cpd (22); vi, H_2, Pd/C; vii, ⁄\⁄\MgBr; viii, Ac_2O, Py; ix, O_3; x, MeO^-, MeOH; xi, NaOCl, AcOH; xii, $HONHSO_3$, I_2; xiii, CF_3CO_2H, H_2O

Scheme 6

Compound (25) was further extended by condensation with 4-butenylmagnesium bromide, and the resulting terminal alkene (26) was converted, by a known procedure as shown, to 8-azi-6,7,8,9,10-pentadeoxy-D-*galacto*-undecose (27).[22] Use of 2-(trimethylsiloxy)furan (28) in the presence of BF_3 etherate as reagent for chain extension allows the addition of a four carbon unit to aldehydes with high disastereoselectivity. An example is given in Scheme 7.[23]





(28)

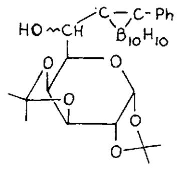
Reagents: i, Cpd (28), $BF_3.Et_2O$; ii, $KMnO_4$; iii, $Me_2C(OMe)_2$, p-TsOH; iv, DIBAL

Scheme 7

In an attempt to increase the water solubility of carborane - antibody complexes, the dialdehyde (23) and several other sugar aldehydes were treated with lithiated dicarba-*closo*-dodecaboranes (29). The reactions were reasonably stereoselective, giving *erythro*- and *threo*-products, *e.g.*, compounds (30) in *ca.* 4:1 ratios.[24] From the same starting compound (23) the 1,6-*C*-linked disaccharide (33) was prepared by fluoride ion mediated condensation with peracetylated β-*C*-glucopyranosyl nitromethane (31) followed by elaboration of the resulting nitroalkene (32) as shown in Scheme 8. By a similar reaction sequence, the *C*-linked β,β-trehalose analogue (35) was available from the acyclic glucose derivative (34).[25]

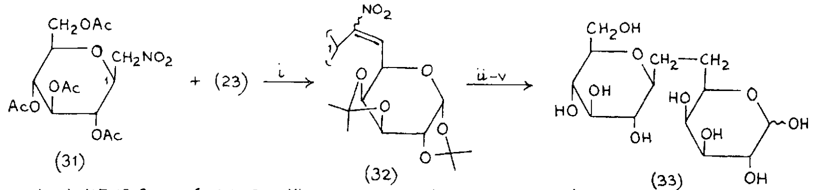
$Li^+ C_2B_{10}H_{10}R$

(29) R = H, Ph, Bu



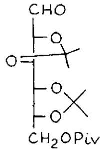
(30)

Mixed Kolbe electrolysis of the sugar carboxylic acids (36) and (38) with fatty acids gave moderate yields of the single product (37) and the mixture (39), respectively, with long unfunctionalised alkyl branches.[26] 1-Deoxy-1-(indolin-3-yl)-α-L-sorbopyranoses (41) were formed from ascorbigen and its derivatives (40) in *ca.* 30% yield on treatment with aqueous alkali.[27]



Reagents: i, KF, 18-Crown-6; ii, $NaBH_4$; iii, Bu_3SnH, AIBN; iv, MeO^-, MeOH; v, H^+

Scheme 8



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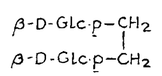
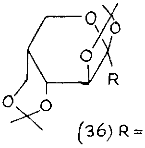


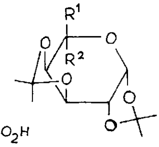
$$\begin{array}{l}\beta\text{-D-Glc-}p\text{-}CH_2\\ \quad\quad\quad\quad\;\;|\\ \beta\text{-D-Glc-}p\text{-}CH_2\end{array}$$

(35)



(36) R = CO_2H

(37) R = $C_{11}H_{23}$

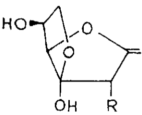


(38) $R^1 = CO_2H$, $R^2 = H$

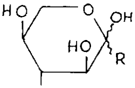
(39) $R^1 = C_7H_{15}$, $R^2 = H$

or

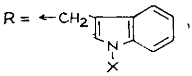
$R^1 = H$, $R^2 = C_7H_{15}$



(40)



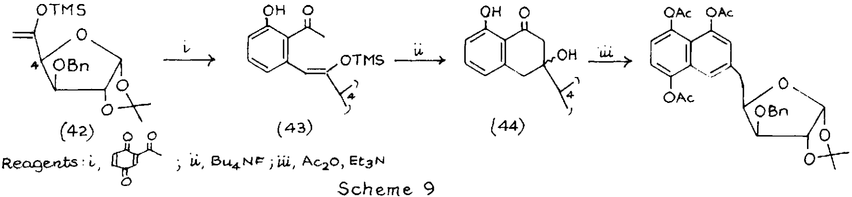
(41)



R = , X = H, Me, All, Bu

A method for the preparation of higher sugars with an aromatic branch has been developed which involves a Michael addition - aldol condensation sequence and uses carbohydrate silylenol ethers, *e.g.* compound (42), as starting materials. As is demonstrated in Scheme 9, the Michael addition product was obtained as the stable silylenol ether (43). On desilylation, aldol condensation took place to give the cyclic hydroxyketone (44) which aromatised under acetylation conditions.[28] The introduction of an aromatic branch by Diels-Alder cyclisation of a carbohydrate diene is referred to in Chapter 19.

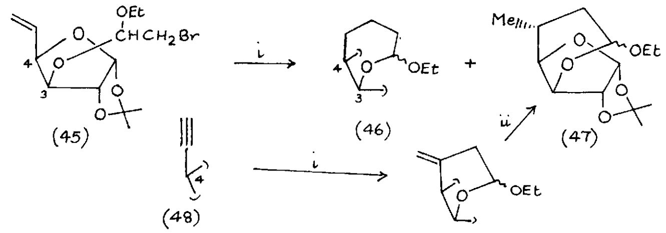
Chain elongation has been accomplished intramolecularly, by addition of the radical derived from the bromoacetal group at O-3 of the 5,6-dideoxy-hex-5-enofuranose



Reagents: i, ; ii, Bu_4NF; iii, Ac_2O, Et_3N

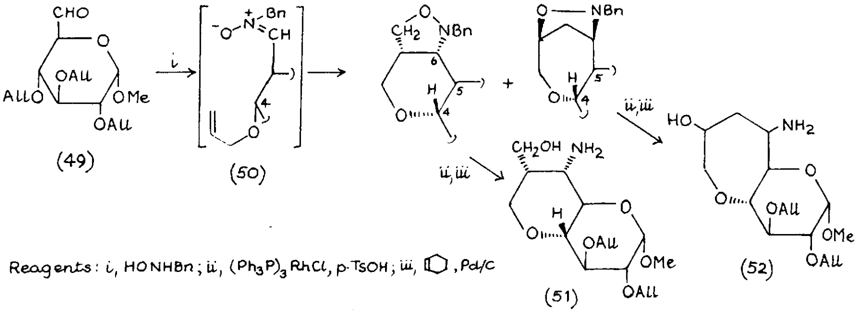
Scheme 9

derivative (45) to the exocyclic double bond (Scheme 10). The addition was stereoselective but lacked regioselectivity, the isomeric functionalised furano-oxepan (46) and furano-pyran (47) being formed in approximately equal amounts. The analogous radical cyclisation of the alkyne (48) on the other hand gave, after hydrogenation, the *exo* addition product (47) exclusively.[29] In another intramolecular chain extension, which is outlined in Scheme 11, the nitrone (50), easily prepared from the 6-aldehydo-D-glucopyranoside derivative (49) with *N*-benzylhydroxylamine, underwent 1,3-dipolar addition to the double bond of its 4-*O*-allyl group to give, after deprotection, the chiral pyrano-pyran- and pyrano-oxepan-derivatives (51) and (52) as the major and minor products, respectively, in 2:1 ratio.[30]



Reagents: i, Bu_3SnH, AIBN; ii, Rh/Al_2O_3, H_2

Scheme 10



Reagents: i, HONHBn; ii, $(Ph_3P)_3RhCl$, p-TsOH; iii, ⌬, Pd/C

Scheme 11

3 Physical Measurements

Recommended values for the thermodynamic and transport properties of pentoses and hexoses and their phosphates, in both the condensed and aqueous phase, have been presented and critically evaluated.[31] The partial molar volumes and expansibilities of some pentoses and hexoses in aequeous solution have been determined,[32] and the viscosities of similar solutions have been measured up to 2.5 mol kg^{-1} at 293.15 -318.15 K; the molar thermodynamic activation parameters for viscous flow were found to be linearly dependent on the solute mol fraction, indicating that the partial molar contributions by the solutes to the activation are independent of their concentration.[33]

The enthalpies of dilution of aqueous solutions containing an oligomer of glycine and either L-arabinose, D-ribose, D-xylose, or D-lyxose have been measured.[34] The glass-to-rubber transition temperature of glucose/fructose and sucrose/fructose binary melt mixtures were determined by differential scanning calorimetry (DSC),[35] and the same technique was used to record the state diagram for aqueous galactose; in addition, the heat of fusion of H_2O in sugar solutions, which can be very different from that of pure water, was calculated.[36]

A symposium report has been published on adsorption and x-ray photoelectron spectral data for a glucose/alumina system, aimed at deriving new information about glucose mutarotation catalysis over basic alumina surfaces.[37] The sorption of galactose by Na-Y, K-Y, and Ba-Y zeolites has been investigated by isopiestic equilibration at 25°C,[38] and in a study of the absorption kinetics for glucose and fructose on KU-2 calcium cation exchange resin, the equilibrium adsorption isotherms were found to depend on the temperature, the degree of crosslinking, and grain size.[39,40]

^{18}O-Isotope shifts in ^{13}C-n.m.r. spectra have been used to follow the kinetics of the oxygen exchange reactions at the anomeric centres of D-glucose, D-mannose, and D-fructose which are catalysed by acids and bases. The exchange rates were slow relative to mutarotation.[41] Evidence from g.c. data on trimethylsilyl derivatives of 2-deoxy-D-glucose and 2-deoxy-D-maltose suggested that the disaccharide in the crystalline state contains 83% of the α and 17% of the β form.[42] The enthalpy and entropy of interaction of cations with hexoses and pentoses is referred to in Chapter 17.

4 Isomerisation

The light-promoted mutarotation of α-D-glucose in DMSO in the presence of aromatic hydrocarbon sensitisers has been reported.[43] It has been confirmed, by use of h.p.l.c., that the mutarotation of α- and β-D-glucopyranose in dilute, neutral aqueous solution is a slow process, taking approximately three hours at ambient temperature to reach completion. The mutarotation rate of the β-compound was 1.4 times that of the α-isomer, and the α:β ratio at equilibrium was 37.2:62.8. In addition, it was found that α-D-glucopyranose complexes more strongly with Ca^{++} ions then does β-D-glucopyranose.[44]

The tautomeric equilibrations of D-*erythro*-2-pentulose and of D-*threo*-2-pentulose in aqueous solution have been studied by ^{13}C-n.m.r. spectroscopy. The α- and β-furanoses and acyclic keto forms were detected at all temperatures, whereas the acyclic *gem*-diols were not observed. Thermodynamic and kinetic parameters for the interconversions were determined and a comparison with the corresponding data for the structurally related aldotetrofuranoses indicated that replacement of H-1 in the latter compounds by hydroxymethyl group significantly decreases the ring-opening and ring-closing rate constants of furanose anomerisation.[45] The furanose-pyranose equilibria of trehalulose, maltulose, and some other α-D-glucopyranosyl-D-fructoses in water, pyridine, and DMSO have been determined with the help of ^{1}H-n.m.r. methodology.[46] Similar studies on the tautomeric equilibria of ribose, glucose, fructose, and related sugars are covered in Chapter 21.

Epimerisation at C-2 of aldoses in alkaline, aqueous or methanolic solution proceeded more rapidly when Ca salts were added. This Ca(II) -promoted epimerisation involved a stereospecific C-1 - C-2 skeletal rearrangement, D-[1-^{13}C] glucose giving D-[2-^{13}C] mannose, and the formation of fructose from either glucose or mannose (Lobry-Alberda rearrangement) was slowed down by the presence of the salt.[47] The previously reported epimerisation and isomerisation of D-glucose by the tetramethylethylene diamine (tetmen) complexes of Ni(II) and Ca(II) (see Vol.21, p.4, refs.22-24 and Vol.23, p.10, ref.45) has been extended to additional monosaccharides. The Ni complex was found to be superior for promoting C-2 epimerisations to give near equilibrium mixtures of, for example, D-galactose and D-talose, or D-ribose and D-arabinose, the isomer with *cis*-disposed OH-2 and OH-4 generally predominating. Ca-tetmen, on the other hand, promoted aldose - ketose isomerisation, for which an intermediate has been postulated.[48] A review covering this area is referred to at the beginning of this Chapter (ref.3).

In aqueous solutions of ammonium molybdate, acyclic D-xylose, D-lyxose, D-glucose, and D-mannose formed binuclear bidentate molybdate complexes involving the hydrated carbonyl group as well as the hydroxy groups at C-2, C-3, and C-4. Epimerisation *via* these complexes was accompanied by skeletal rearrangement; thus D-[2,3,4,5,6-^{13}C$_5$] mannose isomerised to D-[1,3,4,5,6-^{13}C$_5$] glucose.[49]

5 Oxidation

The electrocatalytic oxidation of D-glucose and related polyols on large platinum and gold electrodes was discussed in a symposium report,[50] and the oxidation of glucose and polyols on nickel electrodes[51] and on platinum, rhodium, and iridium electrodes under alkaline conditions[52] has been investigated. Strong inhibition of the oxidation of glucose in dilute $HClO_4$ solution at platinum anodes by adsorbed CO was observed by *in situ* f.t.i.r. reflection-absorption spectroscopy; gluconolactone, carbonylic acids, and CO_2 were the main products.[53]

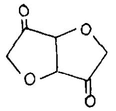
The continuous electrochemical oxidation of D-glucose has been achieved by use of a filtering anode made from carbon fibres and of sodium bromide solution, buffered to pH 9 with sodium hydrogen carbonate, as electrolyte. The optimum NaBr concentration of 0.194 mol dm^{-3} secured a 94% conversion to sodium gluconate.[54] The calcium, copper, magnesium, and zinc salts of various aldonic acids (*e.g.*, gluconic, galactonic, lactonic, and maltonic acid) were obtained in >90% yield by anodic oxidation of the free sugars in NaBr solution containing the appropriate metal carbonate.[55]

The factors affecting the efficiency of the oxidation of D-glucose 1-phosphate and analogues to alduronic acid 1-phosphate by molecular oxygen over platinum on carbon have been examined. A partial loss of starting material occurred through oxidation of secondary OH groups and subsequent C - C bond cleavage. This side reaction is retarded by substituents at C-5, the protecting ability following the order $CO_2^- > CH_2OH > H$.[56] The dianhydro-hexdiulose (53) was the main product isolated from the Pt/C catalysed oxidation of 1,4; 3,6-dianhydro-glucitol (isosorbide) in aqueous solution by molecular oxygen (see Vol.19, p.169, ref.30).[57]

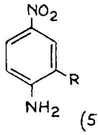
The decomposition of deoxyribose by Fenton's reagent (H_2O_2-Fe^{2+}) has been examined in acidic, neutral, and slightly alkaline media, and in the presence and absence of hydroxy radical scavengers. It has been suggested that both the substrate and the scavengers interact with the metal ions to bring about a site specific Fenton reaction.[58] The oxidation of carbohydrates by alkaline H_2O_2 was found to be accelerated by traces of Fe(II) ions, but larger quantities of the same ions had a retarding effect.[59]

A comparitive study of the reactions induced by ultrasound and gamma rays, respectively, in aqueous solutions of lactose revealed no major differences in product composition. Apart from small amounts of lactobionic acid, only monosaccharides, resulting from oxidative cleavage of the glycosidic bond, were detected, primarily D-galactose, D-glucose, and D-galactonic acid. In addition, products of further oxidation without carbon - carbon bond scission (hexosuloses, hexosulonic acids), as well as degradation products with three to five carbon atoms, were found.[60]

Reports have been published on the kinetics and mechanisms of the oxidations of maltose, lactose,[61] glucono-1,5-lactone 6-phosphate and glucodialdehyde 1-phosphate[62] by Ce(IV), of D-galactose[63] and several other monosaccharides[64] by V(V), all in dilute sulphuric acid solution, and on the effect of pressure on the rates of oxidation of polyhydric alcohols (glycerol, xylitol, glucitol) by V(V) in $HClO_4$.[65] The mechanisms previously proposed for these transition metal oxidations have been confirmed. The kinetics of the two-electron oxidation of D-lyxose with metal ions (Ag^+, Hg_2^+, Hg_2^{2+}) have been investigated and the physico-chemical parameters of the reaction have been recorded.[66] Kinetic and mechanistic studies have appeared on the oxidation of L-arabinose by $KBrO_3$ in aqueous solution,[67] some hexoses (D-glucose, D-mannose,D-fructose)[68] and pentoses (D-xylose, D-ribose, L-arabinose)[69] by chloramine B ($PhSO_2NClNa$) in the presence of alkali, and of melibiose and cellobiose by aqueous, alkaline iodine solution, where HOI is apparently the reactive species.[70]



(53)



R = H, SO_3H, CO_2H

(54)

Nitrogen dioxide has been recommended, in place of the customary nitric acid, as a convenient and inexpensive oxidising agent for the production of oxalic acid from carbohydrates.[71] D-Glucose and D-fructose have been employed for the reduction of the nitro groups of some nitroanilines, such as compounds (54), to amino groups.[72]

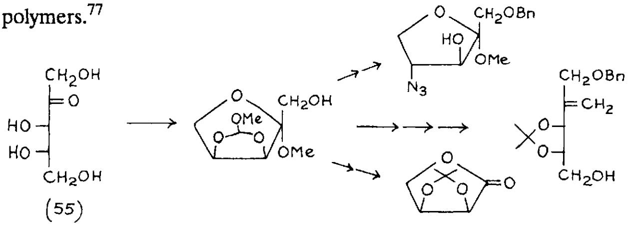
The large kinetic isotope effect observed in the oxidation of D-[6-^{3}H] galactose by galactose oxidase has been exploited to increase its specific activity. As the unlabelled substrate is oxidised faster, incomplete oxidation leaves the starting material enriched in labelled component.[73] In the Bleomycin-mediated oxidative degradation of DNA, 2′-deoxy-4′-pentulose is released. A mechanistic study with ^{18}O-labelled O_2 and H_2O revealed that the solvent is the source of the 4′-carbonyl oxygen atom.[74]

The controlled oxidative degradation of the ketodisaccharide leucrose is covered in Chapter 16.

6 Other Aspects

To provide better understanding of the reactions taking place when sugars are heated at 250°C in the presence or absence of H_2SO_4, the aqueous phase chemistry of glycerol, 2-propanol, 1,4-butanediol, tetrahydrofuran, glyceraldehyde, pyruvaldehyde, and dihydroxyacetone under these conditions has been examined.[75] In a related study, focussed on the formation of 5-hydroxymethyl-2-furfuraldehyde from D-fructose or sucrose in aqueous solution at elevated temperatures with or without acid catalyst, the hypothesis that the fructofuranose ring remains intact throughout has been confirmed.[76]

The rate increasing influence of Cu(II) ions on the non-enzymic browning reaction between D-glucose and glycine (Maillard reaction) has been reinvestigated. At pH 3.00, melanoidin is formed which contains considerable amounts of Cu(II). *In vitro* experiments with model melanoidins and Cu(II) ions indicated that, in general, two protons are released for each ion bound. Melanoidins thus display the properties of acidic forms of anionic polymers.[77]



Scheme 12

The commercially available, unnatural keto sugar L-*erythro*-pentulose (55) shows promise as a new synthon. Some of its useful transformations are illustrated in Scheme 12.[78]

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3

Glycosides

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.—A short review has been published on the use of 1-alkoxy-substituted anomeric radicals for the constructions of β-glycosides (aglycon equatorial).[1]

A highly efficient synthesis of 1,2-*trans*-glycosides which can be applied with acid-labile alcohols employs benzoyl protected glycopyranosyl *P,P*-diphenyl-*N*-tosylphosphinimidates- (eg 1) as glycosylating agents.[2] On the other hand, mainly 1,2-*cis*-ribofuranosides were obtained on treatment of the phosphonium salt (**2**) with alcohols.[3]

A very simple procedure for *O*-glycosidation without the need for metal salts involves heating perbenzylglycosyl chlorides and alcohols in dichloromethane in the presence of tetramethylurea. Cholesterol and tetra-*O*-benzyl-α-D-glucopyranosyl chloride gave 92% of the glycosides (α;β, 60:40). In the case of the α-L-rhamnosyl chloride only α-products were obtained.[4]

D-Lyxose, treated with ethyl(dimethoxy)borane in the presence of acid, gave the glycoside ester (**3**) from which methyl α-D-lyxofuranoside was obtained in 80% yield. In related fashion methyl α-D-mannofuranoside was obtained in similar yield.[5] Alternatively, a wide range of β-D-lyxofuranosides can be made by way of the 5-*O*-acetyl-α-glycofuranosyl bromide of (**3**).[6]

Very interestingly, D-ribose complexed within the resorcinol-dodecylidene cyclotetramer (**4**) in carbon tetrachloride underwent highly efficient and selective conversion to methyl β-D-ribofuranoside.[7] Several methyl β-furanoside derivatives of L-*erythro*-pentulose have been described following synthesis from the commercially available sugar.[8] The α- and β-septanosides (**5**) were obtained in 43% combined yield on treatment of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside with anhydrous pyridinium chloride.[9]

Fischer, Koenigs-Knorr and Schmidt methods have been used to obtain α- and β-D-glucopyranosides of alcohols of chain lengths C_8-C_{16} with and without cationic substituents.[10]

The synthesis of *tert*-butyl glycosides from otherwise acetylated free sugars by treatment with iso-butene and an acid catalyst has been reported. 2,3,4,6-Tetra-*O*-acetyl-D-glucose gave mainly the β-pyranoside while the D-mannose analogue afforded the α-anomer. A rationale for the results was presented.[11]

The use of thioglycosides in glycoside synthesis is referred to in a later section of this Chapter; a novel development involves anodically oxidising the sulphur atom of *S*-aryl 1-thio-D-glucopyranosides in the presence of alcohols to obtain alkyl glucosides (poor anomeric selectivity) together with diaryl disulphides. Mainly β-products were obtained when the peracetylated thioglycosides were used.[12]

Trimethylsilyl tetra-*O*-benzyl-α-D-glucopyranoside treated in dichloromethane with alcohols in the presence of boron trifluoride gives good yields of glycosides (poor anomeric selectivity),[13] and peracetylated glucoses give mainly acetylated allyl β-D-glucopyranosides on reaction with allyl alcohol with this catalyst. Partially benzylated glucose esters react in this way also.[14] Treatment of *N*-Fmoc-protected serine and threonine with penta-*O*-acetyl-β-D-galactose and boron trifluoride as catalyst gave the *O*-linked amino acid β-galactosides.[15]

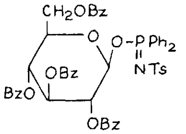
Treatment of glucopyranosyl bromides with alkoxycarbonyl protecting groups at O-2 react, under Koenigs-Knorr conditions, to give corresponding β-glucopyranoside derivatives and 1,2-cyclic carbonates the ratios of the products depending on the promoters used.[16] A study of substituted glycosyl bromides with hindered alcohols at ambient pressure and at 15 kbar showed that high pressure favoured product formation and, generally, orthoester production was selectively favoured.[17] The Koenigs-Knorr approach has also been used to provide a set of epoxyalkyl glycosides [exemplified by (**6**)-(**8**)] as potential inhibitors of β-glycan hydrolysases. Various oligoglucose analogues[18] and substances with related aglycons[19] were reported.

Mono- and di-saccharide glycosides of diethylene glycol and triethylene glycol and analogous hydroxyamines have been made to serve as artificial glycoconjugates,[20] and the liquid crystal properties of various mono-, di- and tri-saccharide α- and β-glycosides of long chain aliphatic alcohols have been reported, and the first liquid crystal glycosides of glucuronic acid and amino-sugars were described.[21]

1,1-Difluoroalkyl glucosides have been noted as being a new class of irreversible inactivators of α-glucosidases,[22] and a set of (perfluoroalkyl)ethyl α- and β-glycosides derived from glucose, galactose and maltose have been synthesised via the sugar 1,2-orthoesters for potential use as surfactants *in vivo*.[23]

The alkylglycosides (**9**)-(**12**) containing unsaturated functionality were made as follows: (**9**), by condensation of methyl D-glucopyranoside and 2-hydroxyethyl methylacylate in the presence of phosphomolybidic acid (α,β, 2:1);[24] (**10**), by opening the unsaturated ring of hexa-*O*-acetyl-D-lactal to give a 4-galactosylenol and treating the product with Wittig reagents;[25] (**11**), by opening the anhydro-ring of 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose with the pentenol in acidic conditions;[26] and (**12**) by treatment of 2-bromoethyl tetra-*O*-acetyl-β-D-glucopyranoside with quinoline.[27]

In the area of enzyme-catalysed syntheses benzyl β-D-glucopyranoside was made by coupling of glucose, or preferably cellobiose, with benzyl alcohol using an immobilized glucosidase and minimum amounts of water.[28] The transfer of β-D-galactopyranose from lactose to various simple chiral alcohols under the catalysis of an *E. coli* enzyme slightly favoured transfer to R-enantiomers and to primary sites.[29]



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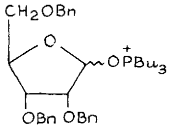

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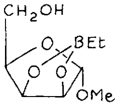

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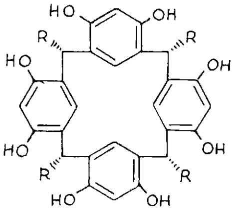
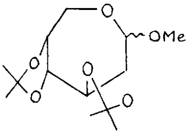


(4) R = $C_{11}H_{23}$



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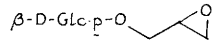

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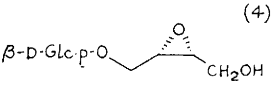

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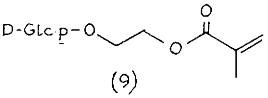

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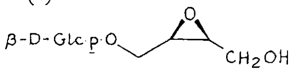

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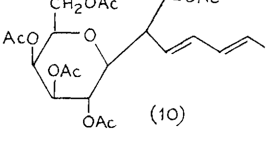

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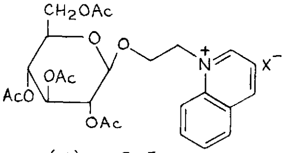
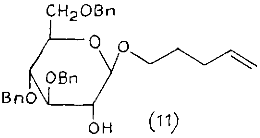


(12) X = Br, I



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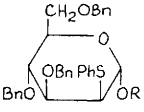

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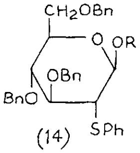
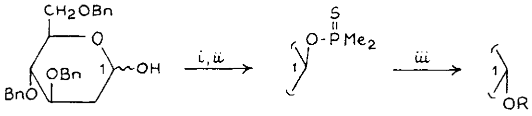


(14)

Tri-*O*-acetyl-D-glucal, treated with alcohols in the presence of triphenylphosphine hydrogen bromide, gives the α,β-2-deoxyglycosidic products in the ratio 4:1.[30] In related fashion, tribenzyl-D-glucal with alcohols and the sulphonium adduct of diphenyldisulphide and phenylselenyl chloride gave 2-phenylthio-α- and β-glycosidic products **(13)** and **(14)** in the ratio 1:3. 2-Deoxy-products are thus available as was exemplified by use of primary and secondary monosaccharide mono-ols.[31] A related study of the iodoalkoxylation of acetylated glycals showed that *trans*-diaxial products were favoured in the hexose series but that selectivity was poor with the pentose compounds, and *trans*-diequatorial products could predominate.[32]

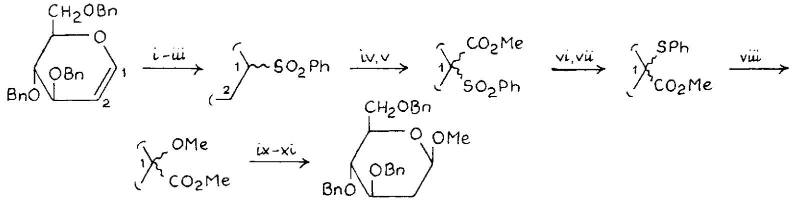
A review has been published (in Japanese) on the synthesis of 2-deoxyglycosides via (i) glycosyl sulphenates, and (ii) thioglycosides activated with phenylselenyl triflate.[33] Specific ways to obtain high proportions of 2-deoxy-α and β-D-*arabino*-hexopyranosides are



Reagents: i, BuLi; ii, $Me_2P(S)Cl$; iii, ROH, $Tr^+ClO_4^-$

Scheme 1

shown in Scheme 1[34] and Scheme 1A,[34A] respectively. Treatment of the 2,6-anhydro-2-thioglycosyl fluoride **(15)** with alcohols and various activators gave the α-products **(16)** with high selectivity. Hence the 2,6-dideoxy-α-glycosides **(17)** could be made by desulphurisation.[35]

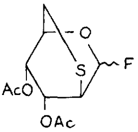


Reagents: i, HCl; ii, PhSH; iii, MCPBA; iv, LDA; v $(MeO)_2CO$; vi, Li naphthalenide; vii, $(PhS)_2$; viii, MeOH, Hg^{2+}; ix, NaOH; x, -OH, DCC; xi, hν

Scheme 1A

Mild acidic methanolysis of 2-deoxypentose and 2,6-dideoxyhexose dimethylacetals gave the methyl furanosides the structural analyses of which were carried out by ^1H and ^{13}C n.m.r. spectroscopy.[35]

Alkyl 2-acetamido-2-deoxy-β-D-glucopyranosides were obtained in high yield on reaction of the peracetate (**18**) with alcohols and zirconium tetrachloride.[36] The corresponding acetylated glycosyl chloride with the anion of luminol, followed by deprotection, gave (**19**) which is a substrate for *N*-acetyl-β-D-glucosaminidase and can be used for its assay since it is not chemiluminescent whereas the product of hydrolysis, luminol, is.[37] In related fashion the water soluble 3,4-dinitrophenyl *N*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside has been prepared to act as an alternative substrate[38] as has 4-[(3,5-dichloro-4-hydroxyphenyl)amino]phenyl-*N*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside.[39]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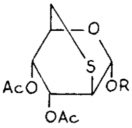
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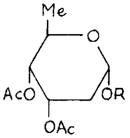
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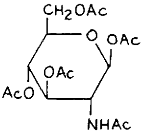
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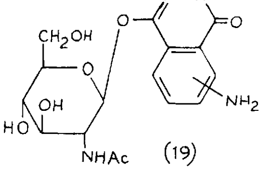
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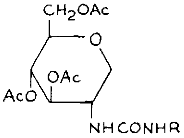
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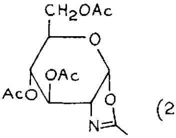
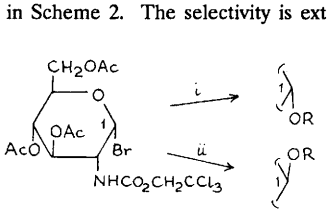

(21)

R = Me, $-C_6H_4-Cl$

The ureido-compounds (**20**) gave the oxazolines (**21**) on treatment with tin tetrachloride, the latter being glycosyl donors.[40] An alternative route to α- or β-glycosides in this series is illustrated in Scheme 2. The selectivity is extremely high and depends

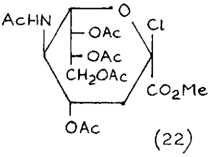


Reagents: i, ROH, $ZnCl_2$; ii, ROH, $ZnCl_2$-TrCl

Scheme 2

upon the absence or presence of the trityl chloride.[41] A study of related *N*-alkoxycarbonyl derivatives has revealed different routes to β-glycosides,[42] and *N*-*p*-methoxybenzylidene imines derived from 2-amino-2-deoxy-D-glucose similarly lead to β-linked products. It is proposed that these groups participate in displacement reactions by way of aziridinium ions.[43] The synthesis of new *O*-2-amino-2-deoxy-D-galactosylpeptides using 2-azido-2-deoxygalactopyranosyl halide derivatives has been reported.[44]

Three reviews have covered issues related to the synthesis of glycosides of sialic acids.[33,45,46] α-Linked glycosides, including di- and tri-saccharides, have been prepared by use of the chloride (**22**) together with alcohols and silver zeolite.[47] The α-glycoside (**23**),



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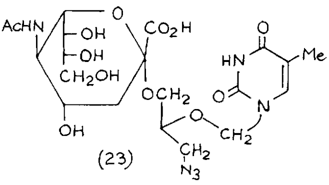
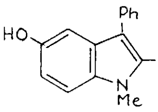


(23)

made together with the β-anomer, is a potent inhibitor of neuraminidase from influenza virus.[48] The synthesis of 2-deoxy-β-D-glycopyranosides via 3-deoxyulosonic acid glycosides has been referred to above.[34A]

Methyl β-D-glucopyranuronate glycosides of palmityl alcohol[49] and *p*-bromophenol[50] have been prepared by Koenigs-Knorr and Mitsunobu methods, respectively.

In the area of aryl glycosides, acetylated glycosyl bromides have been condensed with dihydroxybenzenes,[51] 4-hydroxy-3-methoxyacetophenone and related methoxybenzene derivatives, and 4-hydroxy-benzaldehydes and -anilines containing fluorine in the rings.[53]



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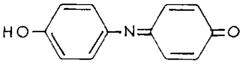

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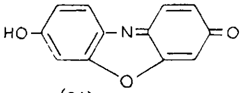

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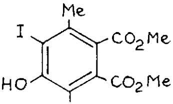

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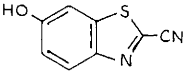

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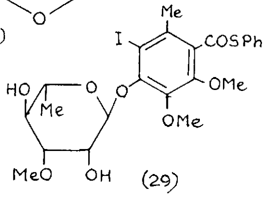
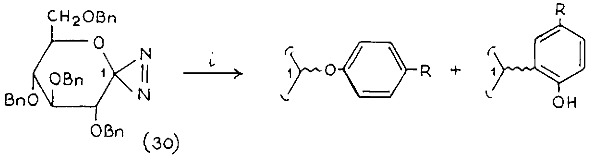


(29)

By similar methods, glycosylated derivatives of compounds (**24**),[54] (**25**),[55] (**26**),[56] (**27**),[57] (**28**)[58] and related phenols have been reported. Analogous acetylated glycosyl fluorides have been used to make substituted aryl α- and β-D-glucopyranosides selectively[59] and compound (**29**) which is the CD-ring system of the calicheamians.[60]

Autocatalytic glycosidation of 2,3-dihydroxy-1,4-naphthoquinone with an acetylated glucose 1,2-orthoester gave the mono- and di-glucosylated products.[61] The alternative glucosylating agent (**30**), treated with phenols, gave a mixture of *O*- and *C*-glycosides with the former predominating (Scheme 3).[62]



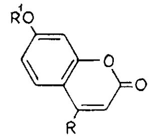
Reagents: i, HO-⟨⟩-R

Scheme 3

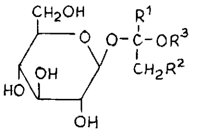
The fluorogenic glycosides (**31**)[63] and (**32**)[64] have been prepared as substrates for the assay of glycosidases, and the synthesis of aryl α-D-mannopyranosides as photoaffinity labels for Con A has been reviewed.[65]

Methyl (tri-*O*-acetyl-α-L-iduronosyl fluoride)uronate has been used to prepare the corresponding β-L-iduronate glycoside of 4-methylumbelliferone.[66]

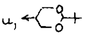
Tietze and coworkers have reported more work on acetal glycosides. 2,3,4,6-Tetra-*O*-acetyl-D-glucose with a range of vinyl ethers, including dihydropyrans, gave, after deacetylation, compounds such as (**33**) on reaction in acidic conditions. There was little diastereofacial differentiation and the largest ratio of the epimers at the new asymmetric centres was 2:1.[67] 1-*O*-Trimethylsilyl sugar acetates are of use in this topic, α- and β-such glucose derivatives giving acetals, eg. (**34**), with retention of anomeric configuration when treated with aldehydes and alcohols in the presence of trimethylsilyl triflate.[68] Extended studies gave access to (**35**), which is an acetal of the anti-cancer agent (**36**), and offers potential means of releasing it at the site of a tumour. It also was made via the 1-*O*-trimethylsilylglucose tetra-acetate.[69] Another route to acetal glycosides involves the condensation of such silyl derivatives with acetals in the presence of trimethylsilyl triflate and tetrabutylammonium fluoride. In this way compound (**37**) was made by use of a silylated 4-hydroxybutanone and then converted into an analogue of (**35**).[70]



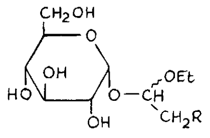
	R	R¹
(31)	Me	β-Glc·NAc
(32)	CH_2CO_2H	β-Gal



(33) R^1 = H, Me; R^2 = H, Et, CH_2SPh; R^3 = Et, Bu,



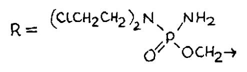
(34) R^1 = H, R^2 = C_4H_9, R^3 = CH_2CH_2Br



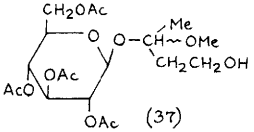
(35)

$OCHCH_2R$

(36)

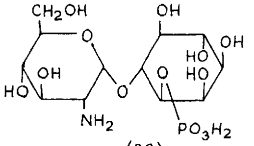


$R = (ClCH_2CH_2)_2N(NH_2)P(=O)OCH_2\rightarrow$



(37)

1.2 Synthesis of Glycosylated Natural Products.—The 2-amino-2-deoxy-α-D-glucosyl-*myo*-inositol phosphate (**38**), which was predicted to have insulin-like activity, has been synthesised,[71] as have 3-*O*-(2-amino-2-deoxy-α-D-galactopyranosyl)-D-*chiro*-inositol[72] and 6-*O*-(α-D-mannopyranosyl)-D-*myo*-inositol which is a fragment of mycobacteria phospholipids.[73] Compound (**39**), which is a key substance for the synthesis of distomycin C (cf. Vol. 22, p.200), was made by use of the corresponding α-mannopyranosyl chloride and the corresponding triol which is solubilized in the THF used by complexing with silver triflate. The β-selectivity of the reaction is notable.[74]



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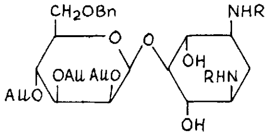
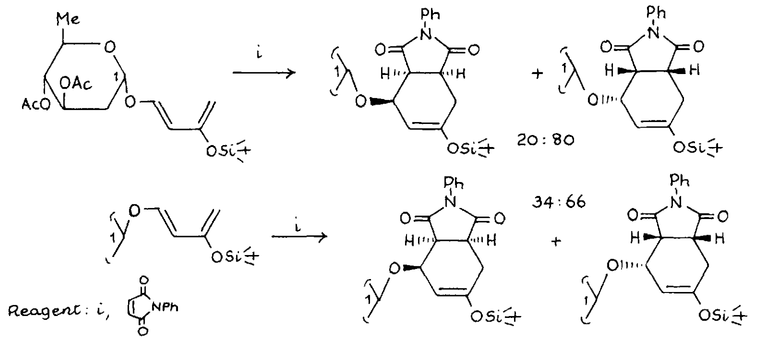


(39) R = Cbz

Extensive work has continued on the synthesis from glycosylated butadienes of functionalized cyclohexanols bonded to sugars (cf. Vol. 23, Chap. 3, refs. 37-39). See Scheme 4[75] and related work in the α-D-glucopyranoside series.[76]

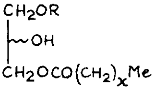
[3-$^2H_1$]-1,2-Di-*O*-tetradecyl-*sn*-glycerol (made from mannitol) and [3-$^2H_1$]- and [3-$^2H_2$]-labelled glycosyl chloride derived from *N*-acetylneuraminic acid were coupled to give deuterated sialyl glycerolipids used for ^2H n.m.r. dynamic studies.[77]

Full details have been published on the synthesis of the (S)- and (R)-3-*O*-acyl-1-*O*-sialosyl-glycerols (**40**), and new preparations of (**41**) and (**42**) have been described involving the use of the trichloroacetimidate method of glycosylation. Some of the

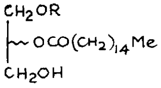


Scheme 4

members of the (**40**) and (**41**) sets showed inhibitory activity against phospholipases A_2



(40) $x = 6, 10, 14$



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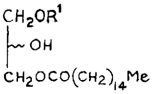

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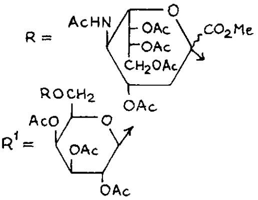
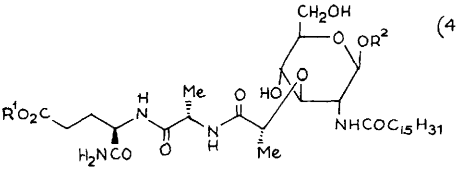
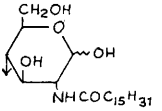


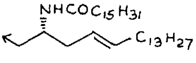
and C.[78] The muramic acid - containing sphingolipids (**43**) and (**44**) have been made,[79] and the high resolution ^1H n.m.r. spectra of the sulphated seminolipid (**45**) have assisted in the structural analysis.[80]

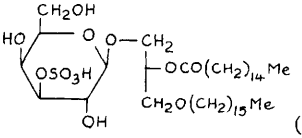


(43) $R^1 = Me$, $R^2 =$



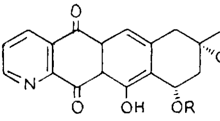
(44) $R^1 = Bu$, $R^2 =$

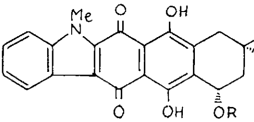




(45)

A review of the synthesis of anthracyclinones by elaboration of anthraquinones includes a section on the use of sugars as chiral templates.[81] Glycosylations of the daunomycinones (**46**)-(**48**) led to the corresponding daunomycin derivatives (**49**)-(**51**).[82-84] The L-*lyxo*-, L-*arabino*- and L-*ribo*-isomers of the isorhodomycin compounds (**52**) have been made and tested for cytotoxicity.[85] Several analogues of the anthracycline antibiotics, eg. (**53**), having a 1,2,3-triazolyl moiety in the sugar, have been described.[86]


(46)
(49)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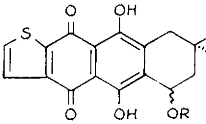
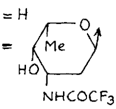
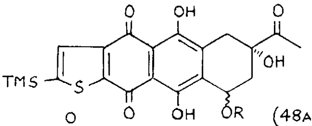
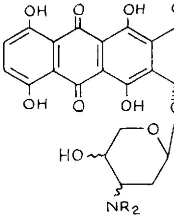
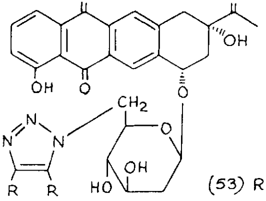

(48)
(51)

(46-48A) R = H
(49-51A) R =




(48A)
(51A)

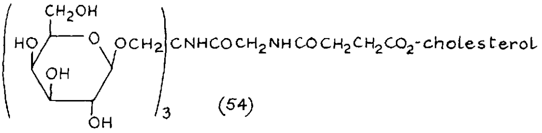

(52) R= H,Me


(53) R = CO_2Et

The 3-β-glucuronide of 18β-glycyrrhetic acid has been prepared as an immunogen for enzyme immunoassay,[87] and the selective synthesis of the 3-*O*-β-D-glucopyranoside of 20(*S*)-protopanoxadiol (ginsenoside) from selectivity protected 12-*O*-acetyldamnar-24-en-3β,12β,20(*S*)-triol has been described.[88]

Steroidal alcohols when condensed with 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl or tetra-*O*-benzyl-α-D-mannopyranosyl chloride in the absence of catalyst or solvent afford good to excellent yields of α-linked glycosides (α,β ratios 10:1).[89] Another report describes the use of cobalt carbonate for activating the condensation of substituted glycosyl halides and steroidal alcohols.[90]

Specific glycosylated steroid derivatives to have been made are the cluster compound (**54**) which can be used to transport cholesterol to specific receptors,[91]

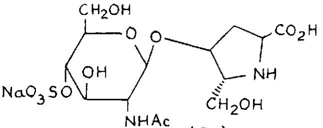


(54)

3-*O*-α-L-arabinofuranosyl chlormadinol acetate,[92] and the mono-β-D-glucuronides of allotetrahydro-cortisol and -cortisone.[93]

A phase-transfer method has been used to prepare various flavonoid glycosides;[94] specifically, quercitin 3-*O*- and 7-*O*-β-D-glucoside and -galactoside and 3,7-di-*O*-β-D-glucoside and - galactoside have been prepared in improved yields. Some of the products are inhibitors of apple β-galactosidase.[95]

Glycosylated derivatives of L-serine, threonine and L-tyrosine have been prepared by use of the *N*-tosylated amino acid methyl esters and 3,4-di-*O*-acetyl-2-deoxy-2-nitroso-β-D-arabinopyranosyl chloride. The 2-oximino products were hydrolysed, reduced and acetylated to give mixtures of the substituted α- and β-D-ribosyl and D-arabinosyl amino acid derivatives.[96] The (hydroxymethyl)hydroxyproline glycoside bulgecin (**55**) has been made using a 2-azido-2-deoxyglucosyl trichloroacetimidate.[97] The polymeric substances (**56**) have been used as synthetic antigens for the preparation of artificial vaccines against tumours,[98] and a set of glycosides, eg. (**57**) and (**58**), have been made from mono- to tetra-saccharides for coupling to proteins to give artificial glycoproteins.[99]



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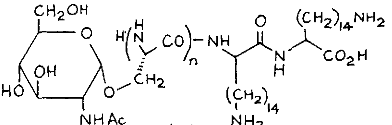

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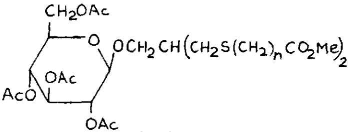

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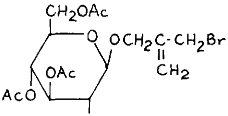
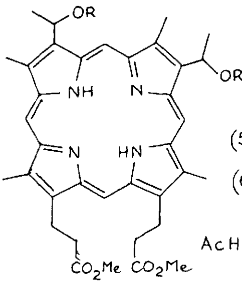


(58)

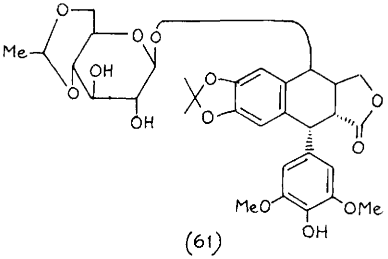
Two modified porphyrins, (**59**) and (**60**), were made as diastereomeric mixtures for use in photodynamic cancer therapy,[100] and the antitumour etoposide VP16 (**61**) was made using 2,3-di(chloroacetyl)-4,6-*O*-ethylidene-D-glucose as glycosylating agent with BF_3

as catalyst.[101] The analogue having an *N,N*-dimethylamino group at C-2 of the sugar, which also shows anti-cancer activity, has been reported.[102] Hydrolysis of the sialic acid glycoside (**62**) produces a highly fluorescent product, making it a suitable substrate for neuraminidase assay.[103]



(59) $R = H, R^1 = \beta$-D-Glc*p*

(60) $R = R^1 = \beta$-D-Glc*p*



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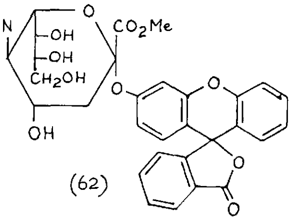

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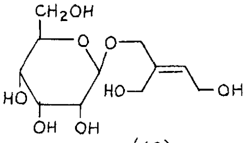
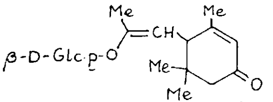
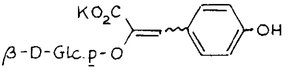


(63)

1.3 *O*-Glycosides Isolated from Natural Products.—As is usual practice, only selected papers are referred to in this section. To add to the list of D-allopyranosides isolated from natural sources the butenyl compound (**63**) has been obtained from the leaves of *Cardiomanes reniforme*.[104] The vinyl glycoside (**64**) occurs in the leaves of *G. pneumonanthe*,[105] and the similar isomeric substances potassium lespedezate and isolespedezate (**65**) were isolated from *Lespedeza cuneata* and also synthesised.[106]



(64)



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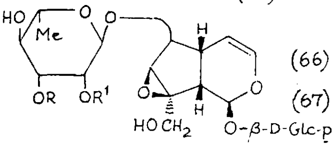
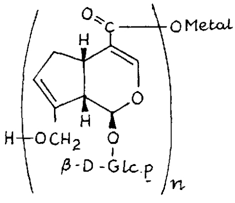


(66) $R = Ac, R^1 = COCH{=}CHC_6H_4OMe$

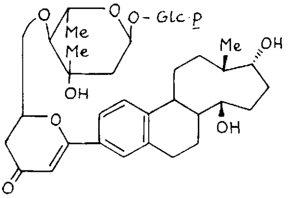
(67) $R = COCH{=}CHC_6H_3(OH)OMe$ $R^1 = Ac$



(68) $n = 3,4$

The new iridoid glycosides (**66**) and (**67**) were found in the roots of *V. pulverulentum*,[107] and the new compounds of this series obtained from *Eucomia ribomoides* seeds are ester trimers and tetramers (**68**) of geniposidic acid.[108]

Carolinoside (**69**), which can be considered to contain a pentenulose unit, is a component of *Solanum carolinense* and is the specific feeding inducing factor for *Manduca sexta*,[109] and lampteroflavin (**70**) is the light emitter of the luminous mushroom *L. japonicus*.[110]



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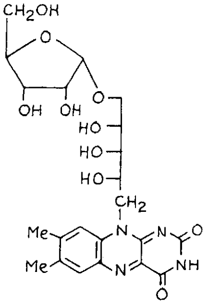


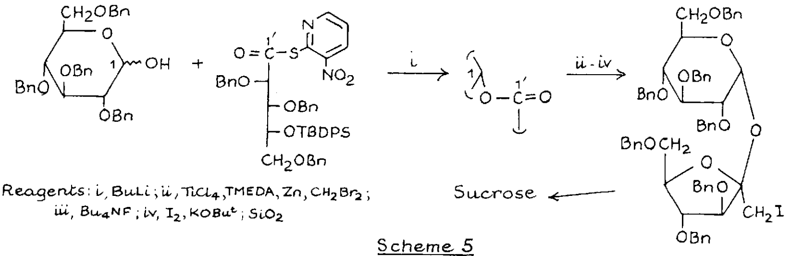
(70)

Four novel and sweet-tasting triterpene glycosides (abrusosides A-D) have come from the leaves of *Abrus precatorius*; their carbohydrate components are not novel.[111]

1.4 Synthesis and Chemical Features of Disaccharides and their Derivatives.—For several successful syntheses of disaccharides from 1-thioglycosides see Section 2 of this Chapter. An extensive review has appeared (in Czech) on the chemistry of sucrose,[112] and its synthesis and that of trehalose, by cell-free enzymic methods using appropriate, coupled synthetase systems, have been described. These afford practical routes to millimolar quantities of the disaccharides.[113] Injection of [1-^{13}C]-D-glucose into crickets allowed the synthesis of 1,1′-labelled trehalose in 27% yield.[114]

A novel synthesis of sucrose is outlined in Scheme 5. Following the methylenation the furanose ring closure was fortuitously stereospecific and was dependent on the presence of the silica.[115]

Sucrose derivatives with substituents at the primary positions undergo selection oxidation with periodate in the glucose ring, the 6,1′,6′-tri-*O*-trilyl derivative reacting at the 2,3-diol, and the TBDMS analogue at the 3,4-position. Products of oxidation were isolated after reduction and acetylation.[116]



Reagents: i, BuLi; ii, $TiCl_4$, TMEDA, Zn, CH_2Br_2; iii, Bu_4NF; iv, I_2, $KOBu^t$; SiO_2

Scheme 5

A highly stereoselective synthesis of "neotrehalosamine" (2-amino-2-deoxy-α-D-glucopyranosyl 2-amino-2-deoxy-β-D-galactopyranoside) has been reported,[116A] and a review (in Japanese) on the enzymic synthesis of xylosylfructofuranoside has been published.[116B] Iron(III) chloride-catalysed dehydration of 2,3-*O*-isopropylidene-β-L-erythrose gave the α,α-linked non-reducing dimer in 44% yield,[116C] and, similarly, treatment of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose with this catalyst[116D] or with boron trifluoride[116E] in the presence of molecular sieves gave the analogous β,β-linked fully substituted dimer.

Some pseudodisaccharides with carbocyclic moieties at the non-reducing position are referred to in Chapter 18.

Reducing disaccharides are now treated according to their non-reducing units. Some D-glucobioses and a range of other reducing disaccharides and higher saccharides have been made by preparative enzymic glycosylations.[117]

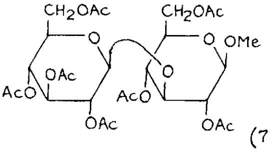
A novel and highly stereoselective method of making 1,2-*cis*-related glycosides involves the use of 1,2-*trans*-related glycosyl thiocyanates with non-participating groups at C-2. Tetra-*O*-benzyl-β-D-glucopyranosyl thiocyanate, treated with 2-,3-,4- and 6-*O*-trityl-D-glucose derivatives in the presence of tritylium perchlorate, gave high yields of the corresponding α-linked disaccharides.[118] In parallel fashion, various monosaccharide mono-ols, with tetra-*O*-benzyl-α-D-glucopyranosyl bromide in the presence of hindered amines and at high pressures, gave good yields of disaccharides with high α,β- ratios (10:1).[119] The triphenylsilyl group can be used to protect the anomeric hydroxyl group during disaccharide synthesis and can be removed selectively in the presence of functions such as the *p*-nitrobenzoyl. It was used in the synthesis of α-(1→6) linked glucobiose derivatives.[120]

Several developments have taken place in the synthesis of 1,2-*trans*-related compounds. Pent-4-enyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (a "disarmed" glycosylating agent) can now be activated by use of *N*-iodosuccinimide and trifluoromethanesulphonic acid which is a powerful source of iodonium ion but still permits reactivity differences between "armed" and "disarmed" pent-4-enyl glycosides to be displayed. The above compound, with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside, gave for example, the cellobiose derivative in 73% yield.[121] In similar fashion, acetylated thioglycosides can be activated, for example *S*-methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside giving β-linked disaccharide products in high yield.[122]

Reaction of the corresponding 1,2-cyanoethylidene glycosylating agent and the 3-trityl ether in the presence of tritylium perchlorate at 1400 MPs gave ultimately only compound (**71**).[122, 123]

Compound (**72**), used with a Lewis acid, has proved to be an efficient agent for making β-linked disaccharides,[124] and the corresponding trichloroacetimidate in the presence of an equivalent of chloral gives high yields of the same products with good β-selectivity. The rationale is that the chloral gives a hemiacetal with the alcohol to be glycosylated and this leads to a bicyclic transition state for the reaction, the chloral acting as a catalyst in the overall process.[125] Low yields are often encountered in silver triflate-promoted glycosidations with tetra-*O*-acetyl-β-D-glucopyranosyl bromide. This has been shown to be due to lack of stereospecificity as well as to acetylation (rather than glycosylating) of the alcohol. Labelling experients showed that the acetyl group at O-2 was transferred - presumably by way of a 1,2-orthoester intermediate.[126]

2,3,4,6-Tetra-*O*-benzyl-α-D-glucosyl fluoride, activated with dimethylgallium choride, gives efficient transfer to primary and secondary alcohols but with almost no stereoselectivity.[127]



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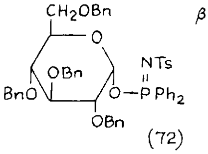

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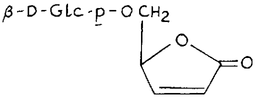


(73)

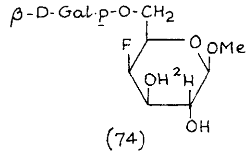
2-*O*-α-D-Glucopyranosyl-L-ascorbic acid has been produced by regioselective transglycosylation (animal or plant α-glucosidase and maltose as donor) and shown to withstand oxidative degradation, thus making it a potentially useful storage form of the vitamin.[128] The glucose-based disaccharide derivative (**73**) has been made by glycosylation of the lactone derived following reaction of isopropylidene-D-glyceraldehyde with $Ph_3P{=}CHCO_2Me$,[129] and 4-*O*-β-D-glucopyranosyl-L-*glycero*-D-*manno*-heptose derivatives, i.e., compounds related to the disaccharide of the inner core of the *Neisseria meningitidis* polysaccharide, have been made by methods involving chain extension of D-*manno*-dialdose.[130]

Tigogenyl β-D-cellobioside has been made by use of the trichloroacetimidate method.[131]

Glycosylation of carbohydrate trityl ethers by use of acylated 1,2-orthoesters and tritylium perchlorate leads to the formation of acyl analogues of the trityl ethers as by-products.[132]

A detailed study has been made of the condensation of (i) 2,4,6-tri-*O*-benzoyl-α-D-galactosyl halides with various substituents at O-3, and (ii) various 1-substituted derivatives of 2,4,6-tri-*O*-benzoyl-β-D-galactose. In the majority of cases β-products predominated, but it was concluded that mechanisms other than the orthoester pathway played parts in the reactions.[133] Selective reaction of 1,6-anhydro-β-D-galactose with tetra-*O*-benzyl-α-D-galactopyranosyl bromide and tetraethylammonium bromide, but in the absence of tin reagents, gave mainly the 3-α-product. The addition of tributyltin oxide resulted in the formation of the 3-β-linked disaccharide as main product, but 4-α- and 3-α- compounds were also produced. Surprisingly, under no conditions used was the equatorial 4-hydroxy group preferentially substituted.[134]

Various modifications of lactose with deoxy-groups at C-3, 4 or 6 of the galactose moiety or with 2-*O*-methyl or 2-amino-2-deoxy- groups at this position have been tested as substrates and inhibitors of enzymes. The last two compounds noted above are potent inhibitors of *E. coli* β-galactosidase.[135] Compounds (**74**) and (**75**) have been made for the study of conformational changes during antibody-antigen complex formation[136] and for glycopeptide research,[137] respectively. The latter was made by glycosylation of 4,6-di-*O*-benzyl-D-galactal followed by NIS-activated iodoglycosidation.



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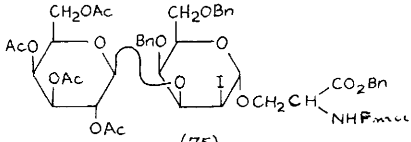
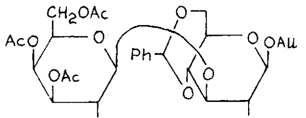
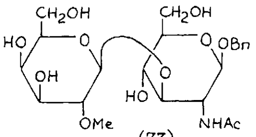


(75)

Compound (**76**) was used to obtain compounds of the 2-amino-2-deoxy-3-*O*-β-D-galactosyl-D-galactose series,[138] and the related methyl ether (**77**) has been made as a transferase acceptor.[139] Peracetylated analogues of (**76**) with bonded serine and threonine and *N*-fluorenylmethyloxycarbonyl (Fmoc) groups have been prepared for use in solid phase glycopeptide synthesis,[140] and a symposium report has dealt with the parent substances as components of tumour-associated antigens.[141] An extension of this work has led to the synthesis of (**78**) and (**79**) (which have T_N and T antigen structures) and to their coupling to bovine serum albumin.[142]



(76)



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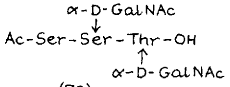
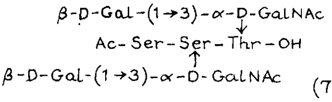


$$\begin{array}{c}\alpha\text{-D-GalNAc}\\ \downarrow\\ \text{Ac-Ser-Ser-Thr-OH}\\ \uparrow\\ \alpha\text{-D-GalNAc}\end{array}$$

(78)



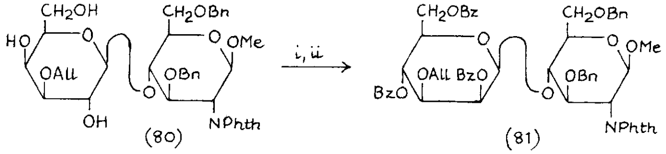
$$\begin{array}{c}\beta\text{-D-Gal-}(1\rightarrow3)\text{-}\alpha\text{-D-GalNAc}\\ \downarrow\\ \text{Ac-Ser-Ser-Thr-OH}\\ \uparrow\\ \beta\text{-D-Gal-}(1\rightarrow3)\text{-}\alpha\text{-D-GalNAc}\end{array}$$

(79)

Methyl 2-*O*-β-D-galactopyranosyl-α-L-rhamnopyranoside is among several disaccharide glycosides to have been prepared in conjunction with *Klebsiella* serotype 40 polysaccharide studies.[143] 5-*O*-(6-*O*-Octyl-β-D-galactopyranosyl)-L-arabinose has been prepared,[143A] as has 5-*O*-β-D-galactofuranosyl-D-galactofuranose. The key step of the latter synthesis involved condensation of penta-*O*-benzoyl-D-galactofuranose with 2,6-di-*O*-benzoyl-D-galactono-(1,4)-lactone which can be made in 62% yield by selective benzoylating of the lactone.[144]

Two papers have dealt with the conformational analysis of mannobioses,[145, 146] the latter considering methyl 3-*O*-mannopyranosyl-α-D-mannopyranoside specifically. A report has appeared on the preparation of methyl 2-*O*-(6-deoxy-6-fluoro-α-D-mannopyranosyl)-α-D-mannopyranoside and of the isomer with the fluorine atom in the "reducing" moiety, and of several related substances.[147] 2-*O*-α-D-Mannopyranosyl-D-mannopyranose has been incorporated into a pentafluorophenylthreonate compound and hence into a glycosylated peptide unit of insulin-like growth factor.[148]

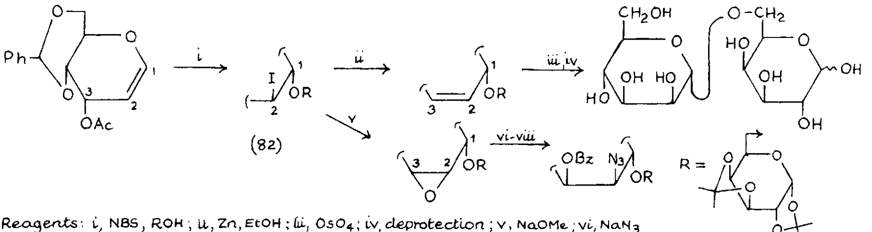
The mannosylglucosamine derivative (**81**) has been made with 52% efficiency by an interesting and unusual "double inversion" procedure (Scheme 6) from the lactosamine



Reagents: i, Tf_2O, Py; ii, Bu_4NOBz

Scheme 6

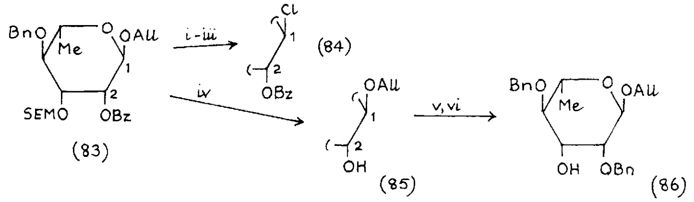
derivative (**80**).[149] Methyl 4-*O*-α-D-mannopyranosyl-α-L-rhamnopryanoside is among several disaccharides to have been made in connection with *Klebsiella* polysaccharide immunological work,[143] and the iodo-compound (**82**) has been used to obtain 6-*O*-α-D-mannopyranosyl-D-galactose and the 2-azido-2-deoxy analogue (Scheme 7).[150]



Reagents: i, NBS, ROH; ii, Zn, EtOH; iii, OsO_4; iv, deprotection; v, NaOMe; vi, NaN_3 vii, Tf_2O, Py; viii, NaOBz

Scheme 7

Compound (**83**), containing the [β-(trimethylsilyl)ethoxy]methyl group (SEM), has found use for access to a rhamnosylating agent (**84**) and to acceptors (**85**) and (**86**) for disaccharide synthesis (Scheme 8). Condensation of (**84**) and (**86**) gave 74% of the β-



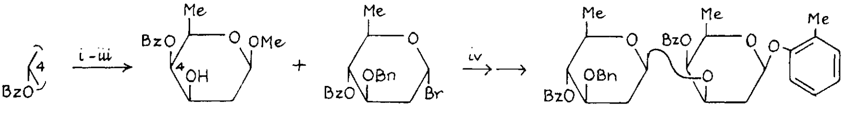
Reagents: i, $Rh(PPh_3)_3Cl$; ii, HgO, $HgCl_2$, H_2O; iii, $Me_2\overset{+}{N}{=}CHCl\ Cl^-$, Py; iv, NaOMe; v, BnBr; vi, MeOH, HCl

Scheme 8

(1→3) linked product.[151] 2-*O*-Methyl-3-*O*-α-L-rhamnopyranosyl-α-L-rhamnose has been made as the 3-aminopropyl glycoside in work connected with cell wall fragments of *Mycobacterium tuberculosis*,[152] and the following have also been prepared: 6-*O*-α-L-rhamnopyranosyl-β-D-glucopyranose (as terpene glycosides),[143] methyl 2-*O*-α- and β-L-rhamnopyranosyl-β-D-galactopyranoside (related to parts of the repeating unit of the capsular polysaccharide from *Streptococus pneumoniae* Type 23),[154] methyl 3-*O*-α- and β-L-rhamnopyranosyl-β-D-galactopyranoside (*Klebsiella* serotype 40 component),[143] and 2-(acrylamido)ethyl 3-*O*-α-L-rhamnopyranosyl-β-D-glucopyranosiduronic acid (repeating unit of K54 antigenic polysaccharide of *E. coli*)[155] and the same glycoside of 2-*O*-β-L-rhamnopyranosyl-β-D-mannose.[156]

In the L-fucose series methyl 2-*O*-α-L-fucopyranosyl-α-L-fucopyranoside sulphated at positions 3 and 4,[157] and at 3′ and 4′[158] have been made in studies of the anticoagulant fucoidan, and a 3-linked trimethylfucosyl compound has been prepared as a 3-aminopropyl glycoside in studies of the cell wall of *Mycobacterium tuberculosis*.[152] Enzymic transfer to methyl β-D-galactopyranoside resulted in α-L-fucosylation at *O*-2 and *O*-6 in 10% total yield.[158A]

In connection with studies of the total synthesis of olivomycin A a review has appeared on the synthesis of the dideoxysugar components from acyclic precursors.[159] In related work model reactions were carried out for the disaccharide coupling of the anthracycline antibiotic mithramycin (see Scheme 9).[160]

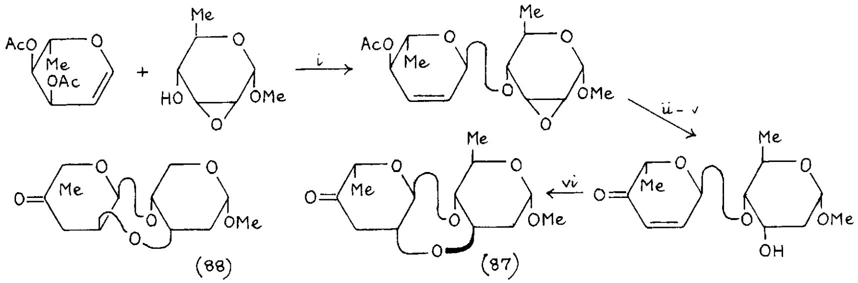


Reagents: i, Et_3N, Δ; ii, Tf_2O ; iii, H_2O ; iv, $AgSiO_4$

Scheme 9

The first syntheses of the ether-bridged and glycosidically-linked disaccharides (**87**) and (**88**), which occur in the anthracycline class II antibiotics (e.g. cinerubin B), have been reported. See Scheme 10 for the route to the former; the latter was made by analogous use of methyl 3-*O*-acetyl-6-bromo-2,6-dideoxy-α-D-*ribo*-hexopyranoside followed by inversion at C-6 by way of the 6-deoxy-5-ene.[161]

Condensation of racemic (**89**) with different monohydroxycarbohydrates in the presence of tin tetrachloride gave mixtures of α-linked diastereomeric 2,3,4-trideoxy-2,3-

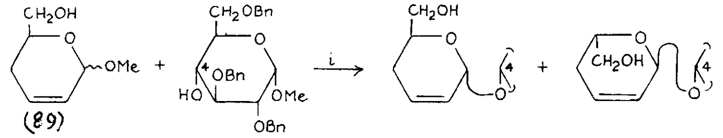


(88) (87)

Reagents: i, $BF_3.Et_2O$; ii, LiI; iii, Bu_3SnH; iv, K_2CO_3, MeOH; v, MnO_2; vi, DBU

Scheme 10

unsaturated disaccharides which could be separated. An example is indicated in Scheme 11.[162]



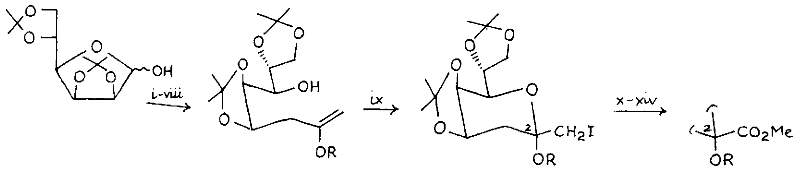
(89)

Reagent: i, $SnCl_4$

Scheme 11

The following D-glucuronic acid derivatives have been synthesised: methyl 2-*O*-(β-D-glucopyranosyluronic acid)-α-L-rhamnopyranoside,[143] 3-*O*-(β-D-glucopyranosyluronic acid)-L-rhamnose[155] and methyl 2-acetamido-2-deoxy-3-*O*-(β-D-glucopyranosyluronic acid)-β-D-galactopyranoside 4- and 6-sulphate and analogues with the two sugar units reversed.[163]

A stereocontrolled synthesis of KDO-containing disaccharides, with high yield in the critical cyclisation step, is illustrated in Scheme 12;[164] a more orthodox approach used

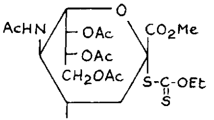


Reagents: i, $Ph_3P{=}CH_2$; ii, PivCl; iii, 9-BBN; iv, H_2O_2, NaOH; v, $RuCl_3$, $NaIO_4$; vi, ROH, DCC; vii, Tebbe reagent; viii, LAH; ix, Bu^tOK, I_2; x, CsOAc, HMPA; xi, NaOMe; xii, $(COCl)_2$, DMSO; xiii, $NaClO_2$, H_2O_2; xiv, CH_2N_2

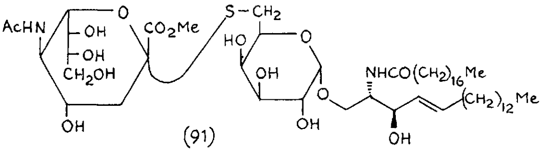
Scheme 12

the acetylated 3-deoxy-3-phenylthio-α-D-glycopyranosyl chloride made from the corresponding 2-ene.[164A]

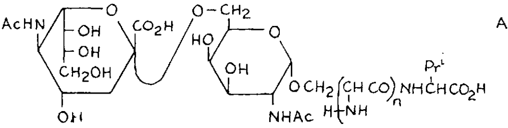
The *N*-acetylneuraminic acid xanthate (**90**) employed with dimethyl(methylthio)sulphonium triflate is a more efficient glycosyl donor than is the corresponding *S*-ethyl thioglycoside, and can be used to give modest yields of disaccharides linked through either primary or secondary hydroxy groups.[165] An independent report has recorded the use of the α-*S*-methyl glycoside and this catalyst together with several dihydroxy compounds. Linkages to primary alcohol groups were highly favoured and α,β ratios were *ca.* 2:1.[166] In related work the ceramide (**91**) was made by way of the 2-thiolate anion which was used to displace bromide from a 6-bromo-6-deoxy-D-galactose derivative.[167] Compounds (**92**) and (**93**) were made using glycosyl halides as sialoglycopeptides corresponding to partial structures of glycophorin A.[168] Further work (cf. Vol. 21, p. 17; Vol. 22, p. 29) using a 3-deoxy-3-phenylthioglycosyl bromide as glycosylating agent has been published.[169]



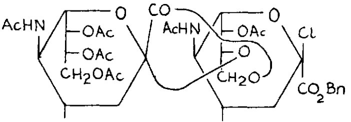
(90)



(91)



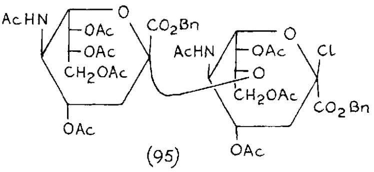
(92) n = 2 (93) n = 3



(94)

Hydrolysis of colominic acid (from *E. coli*), a naturally occurring poly α-(2→8)-linked polysialic acid, gives Neu5Ac-α-(2→8)-Neu5Ac which has been used to prepare the glycosylating derivatives (**94**) and (**95**).[170]

In the area of disaccharides having amino-sugars at the non-reducing ends 2-acetylamido-2-deoxy-α- and β-D-glucose and -galactose have been specifically transferred enzymically to various methyl hexopyranosides.[171] 1,3,4,6-Tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucose used with iron(III) chloride gives good yields of β-products with secondary monosaccharide alcohols.[172] An ingenious alternative approach involves the use of the glycosylsulphonamide (**96**), derived from tri-*O*-benzyl-D-glucal by use of iodonium di-*sym*-collidine perchlorate and benzenesulphonamide. With alcohols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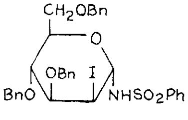
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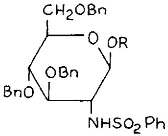
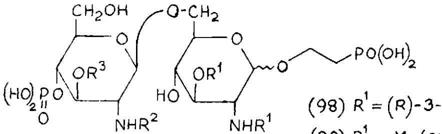

(97)

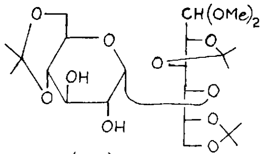
and excess of base β-compounds (**97**) were produced - probably by way of a 1,2-aziridine intermediate. Disaccharide derivatives were prepared, and when mono-ols derived from glycals were involved the products could be reprocessed to give trimeric compounds. Similar work was carried out in the galactal and allal series.[173]

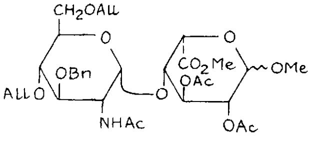
The lipid analogues (**98**)-(**100**), in which the naturally occurring α-glycosyl prosphate group is replaced by a phosphono-oxyethyl group, have been made, the α-anomers having antitumour activity.[174]


$R^2 = C_{14}H_{28}OC_{12}H_{25}$
$R^3 = C_{14}H_{28}OC_{14}H_{29}$

(98) R^1 = (R)-3-hydroxytetradecanoyl α-
(99) R^1 = $Me(CH_2)_{12}CO$- α-
(100) R^1 = " β-

Maltose derivative (**101**) was converted into a corresponding glucosamine compound and the 5,6-acetal was then removed and inversion was effected at C-5 to lead to the heparin related compound (**102**). Related compounds were also described.[175] The spacer modified oligosaccharide (**103**), which has the same number of atoms linking the sugar units as does the core of N-linked glycoconjugates, has been synthesised.[176]


(101)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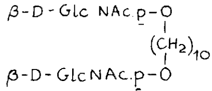
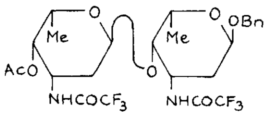

β-D-GlcNAc.p-O
$(CH_2)_{10}$
β-D-GlcNAc.p-O

(103)

2-Acetamido-3-*O*-(3-acetamido-3,6-dideoxy-β-D-glucopyranosyl)-2-deoxy-D-galactose is a unit of the core polysaccharide of *V. parahaemolyticus*.[177] Also in the area of 3-amino-compounds the dimer (**104**) was made in connection with anthracycline oligosaccharide studies. Condensation was effected by use of a TBDMS glycoside with trimethylsilyl triflate as catalyst. Several related products were described as well as some 3-amino-3-deoxyglycals and disaccharide products of their addition reactions.[178]



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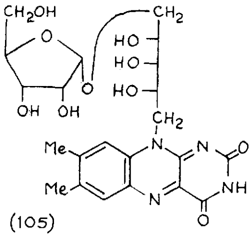
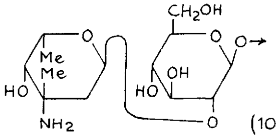


(105)

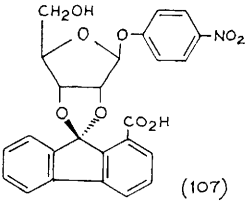
Lampteroflavin (**105**), the bioluminescence emitter of the night mushroom, has been synthesised by condensation of 2,4-*O*-benzylideneriboflavin and 2,3-*O*-*p*-methoxybenzylidene-5-*O*-trityl-β-D-ribose trichloroacetimidate. The compound is assigned the α-configuration (not as illustrated previously) on the basis of nOe data.[179]

3-*O*-α-L-Arabinofuranosyl-D-xylose, its methyl β-pyranoside, methyl 2-*O*-α-L-arabinofuranosyl-β-D-xylopyranoside and methyl 2,3-di-*O*-(α-L-arabinofuranosyl)-β-D-xylopyranoside have been prepared,[180] as has 6-*O*-α-L-arabinofuranosyl-β-D-glucose as several terpene glycosides.[153] In the xylose series 4-*O*-[181] and 6-*O*-[181, 182] β-D-xylopyranosyl-glucose have been synthesised, and several xylobioses have been studied by infrared spectroscopy.[183]

The structure of the branched-chain amino-disaccharide (**106**), a component of a novel glycopeptide antibiotic of the vancomycin group, has been elucidated by FAB mass spectrometry and 2D n.m.r. spectroscopy.[184]



(106)



(107)

1.5 Hydrolysis and other Reactions and Features.—A novel method for following the acid catalysed hydrolysis of sucrose and lactose involves measurement of the rate of reaction of periodate with quenched aliquot portions of the solutions using a periodate-sensitive electrode. In this way sucrose could be determined in the presence of other carbohydrates in the range 0.01-0.1 M, and the method was applied to food products.[185]

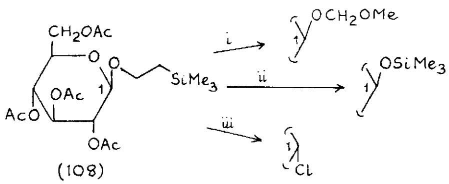
The glycosidic hydrolysis of fluorenone ketal (**107**), which serves as a nucleoside glycosylase enzyme model, has been shown to be intramolecularly catalysed by comparison with analogous compounds.[186]

An *Aspergillus niger* α-glucosidase catalyses the slow hydrolsys of β-D-glucopyranosyl fluoride which competitively inhibits the hydrolysis of *p*-nitrophenyl α-D-glucopyranoside and thus binds at the same site as do substrates of the enzyme.[187]

Alkyl tetra-*O*-acetyl-β-D-glucopyranosides are anomerised to mainly the α-compounds on treatment with the 1,2-cyanoethylidene analogue in the presence of tritylium perchlorate,[188] and heating above their melting point causes inter-unit cleavage in the case of 2,6-dideoxyhexosyl cardenolide glycosides.[189]

Reaction of *t*-butyl 2,3,4,6-tetra-*O*-acetyl α- and β-D-galactopyranoside with Lewis acids in dichloromethane leads to loss of the butyl group, and with added acetic anhydride gives the β-penta-acetate exclusively. The reaction of the β- compound is faster, suggesting an intramolecular complex involving the acid and O-1 and O-5.[190]

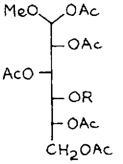
Compound (**108**) reacts with electrophiles much more readily than does the methyl glycoside, and the reactions illustrated in Scheme 13 can be carried out under conditions in which the methyl compound is unreactive.[191] When the third reaction shown in this Scheme was carried out with the tetrabenzyl analogue of (108), as well as the glycosyl chloride being formed, a formate ester group was substituted at C-6. The reaction proceeded in the protected di- and tri-saccharide series and is thus of value for oligosaccharide synthesis.[192]



Reagents: i, $(MeO)_2CH_2$, BF_3 ; ii, Me_3SiOTf ; iii, Cl_2CHOMe, $ZnCl_2$

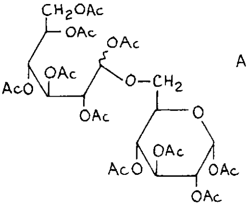
Scheme 13

Methyl β-D-glucopyranoside or its tetra-acetate, treated with acetic anhydride and trimethylsilyl triflate gave the acyclic (**109**), whereas the α-analogues afforded penta-*O*-acetyl-α-D-glucopyranose, and similar results were obtained in the D-mannose series. In related fashion β-glycosides of oligosaccharides gave ring-opened products [methyl β-maltoside affording (110)], whereas the α-anomers afforded the products of glycosidic bond cleavage.[193] It was then found that the interunit linkage of 6-*O*-β-D-glucopyranosyl-D-glucose (gentiobiose) opened on treatment with the reagents to give the unusual (**111**) and, in like manner, in the case of gentiotriose, both non-reducing groups ring opened.[194] That such reactions are not exclusive to 1→6-linked compounds is shown by the finding that the acetolysis of β-(1→4) linked xylan with acetic anhydride, acetic acid and sulphuric acid yields the aldehydrol perester (**112**) as well as a series of oligosaccharide derivatives (**113**) having all of the xylosyl residues in the acyclic form.[195]



(109) R = Ac

(110) R = Ac₄α-D-Glc-p



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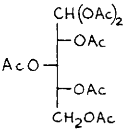

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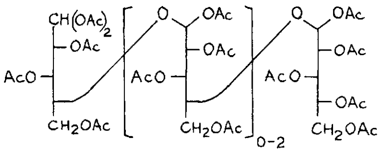


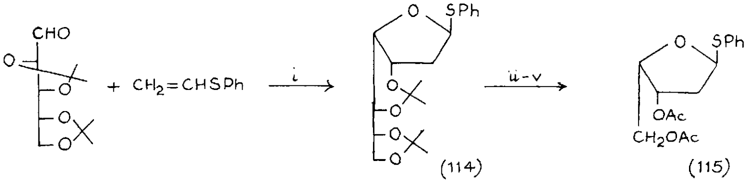
(113)

The micellar structures formed by self assembly of octyl α- and β-D-glucopyranoside and dodecyl β-D-maltoside in water show that the β-anomers form aggregates of similar size to normal ionic micelles, whereas the α-glucoside is sparingly soluble in water and forms very large, non-spherical assemblies.[196] In related work it has been noted that cetyl β-D-glucopyranoside and -galactopyranoside form bilayers, their hydrated states having been examined by differential scanning calorimetry.[197]

2 S-Glycosides

1-Thio-D-glucopyranosides were prepared by treatment of 2,3,4-tri-*O*-benzyl-6-*O*-trimethylsilyl-α-D-glucopyranosyl bromide with thiols in the presence of *N*,*N*-diisopropylethylamine. The α,β-ratios of the products were dependent on the acid strengths of the thiols used.[198]

Contrary to an earlier report (Vol. 22, p. 2) that 2,3-*O*-isopropylidene-D-glyceraldehyde reacts with phenyl vinyl sulphide to give an oxetane, it has now been shown that 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose reacts to give the product of acetal migration (**114**) (Scheme 14) from which the potentially useful thioglycoside (**115**) was obtained.[199]



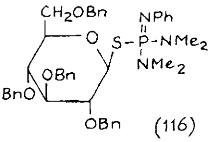
(114) (115)

Reagents: i, $BF_3.Et_2O$; ii, H^+; iii, $NaIO_4$; iv, $NaBH_4$; v, Ac_2O, py

Scheme 14

In the main, interest in thioglycosides centres on their value as *O*-glycosylating agents and several new approaches have been reported. *S*-Aryl-1-thioglucopyranosides underwent photochemically induced cleavage with 1,4-dicyanonaphthalene as an electron transfer reagent, and gave glycosyl cations of potential value as glycosylating agents. In the presence of methanol, however, several products - eg. gluconic acid derivatives - were formed in addition to the methyl glycosides.[200]

The *S*-glucopyranosyl phosphorodiamidimidothioate (**116**) afforded good yields of disaccharides when coupled with several sugar mono-ols in the presence of lutidinium tosylate, the α,β-ratios being about 10:1.[201] Likewise, the *N*-acetylneuraminic acid derivative (**117**), made by use of the corresponding dithiocarbonate, acts as a glycosyl donor when and with silver triflate.[202, 202A]



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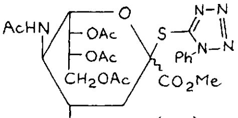
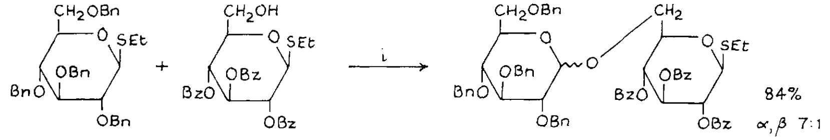


(117)

An interesting new application of *S*-phenyl 1-thioglycosides was based on electrochemical methods which used tetrabutylammonium fluoride as electrolyte in acetonitrile in a divided cell. Benzylated *S*-phenyl 1-thio-β-D-glucopyranoside and 1,2:3,4-di-*O*-isopropylidene-α-D-galactose gave 63% of 1,6-linked disaccharide with an α,β ratio of 1:4, whereas the corresponding acetylated compound afforded a similar yield of the β-linked product. Yields were higher with simple, primary alcohols.[203]

More generally, *S*-ethyl 1-thioglycosides have been used as donors, *S*-ethyl tetra-*O*-benzyl-1-thio-β-D-glucopyranoside having found particular favour since it can be "armed" selectively and coupled to partially benzoylated analogues (see for example, Scheme 15).



Reagent: i, $I(Coll)_2^+ClO_4^-$

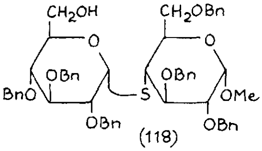
Scheme 15

The products illustrated can then be deesterified and benzoylated to give a further, disaccharide glycosylation reagent.[204] The benzylated glucose thioglycoside has also been activated with methylsulphenyl bromide for coupling to sugar alcohols and resulted in high yields of mainly α-linked products.[205] Other workers have used *S*-ethyl tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside activated with NIS and triflic acid to give β-glycosides and β-glycosyl esters, respectively,[206] and others have favoured the use of bromine in the presence of silver triflate or mercury(II) cyanide and have obtained disaccharides with good yields and with high stereochemical control.[207]

The *S*-linked maltose-based disaccharide (**118**) has been made from 1,6-anhydro-2,3,4-tri-*O*-benzyl-D-glucose and the corresponding 4-trimethylsilylthio-compound, and the method has been extended to give a maltotriose analogue.[208] A review has appeared in Japanese on thioglycoside derivatives of sialic acids.[209]

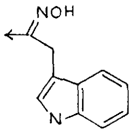
Specific 1-thio-β-D-glucopyranosides to have been synthesised by normal routes are those bearing the *S*-substituents (**119**),[210] (**120**),[211] (**121**) and (**122**).[212] The antibiotic amphotericin mimic (**123**) has, on the other hand, been made by addition of the thiolate anion to the corresponding maleic acid compound. It affects ion transport across vesicle bilayers.[213]

Condensation of (±)-(**124**) with tetra-*O*-acetyl-1-thio-β-D-galactose gave the diastereomers (**125**) and (**126**), the latter, on deacetylation, affording (**127**) which


(118)

$\leftarrow CH_2CH_2CH=CHCH=CH_2$

(119)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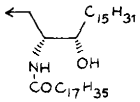
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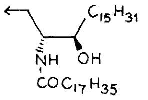
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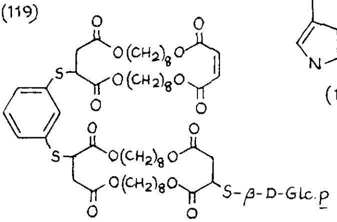
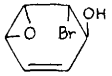

(123)

irreversibly inhibits *E. coli* β-galactosidase.[214] The thioglycoside (**128**) was made as a potential, simplified transition state analogue inhibitor of cytidine monophosphate-KDO synthetase.[215]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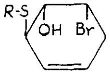
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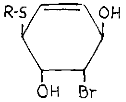
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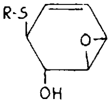
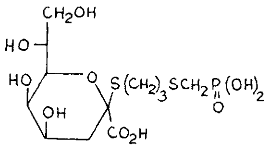
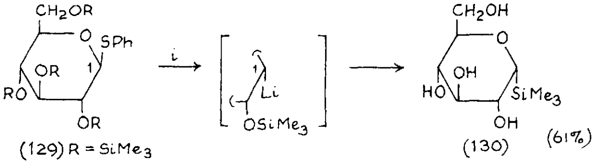

(127)

R = Ac_4β-D-Gal*p*-


(128)

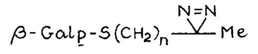
An unexpected rearrangement occurred on treatment of the silylated thioglycoside (**129**) with lithium naphthalenide, with the silyl group migrating from O-2 to C-1 to give the stable *C*-silylated product (**130**) (Scheme 16). A related β-thiomannoside gave only the corresponding glycal derivative.[216]

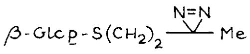


Reagents: *i*, Li naphthalenide

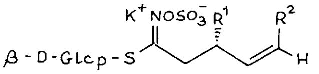
Scheme 16

Diazirines (**131**) and (**132**), which are photolabile, are excellent competitive inhibitors of the corresponding glycosidases and can be used for photolabelling the enzymes.[217]

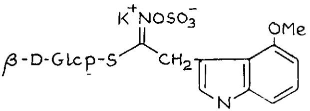

(131) n = 1-3


(132)

The glucosinolate (**133**) is a constituent of oil seed rape and enzymically gives the simple heterocycle goitrogen which is a toxin that represents a serious economic issue regarding the crop. Radiolabelled (**134**) has been synthesised using a chloro-oximino aglycone and the 1-thiosugar and shown to be the biosynthetic precursor of (**133**).[218] Enzymic hydrolysis of the related (**135**) gives the isothiocyanate (**136**).[219]


(133) $R^1 = OH$, $R^2 = H$

(134) $R^1 = H$, $R^2 = {}^3H$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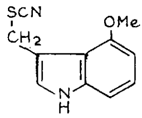
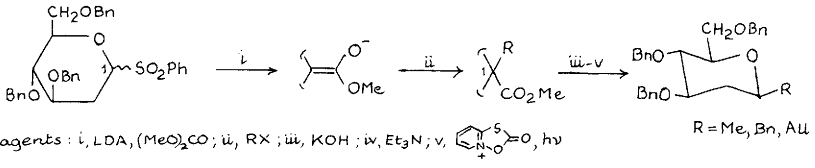

(136)

3 C-Glycosides

A review has been published on the regio- and stereo-selective synthesis of *C*-glycosides from glycal-Pd complexes,[220] and the reaction between reducing sugars and carbonyl compounds which results in *C*-glycosides has been referred to in a further review.[221]

3.1 Pyranoid Compounds.—A further review (in Japanese) has dealt with recent developments in the synthesis of *C*-glycopyranosides and treated the use of oxonium ions, carbanions, radicals and also methods based on sigmatropic rearrangements.[222]

A free radical method which gives 2-deoxy-equatorially substituted products proceeds via 2,6-anhydroaldonic acid derivatives (Scheme 17).[223] Trapping of the C-1 radical derived from tri-*O*-acetyl-α-L-fucopyranosyl bromide with acrylonitrile led to compound (**137**) which has been used to prepare an affinity adsorbent for porcine liver α-L-fucosidase.[158A]

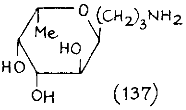


Reagents: i, LDA, $(MeO)_2CO$; ii, RX; iii, KOH; iv, Et_3N; v, hν

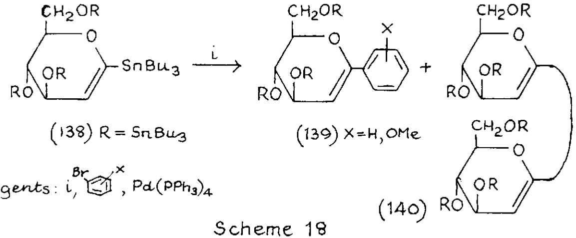
R = Me, Bn, All

Scheme 17

The glycal-tin derivative (**138**), made from the 1-lithio-compound (Hanessian *et al. J. Chem. Soc. Chem. Commun.*, 1986, 926), reacts with acyl bromides in the presence of a palladuim catalyst to give 1-acylglycals (**139**); in addition significant proportions of the C-C linked dimer (**140**) were formed (Scheme 18).[224] Parallel work was conducted with



(137)



(138) R = $SnBu_3$

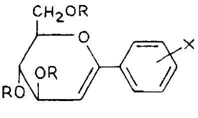
(139) X = H, OMe

(140)

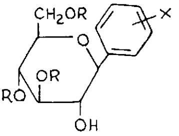
Reagents: i, $Pd(PPh_3)_4$

Scheme 18

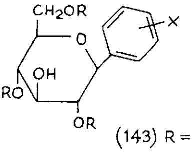
TBDMS-protected compounds and the resultant analogues (**141**) of (**139**) were subjected to hydroboration at pH 7 to give the aryl β-*C*-glucosides (**142**). When the oxidation step was carried out at high pH values silyl migration occurred and the isomeric 3-hydroxy-compounds (**143**) were isolated.[225] Extension of this work afforded (**144**) and hence, by



(141) = Si

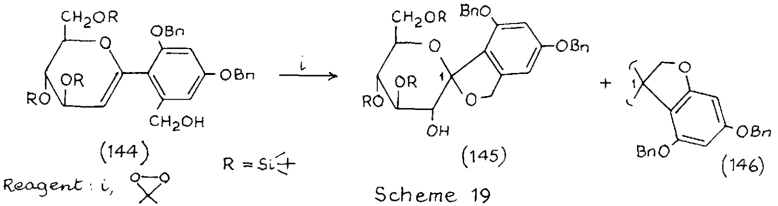


(142) R = Si



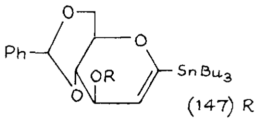
(143) R = Si

oxidative cyclisation, the spiroketals (**145**) and (**146**) (Scheme 19) the former of which represents the related portion of the papulacandins and can be obtained with high selectivity by acid treatment of the mixed products.[226] In closely related work the tin derivative (**147**) was made from the analogous 1-phenylsulphone and converted into the spiroketal akin to (**145**) and, by hydroboration, into a derivative of the natural

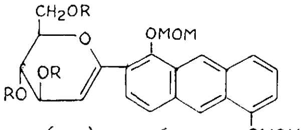


Scheme 19

corresponding β-*C*-glucopyranoside derivative.[227]

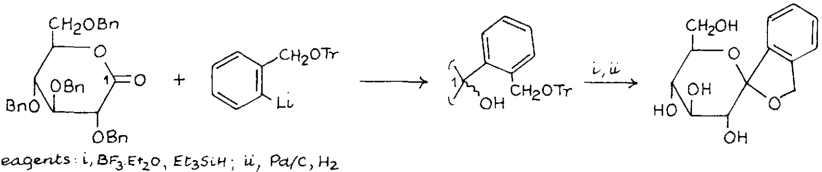


(147) R = Si



(148) R = Si

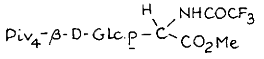
A different approach to spiroketals of this series is illustrated in Scheme 20.[228] The anthracene derivative (**148**) was made from the glycal by way of the 1-lithio-derivative and reduced to the 2-deoxy-β-*C*-glycoside.[229]



Scheme 20

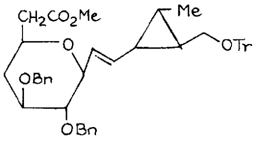
More directly, aryl-β-*C*-glucosides have been made by use of 2,3,4,6-tetra-*O*-benzyl-α-D-glucose *p*-nitrobenzoate,[230] 3,5-dinitrobenzoate[231] and chloride.[232] β-Naphthol coupled with 1-*O*-acetyl-3,4-di-*O*-benzoyl-2,6-dideoxy-α-L-*lyxo*- and -*ribo*-hexose gave the α-naphthyl *C*-glycosides by way of *O*-glycosidic intermediates.[233] Compounds (**148A**) [234] and (**149**)[235] have been made by use of the glycosyl bromide and fluoride, respectively. The latter product was converted into (+)-ambruticin (Chapter 24).

Palladium-catalysed acylation of tri-*O*-acetyl-D-glucal is known to give (**150**) as major product and now, by x-ray analysis of its deacetylated derivative, the minor product has been shown to be also the α-linked (**151**) and not β- as initially indicated (*Can. J.*

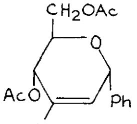


$\mathrm{Piv_4\text{-}\beta\text{-}D\text{-}Glc}p\text{-}\overset{\mathrm{H\ \ NHCOCF_3}}{\mathrm{C}}\text{-}\mathrm{CO_2Me}$

(148A)



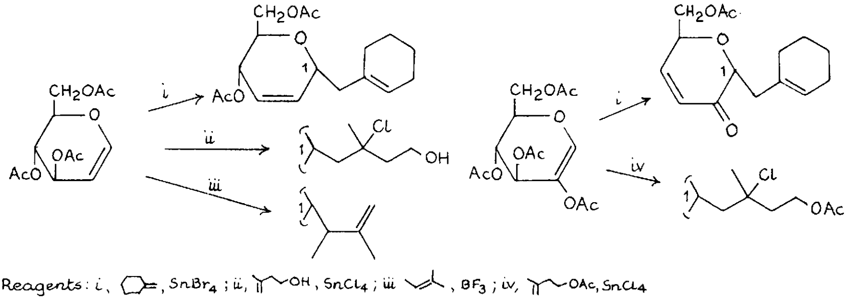
(149)



(150) R = OAc

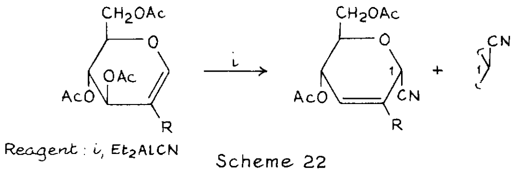
(151) R = H

Chem., 1983, *61*, 533).[236] A large range of 2,3-unsaturated *C*-glycosides have been made in good yields from glycal and "2-hydroxyglycal" esters and alkenes as exemplified in Scheme 21.[237] Related rearrangements are illustrated in Scheme 22, the anomeric



Scheme 21

configurations of the products being assigned by their $^{1}J_{\text{C-1-H}}$ values, compounds with the cyano-groups *cis*- and *trans*- to the C-5 group having values of <155 Hz and 160 Hz, respectively.[238]



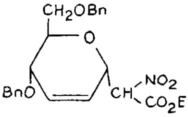
Scheme 22

Additions to tri-*O*-acetyl-D-glucal that resulted in 2-azido-2-deoxyglycosyl cyanides are referred to in Chapters 9 and 10. 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl cyanide has been converted into the corresponding amide, the acid and hence *N,N*-substituted amides.[239] 2-Acetamido-2-deoxy-β-D-glucopyranosyl nitromethane has been made from the free sugar and nitromethane and converted into the *C*-glycosylmethylamine analogue.[240]

Compound (**152**), on denitration under radical conditions, affords access to the acetic ester derivatives (**153**) the mass spectroscopy of which was examined in detail. Normal methods failed to distinguish the anomers but e.g. mass-analysed ion kinetic energy methods did distinguish.[241, 242]

The first example of a steroidal *C*-glycoside has been produced by use of tetra-*O*-benzyl-D-glucopyranosyl trifluoroacetate (**154**).[243]

Aloins A (**154**) and B (**155**) and related *C*-glycosides have been studied by nOe and CD methods to obtain conformations and absolute configurations,[245] and conformational studies by molecular mechanics have been carried out on the palytoxin-related compounds (**156-158**).[245]



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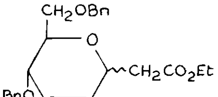

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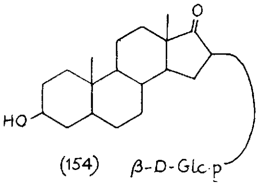

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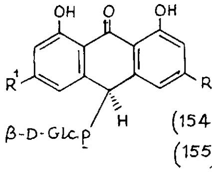
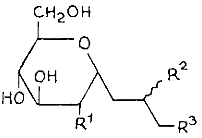


(154A) R^1=H, R^2=CH$_2$OH
(155) R^1=CH$_2$OH, R^2=H



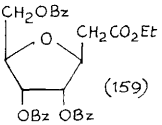
	R^1	R^2	R^3
(156)	H	OH	OH
(157)	OH	OH	OH
(158)	OH	H	H

3.2 Furanoid Compounds.—An n.m.r. proton-proton coupling constant method has been applied to the anomeric configurational determination of *C*-glycosidic analogues of 2-deoxy-D-*erythro*-pentofuranosides.[246]

A novel Reformatsky reaction using ethyl bromoacetate-zinc-titanium tetrachloride has been applied with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose to give the β-linked product (**159**).[247] Compound (**160**), obtained by use of a Grignard reagent and a glycosyl chloride, has been made as a nucleoside analogue and incorporated into oligonucleotides for studies of duplex stability.[248]

2,3,5-Tri-*O*-benzyl-D-arbinose with magnesium phenates gave *o*-hydroxyphenyl *C*-

glycosides of mainly the β-configuration,[249] and 2,3:4,5-di-*O*-isopropylidene-aldehydo-D-arabinose with 1-phenyl-3-trimethylsilylprop-1-ene and boron trifluoride afforded the *C*-glycosidic product of acetal migration (**161**).[199] In common with results reported by O.R. Martin, 2,3,5-tri-*O*-benzylpentoses react with boron trifluoride to give products of internal dehydration e.g. (**162**) which was produced in 95% yield from the L-arabinose compound.[250] Martin *et al.* have reported several reactions of compounds such as (**162**) including hydrogenolysis of the benzylic furanose C-1-O-4 bond and ruthenium tetraoxide oxidation of the central ring to a lactone and subsequent hydrolysis to α-*C*-glycosides with an *o*-carboxy-group in the "aglycone".[251]



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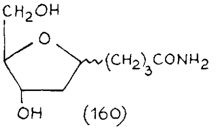

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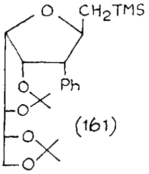

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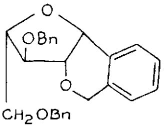

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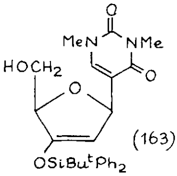
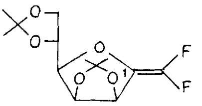
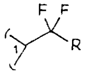


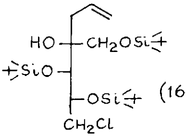
(163)



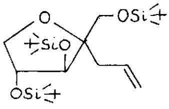
(164)



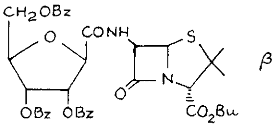
(165)



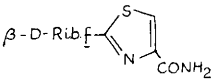
(166)



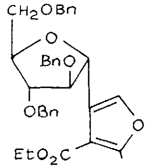
(167)



(168)



(169)

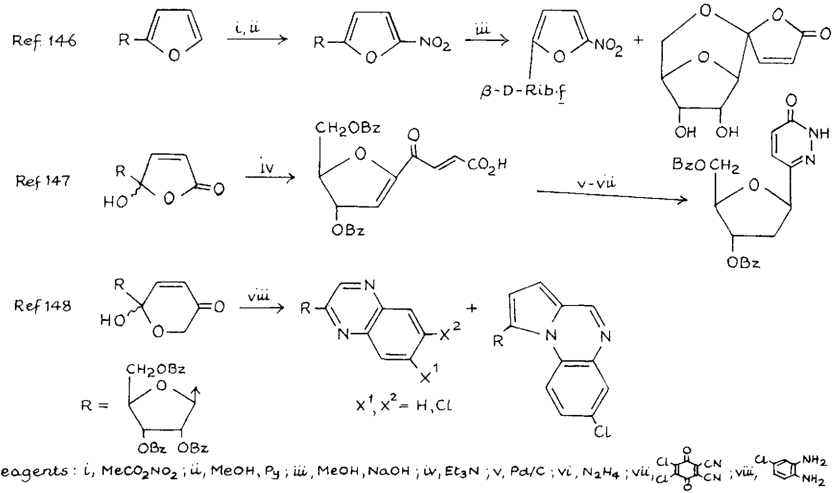


(170)

2,3-*O*-Isopropylidene-L-lyxose, used in the synthesis of erythroskyrin which contains a furofuran system related to the furopyran system of (**162**), is referred to in Chapter 24. Compound (**163**) has been made by palladium-catalysed rearrangement of the corresponding glycal[252] (see Chapter 20 for related compounds). The alkene (**164**), by radical addition reactions using butyl, cyclohexyl, dodecyl bromide or iodide and tributyltin hydride, gave access to difluoromethylene-linked products (**165**),[253] and base-catalysed cyclisation of the Grignard product (**166**) gave the ketose *C*-glycoside (**167**).[254]

Several *C*-glycosides have been produced by elaboration of simple anomeric substituent groups. Thus, for example, the corrresponding glycosyl carboxylic acid has been condensed to give the penicillin derivative (**168**) and hence, via the sulphoxide which was treated with triphenylphosphate, the antitumour compound tiazofurin (**169**).[255] More simply, the corresponding aldehyde, chain extended with lithio-1,3-dithiolane and the product treated with ethyl acetoacetate, afforded the furan (**170**).[256]

Three papers have appeared on the modification of known *C*-glycosides bearing furan- or pyran-based anomeric substituents (Scheme 23).[257-259]



Scheme 23

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4
Oligosaccharides

1 General

As in previous volumes, this Chapter deals with specific tri- and higher oligosaccharides; most, but not all papers cited relate to their synthesis by chemical methods. It does not cover compounds made by oligomerisation of monosaccharide derivatives but, for the first time, a separate section on cyclodextrins is included which deals mainly with their chemical syntheses and modifications. Their use, for example as catalysts, and other aspects are not covered.

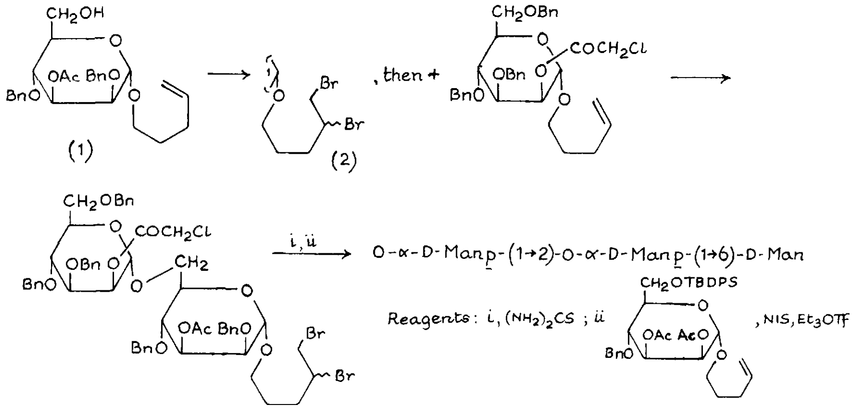
In most cases the block synthesis of a compound is dealt with in the section appropriate to the product, and oligosaccharide derivatives are frequently treated under the heading of the parent compounds, the substituents etc. being disregarded.

An important databank containing references to all published structures of carbohydrates larger than disaccharides has been developed.[1]

One review has covered the synthesis and conformational and X-ray analysis of the saccharide chains of the core regions of glycoproteins,[2] and another the conformations of the carbohydrate chains of glycoproteins and glycolipids.[3] The following reviews have dealt with enzymological features of oligosaccharide chemistry: the direct formation of oligosaccharides by enzymic transglycosylation,[4] the production of oligosaccharides from sucrose[5] and by transfructosylation using micro-organism enzymes e.g. levansucrase,[6] the synthesis of xylose oligosaccharides and their glycosides by use of β-xylanase,[7] and the preparation of chito- and *N*-acetylchito-oligosaccharides by use of chitinases.[8] Alternatively, chitose oligosaccharides can be obtained by acid-catalysed hydrolysis of chitosan, and the first 15 oligomers have been isolated.[9]

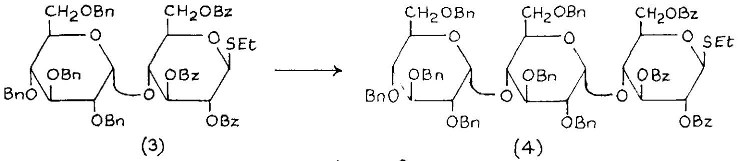
During lactose hydrolysis by *Bifidobacterium bifidum* transglycosylation occurred to give several products with β-(1→3) linked D-galactose substituent groups.[10] A conference report described the synthesis of several oligosaccharides by enzymic methods: *N*-acetyllactosamine by a cyclic process involving six immobilised enzymes, trisaccharides formed by galactosylation of chitobiose, and by linking *N*-acetylneuraminic acid to *N*-acetylactosamine, α- and β-cyclodexteris and several acyclic D-glucose oligomers by use of α-D-glucosyl fluoride and an α-glucosidase, and galactose - containing disaccharides using the α-galactosyl fluoride and corresponding enzyme.[11]

Fraser-Reid and colleagues have generalised the use of 4-pentenyl glucosides in glycosidations and have extended the concept of "armed" and "disarmed" compounds (cf. *J. Am. Chem. Soc.*, 1988, *110*, 2662). Bromine adducts (eg **2**) deactivate the unsaturated reagents; thus (**1**) becomes an acceptor and can later be used as a donor (Scheme 1).[12]



Scheme 1

An elegant extension of the "armed"/"disarmed" concept is illustrated in Scheme 2 which shows the "disarmed" glycosylating agent (**3**) used, after debenzoylation and benzylating, in a glycosylation capacity to produce the trimer (**4**).[13]



Scheme 2

2 Trisaccharides

2.1 Linear Homotrisaccharides.—4-*O*-α-D-Glucopyranosyl-α,α-trehalose has been made by use of a glycosyl fluroide,[14] and enzymic methods have been used to transfer β-D-galactose or α- or β-D-glucose to the 4- or 6- positions of the disaccharide.[15] β-(1→3) and β-(1→6)-linked D-glucose trisaccharides have been made as L-serine glucosides,[16] and the corresponding α-(1→4)trimer has been prepared as the α-glycoside of the primary alcohol (**5**) and thereby photolabile to serve as a probe for malto-oligosaccharide enzyme binding sites.[17] The α-(1→6)glucotriose has been *N*-linked to glycylproline[18] and to L-asparagine[19] (the latter by use of pentenyl glucoside methods). Enzymic hydrolysis of specifically modified γ-cyclodextrins have given the α-(1→4) linked glucotrioses with a sulphonate ester group at the primary site of non-reducing moiety, and with a 2,3-anhydro group (*allo*- and *manno*-isomers both obtained) in the central sugar unit.[20] The α-(1→2), α-(1→6) and α-(1→6), α-(1→6)-D-mannotrioses have been synthesised as β-glycosides,[21] and special interest has been shown in the preparation of β-(1→6) linked D-galactotrioses (as methyl glycosides) having deoxy-groups at the three different 3-positions[22] and 4-positions[23] for studies of antibody binding. The α-(1→4),α-(1→4) and β-(1→4),α-(1→4) linked trimers of D-galacturonic acids have been made in connection with studies of plant hormones.[24]

α-(1→3) Linked L-rhamnotriose has been found to occur in plant bark as a tetra-acetate hexanoate,[25] and the α-(1→2) linked L-fucose trimer has been made as the methyl α-glycoside.[26]

2.2 Linear Heterotrisaccharides.—Compounds noted in this Section are treated according to the nature of their reducing terminal moieties. The following compounds (or derivatives of them) terminating in D-glucose have been synthesised: *O*-β-D-Glc*p*NAc-(1→6)-*O*-α-D-Glc*p*-(1→2)-*O*-α-D-Glc*p*-Me,[27] *O*-α-D-Ara*f*-(1→2)-*O*-α-D-Man*p*-(1→2)-D-Glc (a component of ristomycin),[28] *O*-β-D-Glc*p*NAc-(1→2)-*O*-α-D-Man*p*-(1→6)-β-D-Glc*p* (as the *p*-nitrophenyl glycoside and having a 4-*O*-methyl substituent on the central unit),[29] the internal lactone (**6**) of an *N*-acetylneuraminic acid-containing trisaccharide[30] and *O*-α-D-Glc*p*-(1→5)-*O*-β-D-Fru*p*-(1→6)-D-Glc.[31] In addition, considerable attention has been given to glycosylated lactoses: *O*-α-D-Gal*p*-(1→6)-*O*-β-D-Gal*p*-(1→4)-D-Glc,[32] *O*-α-D-Gal*p*-(1→4)-*O*-β-D-Gal*p*-(1→4)-D-Glc (as a ceramide glycoside),[33] *O*-β-D-Gal*p*NAc-(1→4)-*O*-β-D-Gal*p*-(1→4)-D-Glc[34] and, especially, the gangliosidic *O*-α-D-Neu*p*NAc-(2→3)-*O*-β-D-Gal*p*-(1→4)-D-Glc and analogues[35-37] as well as a (2→6),(1→4) bonded trisaccharide as a steroidal glycoside.[38]

Compounds terminating in D-mannose are: *O*-α-D-Gal*p*-(1→3)-*O*-α-D-Man*p*-(1→6)-D-Man, *O*-α-D-Glc*p*-(1→3)-*O*-α-D-Man*p*-(1→6)-D-Man and the same compounds with the (1→3) and (1→6) linkages exchanged,[39] *O*-β-D-Glc*p*-(1→4)-*O*-β-D-Man*p*-(1→4)-D-Man (partial hydrolysis product of a seed polysaccharide),[40] *O*-β-D-Glc*p*UA-(1→2)-*O*-α-L-Rha*p*-(1→3)-D-Man,[41] 3,6-dideoxy-α-D-*xylo*-hexosyl-(1→3)-*O*-α-and β-L-Rha*p*-(1→2)-D-Man[42] and *O*-β-D-Gal*p*NAc-(1→4)-*O*-β-D-Glc*p*NAc-(1→2)-D-Man.[43]

Derivatives of D-galactose to have been reported are: *O*-β-D-Glc*p*-(1→4)-*O*-α-L-Rha*p*-(1→2)-D-Gal,[44] *O*-β-D-Man*p*-(1→4)-*O*-α-L-Rha*p*-(1→3)-D-Gal[45] and *O*-β-D-Gal*p*-(1→4)-*O*-β-D-Glc*p*NAc-(1→3)-D-Gal.[46, 47]

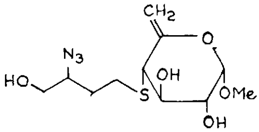
Compounds terminating in aminohexoses are: *O*-β-D-Glc*p*NAc-(1→3)-*O*-β-D-Gal*p*-(1→4)-D-GlcNAc (as a tris-sulphate ester),[48] *N*-acetyl-lactosamine with a sialic acid bonded to the primary position of the D-galactose,[49] *O*-α-KDO-(2→6)-β-D-Glc*p*NH$_2$-(1→6)-D-GlcNH$_2$,[50] *O*-α-KDO-(2→4)-*O*-α-D-KDO-(2→6)-D-GlcNH$_2$ (the aminosugar present as a lipid A subunit)[51] and the trimer (**7**) of relevance in anthracycline chemistry.[52]

Deoxy-sugar trisaccharides to have been reported are: *O*-α-L-Rha*p*-(1→2)-*O*-β-D-Gal*p*-(1→4)-L-Rha,[53] *O*-α-D-Gal*p*-(1→3)-*O*-α-D-Glc*p*-(1→3)-L-Rha,[54] and the anthracycline trisaccharide (**8**).[55]

Two D-xylose derivatives to have been reported are *O*-α-L-Fuc*p*-(1→2)-*O*-β-D-Gal*p*-(1→2)-D-Xyl[56] and *O*-β-D-Gal*p*-(1→3)-*O*-β-D-Gal*p*-(1→4)-*O*-β-D-Xyl*p*-L-serine.[57]

2.3 Branched Homotrisaccharides.—The *O*-serine glycoside of *O*-β-D-Glc*p*-(1→3)-*O*-[β-D-Glc*p*-(1→6)]-D-Glc*p* has been synthesised in connection with studies on the solid phase synthesis of glycopeptides.[16]

2.4 Branched Heterotrisaccharides.—Compounds are again listed according to their reducing units. The following have been synthesized or, occasionally, obtained from natural sources: *O*-β-D-Gal*p*-(1→2)-*O*-[β-D-Glc*p*-(1→3)]-D-Glc,[58] *O*-β-D-Glc*p*-(1→2)-*O*-[α-L-Rha*p*-(1→6)]-D-Glc,[59] *O*-α-L-Rha*p*-(1→3)-*O*-[β-D-Gal*p*-(1→6)]-D-Glc,[60] *O*-β-D-Glc*p*NAc-(1→2)-*O*-[β-D-Glc*p*NAc-(1→4)]-D-Man,[61] *O*-β-D-Glc*p*-(1→4)-*O*-[α-L-Rha*p*-(1→2)]-D-Gal,[53] *O*-β-D-Glc*p*-(1→4)-*O*-[β-D-Man*p*-(1→3)]-D-Gal, and related compounds required for conformational studies,[62] *O*-β-D-Glc*p*NAc-(1→4)-*O*-[α-L-Fuc*p*-(1→6)]-D-Glc*p*NAc,[63, 64] *O*-β-D-Gal*p*-(1→4)-*O*-[β-D-Glc*p*-(1→6)]-D-Glc*p*NAc,[65] and *O*-α-D-Hep*p*-(1→7)-*O*-[α-D-Glc*p*-(1→3)]-D-Hep.[66] The unusual compound (**9**), a component of calicheamycin, and containing a branched trisaccharide with an oxyamino linkage, has been prepared.[67]



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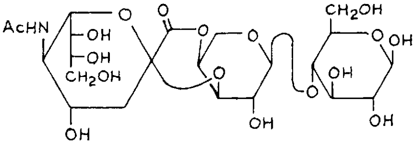

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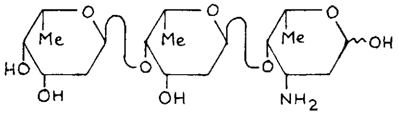

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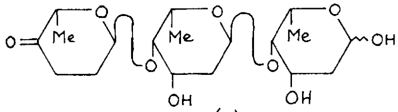

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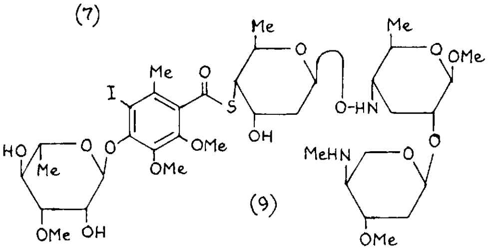

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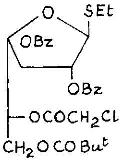


(10)

3 Tetrasaccharides

3.1 Linear Homotetrasaccharides.—The chloroacetyl thioglycoside (**10**), on activation with *N*-iodosuccinimide and trifluoromethanesulphonic acid, gave access to the β-(1→5)-linked tetramer of galactofuranose which is an immuno-active compound found in extracellular polysaccharides of *Aspergillus* and *Penicillium* species.[68]

3.2 Linear Heterotetrasaccharides.—The following compounds (or their derivatives) having hexoses at the reducing termini have been reported: *O*-α-D-Gal*p*-(1→6)-*O*-α-D-Gal*p*-(1→6)-*O*-α-D-Gal*p*-(1→6)-D-Glc,[69] *O*-β-D-Gal*p*-(1→2)-*O*-α-D-Xyl*p*-(1→6)-*O*-β-D-Glc*p*-(1→4)-D-Glc (a plant cell wall component with anti-auxin activity),[70] *O*-α-D-Glc*p*-(1→4)-*O*-α-D-Xyl*p*-(1→4)-*O*-α-D-Xyl*p*-(1→4)-D-Glc, wanted for studies of amylase,[71] *O*-β-D-Glc*p*NAc-(1→3)-*O*-β-D-Gal*p*-(1→4)-*O*-β-D-Glc*p*NAc-(1→3)-D-Glc, made as a trisulphate fragment of keratan sulphate,[72] and *O*-α-Neu*p*Ac-(2→6)-*O*-β-D-Gal*p*-(1→4)-*O*-β-D-Glc*p*NAc-(1→2)-D-Man, prepared by use of immobilised transferases.[73]

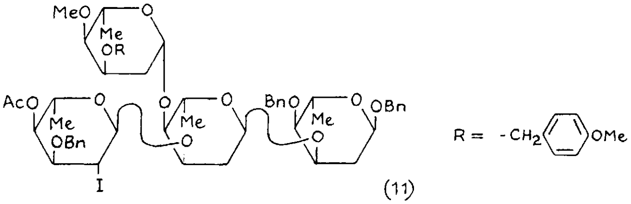
Compounds with 2-amino-2-deoxyhexoses at the reducing end are: *O*-β-D-Gal*p*-(1→4)-*O*-β-D-Glc*p*NAc-*O*-β-D-Gal*p*-(1→4)-D-Glc*p*NAc also the hexa- and octa-saccharides with two and three *N*-acetyl-lactosamine units,[74] *O*-β-D-Glc*p*NH$_2$-(1→4)-*O*-β-D-Man*p*-(1→4)-*O*-β-D-Glc*p*NH$_2$-(1→4)-Glc*p*NH$_2$,[75] and *O*-α-KDO-(2→8)-*O*-α-KDO-(2→4)-*O*-α-KDO-(2→6)-D-Glc*p*NAc, the tetrasaccharide of the genus-specific lipopolysaccharide of *Chlamydia*.[76]

Tetramers containing deoxy-sugars to have been synthesised are: *O*-α-D-Gal*p*-(1→3)-*O*-α-D-Glc*p*-(1→3)-*O*-α-L-Rha*p*-(1→4)-D-ribitol, an *S. Pneumoniae* polysaccharide unit,[54] and a tetrasaccharide component of the orthosomycins (Chapter 19) containing a spiro-ortholactone feature.

3.3 Branched Homotetrasaccharides.—A tetramer representing the branching point of amylopectin has been conformationally analysed by theoretical methods.[77]

3.4 Branched Heterotetrasaccharides.—Compounds of this category having hexoses at the reducing termini have been synthesised: *O*-α-D-Man*p*-(1→3)-*O*-[β-D-Xyl*p*-(1→2)]-β-D-Man*p*-(1→4)-*O*-β-D-Glc*p*(1→1)Cer,[78] *O*-α-D-Ara*f*-(1→2)-*O*-α-D-Man*p*-(1→2)-*O*-[α-L-Rha*p*-(1→6)]-α-D-Glc*p*Pr,[79, 80] *O*-β-D-Glc*p*NAc-(1→2)-*O*-α-D-Man*p*-(1→3)-*O*-[α-D-Man*p*-(1→6)]-β-D-Man*p*,[81] *O*-β-D-Gal*p*-(1→4)-*O*-β-D-Glc*p*NAc-(1→3)-*O*-[β-D-Glc*p*NAc-(1→6)]-β-D-Gal*p*CD$_3$.[46]

Tetramers with terminal amino- or deoxy-sugars are as follows: *O*-α-L-Fuc*p*-(1→2)-*O*-β-D-Gal*p*(1→3)-*O*-[α-L-Fuc*p*-(1→4)]-GlcNAc,[82] *O*-α-L-Rha*p*-(1→2)-*O*-[β-D-Glc*p*NAc-(1→3)]-*O*-α-L-Rha*p*-(1→3)-L-Rha,[83] *O*-β-D-Glc*p*UA-(1→6)-*O*-α-D-Glc*p*-(1→2)-*O*-[β-D-Glc*p*-(1→3)]-L-Rha,[84] *O*-β-D-Glc*p*-(1→4)-*O*-[α-L-Rha*p*-(1→2)]-*O*-β-D-Gal*p*-(1→4)-L-Rha,[53] and the iodo-derivative (**11**) of a kijanimicin tetrasaccharide which was required for studies of conformational flexibility.[85]



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4 Pentasaccharides

4.1 Linear Pentasaccharides.—Syntheses of the following have been reported: *O*-α-D-Neu*p*Ac-(2→3)-*O*-β-D-Gal*p*-(1→3)-*O*-β-D-Gal*p*NAc-(1→4)-*O*-β-D-Gal*p*-(1→4)-*O*-β-D-Glc*p*-Cer (which is the first synthesis of *ganglio*-ganglioside GM1b),[86] the isomer having 2-acetamido-2-deoxy-D-glucose as the central unit,[87] *O*-β-D-Glc*p*UA-(1→3)-*O*-β-D-Gal*p*-(1→4)-*O*-β-D-Glc*p*NAc-(1→3)-*O*-β-D-Gal*p*-(1→4)-β-D-Glc*p*-Ar,[88] *O*-α-L-Rha*p*-(1→2)-*O*-α-L-Rha*p*-(1→3)-*O*-α-L-Rha*p*-(1→3)-*O*-β-D-Glc*p*NAc-(1→2)-L-Rha,[89] *O*-α-KDO-(2→4)-*O*-α-KDO-(2→4)-*O*-α-D-KDO-(2→6)-*O*-β-D-Glc*p*NH_2-(1→6)-D-GlcNH_2 (the inner core region of lipopolysaccharides; 3-hydroxytetradecanoyl groups were bonded to the amino-centres),[90] and analogues of the highly sulphated heparin pentasaccharide in which the L-iduronate or the D-glucuronic groups were replaced by acyclic acidic linkages.[91]

4.2 Branched Pentasaccharides.—*p*-Trifluoroacetamidophenyl 3,6-di-*O*-{2-*O*-[α-D-mannopyranosyl 6-disodium phosphate]-α-D-mannopyranosyl}-α-D-mannopyranoside, a part of the recognition marker on lysosomal enzymes, has been synthesised[92] and two L-fucose-containing pentasaccharides have been isolated from goats' milk. They are *O*-β-D-Gal*p*-(1→4)-*O*-[α-L-Fuc*p*-(1→3)]-*O*-β-D-Glc*p*NAc-(1→6)-*O*-β-D-Gal*p*-(1→4)-D-Glc and an isomer having the terminal galactose unit bonded (1→3) and the fucose side group attached (1→3) to the reducing D-glucose moiety.[93]

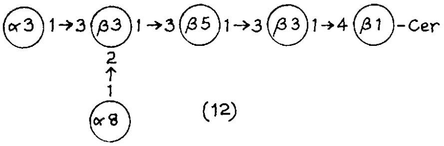
5 Hexasaccharides

Several reports on α-cyclodextrin chemistry are noted in Section 7 of this Chapter. Enzymic transfer has allowed the preparation of the corresponding hexaose from *N*-acetylchitotetraose or from the corresponding disaccharide,[94] and a solid phase synthesis has yielded an aminohexosyl-containing hexameric fragment of the *H. influenzae* type *b* capsular polysaccharide.[95]

Because of their increasing complexity, specific oligosaccharide structures will henceforth be represented diagrammatically by an increasingly abbreviated method. Sugars will be numbered as follows, and linkages will be indicated in the usual way:

①	**D-Glc*p***	②	**D-Man*p***	③	**D-Gal*p***
④	**D-Glc*p*NHAc**	⑤	**D-Gal*p*NAc**	⑥	**Neu*p*Ac**
⑦	**L-Rha*p***	⑧	**L-Fuc*p***	⑨	**D-Xyl*p***
⑩	**D-Glc*p*NH$_2$**				

Syntheses of hexamers with structures (**12**) (component of the glycosphingolipid of a macrophage receptor,[96] (**13**) (elicitor-active compound),[97] (**14**) (ganglioceramide)[98] and (**15**) (core of glycophosphatidyl inositol anchor of *Trypanosoma brucci*)[99] have all been reported.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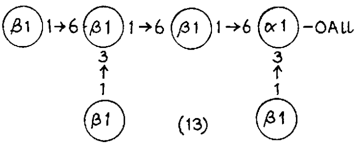
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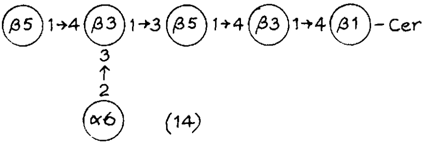
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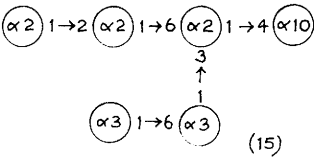
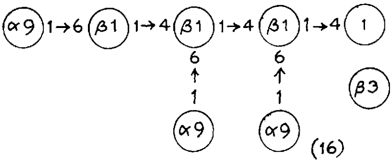

(15)

6 Higher Oligosaccharides

The coding for the sugars used in the diagrams is given in Section 5 above.

6.1 Heptasaccharides.—Syntheses have been reported of (**16**) (shows anti-auxin activity on plant stem growth),[100] (**17**) (for immunoglobulin-antigen binding studies),[101] (**18**) (core of bisected complex bacterial glycan),[102] (**19**) (part of a tumour-associated glycolipid),[103] and (**20**) (repeating unit of *S. flexneri* polysaccharide).[104]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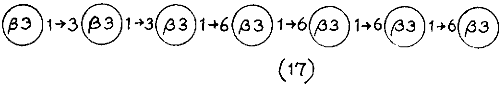
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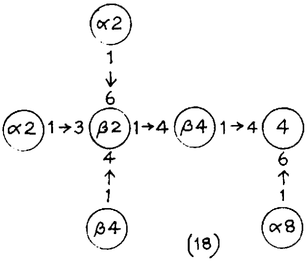

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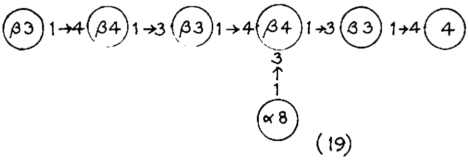

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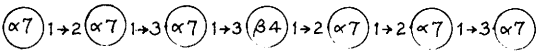

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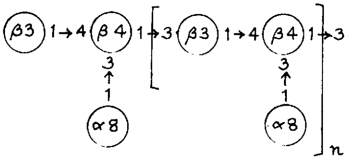
6.2 Octasaccharides.—The total synthesis of the Le^x family of glycosphingolipids (**21**) - (**23**) has been achieved, the second being an octasaccharide.[105]

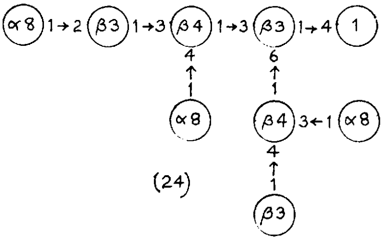


(21) n = 0

(22) n = 1

(23) n = 2

6.3 Nonasaccharides.—Compound (**24**) is a newly characterised constituent of human milk[106] and the syntheses of (**25**)[107] and (**26**)[100] have been carried out.



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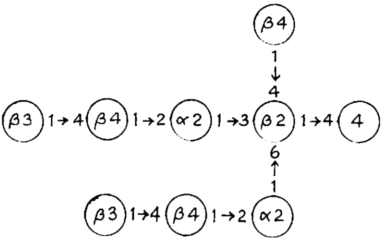

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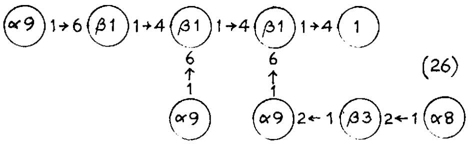
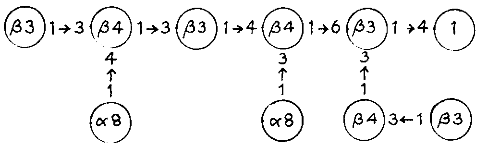


(26)

6.4 Decasaccharides.—Compounds (**27**) and (**28**) have been isolated from human milk.[106]



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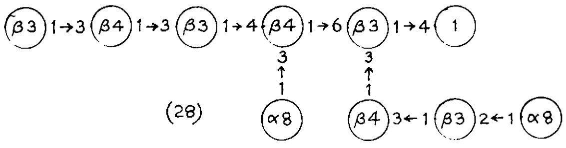

(28)

6.5 Dodecasaccharides.—The phytoalexin elicitor of soyabean comprising twelve galactopyranuronic acid units linked α-(1$\rightarrow$4) has been synthesised.[108]

6.6 Cyclo-oligosaccharides.—In this Section, only chemical features of compounds will be noted; their catalytic activities etc are not covered.

Compounds of D-glucose.—Proceedings of the Fourth International Symposium on Cyclodextrins have appeared.[109] FAB and tandem mass spectra of 30 modified cyclodextrins have been reported,[110] and it has been established that, in comparison with the internal bonds of linear oligosaccharides, the glycosidic bonds of α-, β- and γ-cyclodextrins are 1.5 fold more stable, approximately as stable, and 1.5 fold less stable, respectively, to acid-catalysed hydrolysis.[111]

β-Cyclodextrin analogues based on 2-acetamido-2-deoxy-D-glucose have been prepared and their complexing abilities have been studied,[112] and a β-(1$\rightarrow$3) linked analogue has been synthesised by way of a 4,6:4,'6'-di-*O*-ethylidene cellobiose derivative.[113] In the series of β-(1→6)-linked compounds cyclogentiotriose and cyclogentiotetraose have been made by cyclisation of suitable linear compounds.[114]

The isomeric $6^A,6^B$-, $6^A,6^C$- and $6^A,6^D$- di-*O*-α-D-glucopyranosyl-β-cyclodextrins have been isolated,[115] and α-cyclodextrin can be enzymically transferred to D-glucose derivatives provided the anomeric position is substituted and O-4 is not.[116]

Major products available following partial methylation of α- and γ-cyclodextrins were the products of substitution at O-2 and O-6 of each glucose unit and, in each case, the compounds formed by introduction of one further methyl group at one of the O-3 positions.[117] The β-cyclodextrin, methylated at each O-2 and O-6 site and with one 2-(4-imidazolyl)ethyl group, is strongly catalytic of the hydrolysis of *p*-nitrophenyl acetate.[118]

β-Cyclodextrin $6^A,6^B$-diodide has been converted into 6-thiol analogues and, by use of these derivatives, "clam-shell" binding compounds have beeen obtained.[119] In related work β-cyclodextrins have been "capped" with crown ethers to give compounds with pairs of complexing cavities,[120] and other derivatives having anthraquinone in the "capping" position have been prepared. Irradiation led to reduction of the quinone and oxidation of one of the primary hydroxyl groups of the cyclodextrin to the aldehyde.[121]

β-Cyclodextrin 2-tosylate afforded the 2-deoxy-2-imidazolyl analogue which is 70 times more active as a catalyst of *p*-nitrophenyl acetate hydrolysis than is the 6-substituted compound.[122]

Compounds of other sugars.—The α-(1→4) linked cyclomannohexaose with substituents at all the O-2 sites has been made by cyclisation of a differently O-2,O-3 substituted linear compound.[123] Cyclo-[(1→6)-β-D-galactofuranose]oligosaccharides have been made by an improved procedure involving the condensation of di- and tri-saccharide units. Compounds containing 2,3,4,6,8 and 9 sugar units in the rings were isolated.[124, 125]

2,3,4-Tri-*O*-benzyl-α-L-rhamnosyl chloride, on heating, gave the first L-series cyclo-oligosaccharides.[126]

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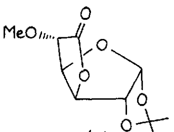
5

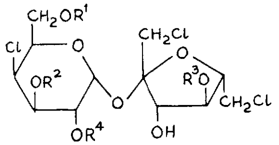
Ethers and Anhydro-sugars

1 Ethers

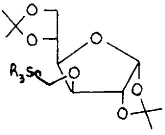
Methyl Ethers. - Significant oxidation of the alditol moieties of oligoglycosyl alditols occurs when MeI/NaOH/DMSO is used for *O*-methylation, whereas Hakamori methylation is not subject to this extraneous reaction. The oxidised alditols are all converted into methyl glycosides during the methylation.[1] The partial methylation of methyl α-and β-D-threofuranoside employing MeI/NaOH/MeCN is faster at O-2 than at O-3 for both anomers.[2] Methyl 2-*O*-methyl-α,β-L-fucofuranoside, *i.e.* glycosides of component sugars of some glycolipids, have been synthesized from D-glucuronolactone *via* the methyl ether (1).[3]



(1)



(2) $R^1 = Me, R^2 - R^4 = H$
(3) $R^1 = R^3 = R^4 = H; R^2 = Me$
(4) $R^1 = R^2 = R^4 = H; R^3 = Me$
(5) $R^1 = R^3 = H; R^2 = R^4 = Me$

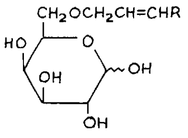


(6) R = Me or cyclohexyl

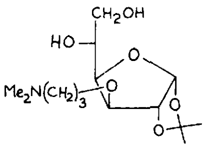
The deoxychlorosucrose *O*-methyl ether derivatives (2) - (5) have been synthesized from appropriate partially protected precursors.[4] Some partially methylated cyclomalto-hexaose and -octaose compounds are mentioned in Chapter 4. Complete ^1H- and ^{13}C- n.m.r. assignments have been made for a number of *O*-methyl derivatives of α- and β-D-galactopyranose.[5] 3-*O*-Stannylmethyl ethers (6) have been reported.[6]

Other Alkyl and Aryl Ethers. - Some acetylated 3-*O*-alkyl-D-glucopyranose derivatives have been prepared by alkylating 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with $Me(CH_2)_nCH_2Br$ followed by deprotection and acetylation with Ac_2O/NaOAc.[7] A number of 6-*O*-fluoroalkenyl-D-galactose derivatives (7) have been reported as new surfactants for biomedical uses,[8] and the syntheses of 2-,3-, and 4-*O*-triphenylmethyl ethers of methyl (methyl α-D-mannopyranosid)uronate derivatives have been described.[9] Further work on the relative reactivity of hydroxyl groups in methyl α-D-glucopyranoside with pentyloxymethyl chloride has been published (see SPR Vol. 22, p. 57).[10]

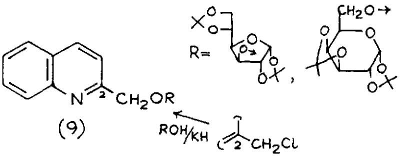
The synthesis of the novel antiinflammatory agent amiprilose (8) from D-glucose has been achieved as well as that of the enantiomer of (8) from L-glucose.[11] Some muramyl-containing glycosphinglolipids are noted in Chapter 3.



(7) $R = C_nF_{2n+1}$, n = 4,6,8



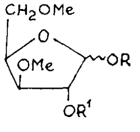
(8)



(9)

A pyridin-2-ylmethyl ether has been used as a hydroxyl protecting group; the compounds (9) were prepared and deprotected with $CuCl_2/DMF/H_2O$.[12] The 2-(methylthio)-phenylthiomethyl (MPTM) group has been utilised as a protecting group for the 2′-hydroxyl group in oligoribonucleotide synthesis.[13]

A new, efficient procedure for the benzylation of sugar derivatives having 3 to 8 hydroxyl groups per molecule used a two-phase system with a phase-transfer catalyst and almost stoichiometric amounts of the alkylating agent. Crucial to the success of the reaction was the use of a co-catalyst (*e.g.* a tertiary alcohol) and/or a co-solvent (*e.g.* DMSO).[14] Methyl 2′-*O*-benzyl-*β*-D-lactoside was prepared during the synthesis of a number of lactoside analogues.[15] Further work has been published on the intramolecular *C*-glycosidation of some 2-*O*-benzyl ether derivatives (see SPR Vol. 23 p41). While the methyl glycoside (10) underwent no reaction with $SnCl_4$, the acetate (11) gave condensation product (12) (67%). Methyl glycoside (13), with the more reactive 3-*O*-methylbenzyl ether, afforded 85-90% of product (14).[16,17]

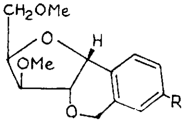


(10) $R = Me, R^1 = Bn$

(11) $R = Ac, R^1 = Bn$

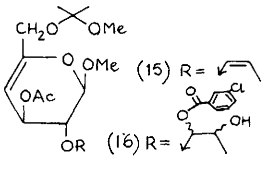
(13) $R = Me,$

$R^1 = CH_2C_6H_4OMe(m)$



(12) R = H

(14) R = OMe



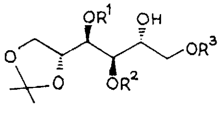
(15) R =

(16) R =

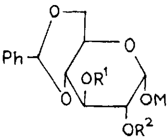
(17) R = H

An effective and selective debenzylation procedure applicable in the presence of acetyl-, benzoyl-, tosyl-, (2-methoxyethoxy)methyl- and glycosidic linkages employed a photolytic procedure ($NBS/CCl_4/CaCO_3/H_2O$, h*ν*).[18] The selective hydrogenolysis of some benzyl glycosides in the presence of benzyl ethers has been effected using transfer hydrogenation with ammonium formate as hydrogen donor.[19] A detritylation procedure using *p*-toluenesulfonic acid in CH_2Cl_2 was reported to be selective in the presence of isopropylidene, MOM-, MEM-, and TBDMS-groups and glycosidic linkages.[20] A new method for the removal of *O*-propenyl groups was exemplified with ether (15). Oxidation with MCPBA afforded the stable ester (16) which, on subsequent treatment with Et_3N, gave the free alcohol (17) following a 1,2- ester migration in the appended group. The reagents did not interfere with the internal vinyl ether function in (15).[21]

Silyl Ethers. - The migration of a t-butyldiphenylsilyl group has been observed under basic conditions (K_2CO_3/MeOH). Thus the D-mannitol derivatives (18) and (19) both gave silyl ether (20) after a series of 1,2- shifts. Under the same conditions the 2-*O*-silyl ether (21)



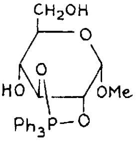
(18) $R^1 = SiPh_2Bu^t$, $R^2 = R^3 = H$
(19) $R^1 = R^3 = H$, $R^2 = SiPh_2Bu^t$
(20) $R^1 = R^2 = H$, $R^3 = SiPh_2Bu^t$



(21) $R^1 = H$, $R^2 = SiPh_2Bu^t$
(22) $R^1 = SiPh_2Bu^t$, $R^2 = H$

afforded an equilibrium mixture (2:1) in favour of the 3-*O*-silyl ether (22).[22] Trimethylsilyl triflate below 0°C has been used to cleave t-butyldimethylsilyl and triphenylsilyl ethers to give the parent alcohols, whereas t-butyldiphenylsilyl ethers are stable under these conditions.[23] Alternatively t-butyldiphenylsilyl ethers are cleaved in the presence of t-butyldimethylsilyl ethers with NaH/HMPA.[24]

2 Intramolecular Ethers (Anhydro-Sugars)



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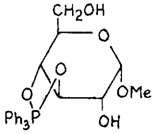

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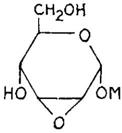

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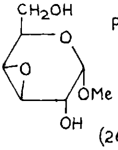
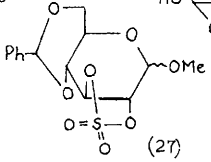
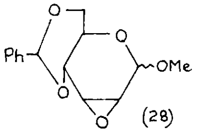


(26)

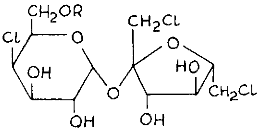


(27)

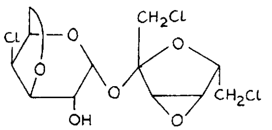


(28)

Oxirans.- Methyl α-D-glucopyranoside afforded two rapidly equilibrating isomeric dioxaphospholanes (23) and (24) on reaction with diethoxytriphenylphosphorane. On thermolysis they gave both the 2,3- and 3,4- epoxides (25) and (26), whereas in the presence of LiBr the allopyranoside (25) was formed exclusively.[25] Attempted nucleophilic displacements applied to both anomers of cyclic sulfate (27) (PhOK/MeCN) resulted in high yields of the corresponding anomer of the *allo*-epoxides (28).[26] Treatment of sucrose derivative (29) with Ph_3P/DEAD gave a mixture of di-anhydride (30) and epoxide (31). The latter was better synthesized by treating silyl ether (32) under the same conditions.


(29) R = H

(32) R = $SiPh_2Bu^t$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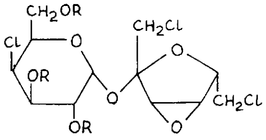
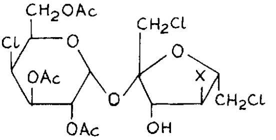
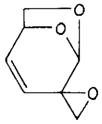
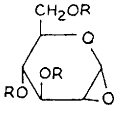

(31) R = H

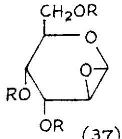
(33) R = Ac


(34) X = F, Cl, Br, I, N_3


(35)

The triacetate (33), with nucleophiles (X^-), gave the corresponding 4′-substituted derivatives (34).[27] The epoxidation of *trans*- and *cis*- 1,2,4,5-tetradeoxy-6,7-*O*-isopropylidene-D-*glycero*-hept-4-en-3-ulose by alkaline H_2O_2 gave a mixture of 4,5-anhydro-1,2-dideoxy-6,7-*O*-isopropylidene-D-*arabino*- and D-*xylo*-3-heptulose which was resolved by chromatography.[28] The *spiro*-epoxide (35) has been produced from levoglucosenone using the Corey procedure ($NaH/Me_3S^+I^-/DMSO/THF$).[29] Further examples of oxidation of glycals with 3,3-dimethyldioxirane have afforded 1,2-epoxides (36) - (39).[30]


(36) R = Si$\equiv$+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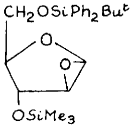
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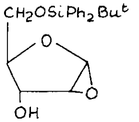
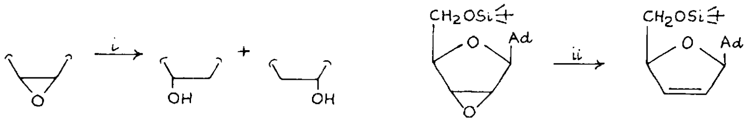

(39)

Treatment of epoxides with Cp_2TiCl and 1,3-cyclohexadiene caused reductive opening of the epoxide by a radical mechanism (Scheme 1), sometimes with a different regioselectivity to that obtained with metal hydride reagents. When the reaction was conducted on epoxide (40) in the absence of cyclohexadiene as a H$^{\bullet}$ donor, deoxygenation occurred to give the unsaturated product (41).[31] Some attempts to open an epoxide by intramolecular delivery of a nitrogen nucleophile to synthesize lincomycin are outlined in



Reagents: i, Cp_2TiCl, ; ii, Cp_2TiCl

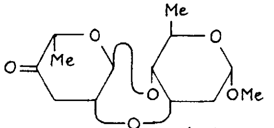
(40) (41)

Scheme 1

Chapter 19. It was found that in aqueous base 3,4-anhydro-2,6-dideoxy-D,L-*ribo*- and -*xylo*-hexose dimethyl acetals isomerise much more quickly to the corresponding 4,5-epoxides than they undergo oxirane ring cleavage.[32]

Other Anhydrides.- A review on the ring-opening polymerisation of 1,6-, 1,3-, and 1,2-anhydrosugar derivatives has been published in Japanese.[33] The cyclisation of several selectively protected glucosyl acetate derivatives has been investigated for the production of 1,6-anhydro-glucose compounds. Treatment of 1,2,3-tri-*O*-acetyl-6-*O*-benzyl-4-*O*-chloroacetyl-α,β-D-glucopyranose with $SnCl_4$ afforded the corresponding 1,6-anhydro-derivative.[34] The pyrolysis of cellobiitol has been studied as a model for cellulose. A 32% yield of 1,6-anhydro-β-D-glucopyranose was obtained along with 70% of D-glucitol and its anhydrides.[35] The conformational properties of 1,6-anhydro-β-D-glucopyranose are discussed in Chapter 21.

Treatment of 1,2,3-tri-*O*-benzoyl-α-β-D-ribofuranose with trimethylsilyl triflate gave 1,5-anhydro-2,3-di-*O*-benzoyl-β-D-ribofuranose.[36] A ten step synthesis of 2,5-anhydro-3,4-diacetamido-3,4-dideoxy-L-arabinose ethylene acetal, a key chiral synthon in a route to (+)- oxybiotin, was achieved starting from a 2,5-anhydro-D-xylose derivative.[37] 2,3,6-Tri-*O*-benzyl-α-D-glucopyranosyl chloride has been converted (NaH/THF) in high yield to 1,4-anhydro-2,3,6-tri-*O*-benzyl-D-glucopyranose,[38] and the same treatment of 2,4,5-tri-*O*-benzyl-α-D-galactopyranosyl chloride gave 1,3-anhydro-2,4,6-tri-*O*-benzyl-β-D-galactopyranose.[39] Attempted displacements (NaN_3/DMF) applied to 1-*O*-acetyl-4-*O*-mesyl-α-D-glucopyranose derivatives furnished 1,4-anhydro-β-D-galactopyranose derivatives rather than the expected 4-azides.[40]



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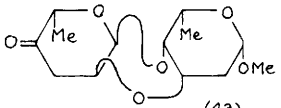

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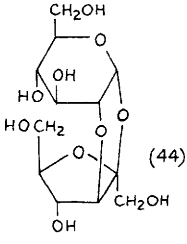

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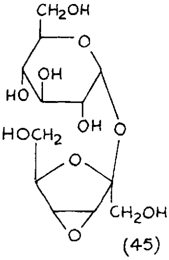

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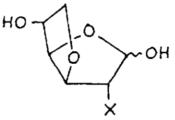
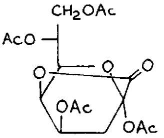


(46) X = OH,NHAc



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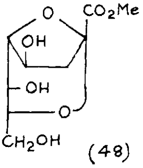

(48)

The first synthesis of ether-bridged and glycosidically linked disaccharides (42) and (43) which occur in the anthracycline class II antibiotics has been reported. The ether linkages were established by intramolecular Michael condensations.[41] 2,3′-Anhydrosucrose (44) has been prepared by intramolecular oxirane cleavage of epoxide (45) under basic conditions.[42] Conformational studies of 3-*O*-(3,6-anhydro-α-D-galactopyranosyl)-β-D-galactopyranose, methyl 3,6-anhydro-4-*O*-β-D-galactopyranosyl-α-D-galactopyranoside, and 2,7-anhydro-L-*glycero*-β-D-*manno*-octulopyranose are mentioned in Chapter 21. The free sugars D-glucose and 2-acetamido-2-deoxy-D-glucose in anhydrous HF with HCO_2H or HOAC form the corresponding 3,6-anhydrofuranoses (46),[43] and the 1,5-lactone (47) in MeOH/HCl gave the 2,7-anhydrooctulonate (48).[44] Attempted benzylation (NaH/BnCl/THF) of 3-*O*-t-butyldimethylsilyl-6-*O*-tosyl-D-glucal caused silyl migration and subsequent anhydride formation to give 3,6-anhydro-4-*O*-t-butyldimethylsilyl-D-glucal.[45]

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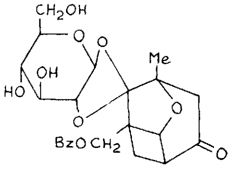
6

Acetals

A review on the reactions of sucrose which includes the protection of hydroxyl groups by acetalation is referred to in Chapter 3.

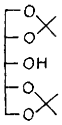
Lactiflorin, a constituent of several *Paeonia* species originally identified as the glucoside of a cage monoterpene lactone, has now been assigned the β-D-glucose 1,2-*O*-ketal structure (1) after a reinvestigation of its spectral properties.[1] A different structural reassignment is covered in Chapter 5.



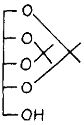
(1)

1 Isopropylidene and Benzylidene Acetals

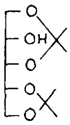
Under conditions of kinetic control (excess of 2-methoxypropene - catalytic *p*-toluenesulphonic acid) the four diacetonides (2)-(5) were formed from ribitol in 36, 3, 12, and 5% yield, respectively, the last two being new compounds. Similarly, erythritol gave 50% and 18%, respectively of the known diacetals (6) and (7) and, in addition, the new 1,3:2,4-derivative (8) as a minor product.[2] With the same reagent, 4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose reacted to give the 2′,3′-monoacetonide (9) and traces of the 6-*O*-(2-methoxy-prop-2-yl) derivative (10).[3] The partial acetylation of these compounds and their conversion to selectively monomethylated products is covered in Chapter 5, and improved procedures for the preparation of di- and tri-*O*-isopropylidene derivatives of *myo*-inositol in Chapter 18.



(2)



(3)



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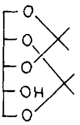

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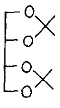

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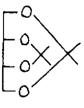

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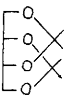
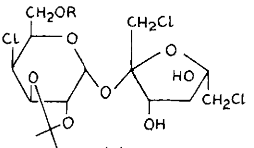
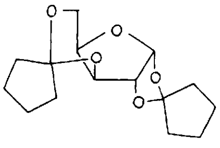


(8)

A new, simple and efficient method for the synthesis of benzylidene acetals of mono- and di-saccharides by use of benzaldehyde in a mixture of DMF and dimethylsulphate has been reported. The acetal formation is promoted by a dimethylsulphate - dimethylformamide adduct and no added acid catalyst is required.[4]



(9) R = H
(10) R = CMe_2OMe



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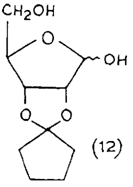
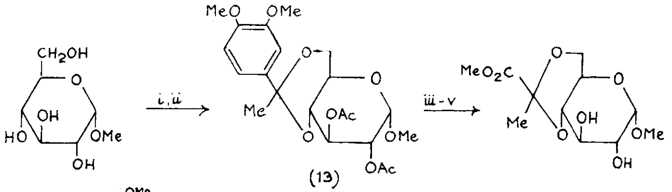


(12)

2 Other Acetals

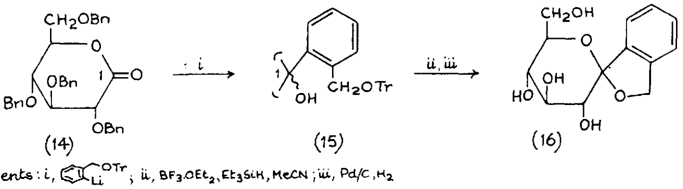
Methyl 4,6-*O*-methylene-α-D-mannopyranoside was the only product isolated from the LiBr-catalised transacetalation of the unprotected methyl glycoside with dimethoxymethane.[5] Cyclopentylidene derivatives of pentoses have been prepared in moderate yields by treatment of the free sugars with cyclopentanone in the presence of copper(II) sulphate and sulphuric acid. D-Xylose formed the diacetal (11) (also used in Scheme 3 below), whereas from D-ribose the 2,3-monoacetal (12) was obtained.[6] A novel, selective synthesis of (*S*)-configurated 4,6-pyruvate acetals of methyl D-hexopyranosides is illustrated in Scheme 1. It relies on transacetalation from the dimethyl acetal of 3,4-dimethoxybenzophenone to give, after acetylation, preferentially the intermediate (13) with an axial aryl substituent which, on oxidation, suffers rapid degradation to a carboxylic acid group.[7]

The glycosidic spiroketal (16) was formed in good overall yield by cyclisation of the strategically functionalised hemiketal (15), obtained from perbenzylated gluconolactone (14) as shown in Scheme 2. Although formally the cyclisation is not reductive, the presence



Reagents: i, $MeC(OMe)_2C_6H_3(OMe)_2$, $CuSO_4$, H_2SO_4; ii, Ac_2O, Py; iii, RuO_2, $NaIO_4$; iv, CH_2N_2; v, MeO^-, MeOH

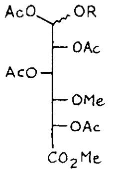
Scheme 1



Scheme 2

of Et_3SiH greatly improves its efficiency.[8] Acetal glycosides, useful as pro-drugs, are referred to in Chapter 3.

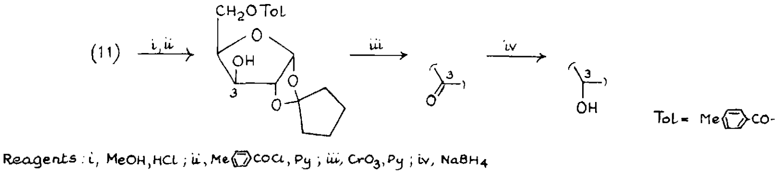
Acetolysis of methyl (methyl 4-*O*-methyl-β-D-glucopyranosid)uronate with acetic acid and a Lewis acid (*e.g.*, $BF_3.OEt_2$, $AlCl_3$) gave the acylal (17) in almost quantitative yield. When sulphuric acid was used as catalyst, a number of intermediates such as the mixed acetals (18) could be isolated.[9] The x-ray crystal structure of (*R*)-(18) is referred to in Chapter 22.



(17) R = Ac
(18) R = Me

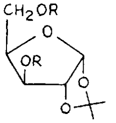
3 Reactions of Acetals

Sugar cyclopentylidene acetals hydrolyse slightly faster than the corresponding isopropylidene derivatives. 1,2:3,5-Di-*O*-cyclopentylidene-α-D-xylose (11) was fully deprotected by use of strong acid resin and methanol, whereas use of methanolic HCl allowed the selective removal of the dioxane ring. This selectivity has been exploited, for



Scheme 3

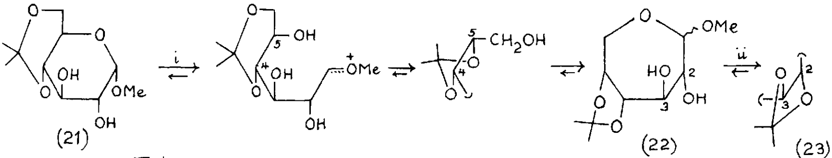
example, in the *xylo* → *ribo* conversion shown in Scheme 3.[6] The relative lability of xylose 3,5-acetals is further illustrated by the formation of the 1,2-monoacetonide (20) from 1,2:3,5-di-*O*-isopropylidene-β-D-xylose (19) under hydrogenolysis conditions (Pd/C-H_2-EtOH; 300 kPa).[10]



(19) R,R = $>CMe_2$

(20) R = H

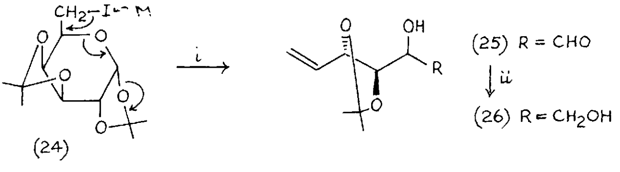
On exposure to pyridinium chloride at 90°C methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (21) ring-expanded to give a mixture of the anomeric glucoseptanoside derivatives (22). The greater stability of a dioxolane relative to a dioxane ring is thought to be the driving force for this isomerisation. The final product (23) of the reaction was isolated in 43% yield and a possible route to this compound is outlined in Scheme 4.[11]



Reagents: i, $\text{C}_5\text{H}_5\overset{+}{\text{N}}\text{HCl}^-$; ii, Cpd. (21)

Scheme 4

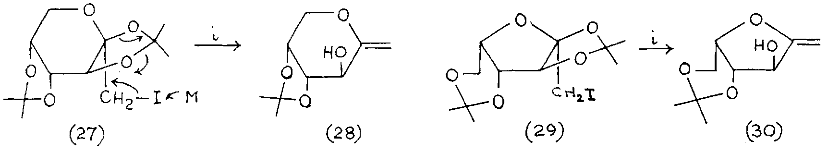
As part of an ongoing study of the action of metal graphite reagents on deoxyhalo-sugars (see Vol. 22, p.136), a number of di-*O*-isopropylidene derivatives of primary deoxyiodohexoses were exposed to CK_8 (potassium-graphite laminate) in THF (Schemes 5 and 6). The D-galactose derivative (24) underwent smooth fragmentation with opening of the tetrahydropyran ring and loss of an acetal group to give the enal (25) [isolated as its reduction product (26)] in 80% yield. No dehydrohalogenation was observed. Fragmentation of the diacetonides (27) and (29) of 1-deoxy-1-iodo-β-D-



Reagents: i, CK_8, THF ; ii, $NaBH_4$

Scheme 5

fructopyranose and -α-D-sorbofuranose, respectively, proceeded however without ring



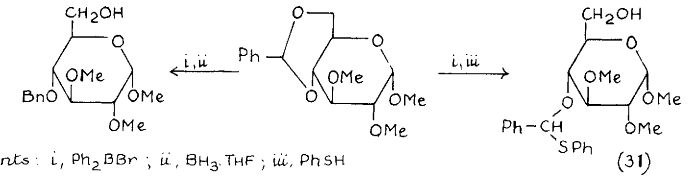
Reagents: i, CK$_8$, THF

Scheme 6

opening, bond-scission taking place between C-2 and the oxygen atom of the isopropylidene groups. The exocyclic alkenes (28) and (30) were obtained in high yields.[12]

The conversion of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose to 1,2-*O*-isopropylidene-β-D-tagato-pyranose is covered in Chapter 2, and the use of 1,2-*O*-cyanoethylidenated glucopyranose derivatives in disaccharide synthesis is referred to in Chapter 3.

Dimethyl- or diphenyl-boron bromide in combination with borane have been used for the regio-controlled reductive opening of benzylidene acetals to give hydroxy benzyl ethers in moderate to high yields. An example is given in Scheme 7. Use of benzenethiol instead of borane afforded the hydroxy *O*,*S*-acetal (31).[13]



Reagents: i, Ph$_2$BBr; ii, BH$_3$.THF; iii, PhSH

Scheme 7

References

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7
Esters

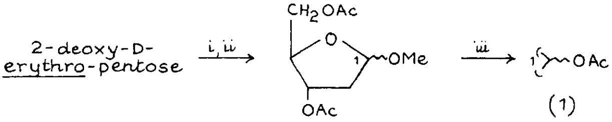
The selective enzymatic acylation and deacylation of carbohydrates and related compounds have been reviewed.[1] In another, extensive review on the chemistry of acetic formic anhydride, several examples of its application to the preparation of carbohydrate formates are given.[2] A further review, in Czech, entitled "The Chemistry of Sucrose", which contains material relevant to this Chapter, is referred to in Chapter 3.

1 Carboxylic Esters

1.1 Synthesis and Reactions.

- The acylation, especially acetylation and benzoylation, of sugars (*inter alia*) by use of a polymer supported imidazole catalyst has been reported.[3]

1,3,5-Tri-*O*-acetyl-2-deoxy-α,β-D-*erythro*-pentofuranose (1) has been prepared in high overall yield by the simple and convenient reaction sequence shown in Scheme 1.[4] An improved synthesis of methyl 3-deoxy-α-D-*manno*-2-octulopyranosonate peracetate (2), involving sequential treatment of the ammonium salt of KDO with acetyl chloride and diazomethane, gave 83% of the desired product and 4.5% of the lactone (3).[5] The hydrolysis of this lactone is covered in Chapter 5. UDP-Glucose, rarely modified chemically up to now because of its poor solubility, has been successfully acetylated by acetic anhydride in the present of *N*-methylimidazole or pyridine-DMAP in THF containing either $Bu_4N^+F^-$ or $LiOAc.2H_2O$ to promote its dissolution.[6] To aid in the quantitative determination of apiose by the alditol acetate method, the acetylation of apiitol has been studied.[7]



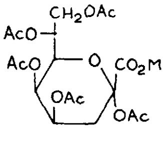
(1)

Reagents: i, HCl, MeOH ; ii, Ac_2O, Py ; iii, Ac_2O, H_2SO_4, HOAc

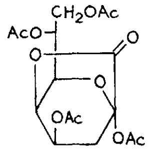
Scheme 1

Fully (monochloro)acetylated α-D-glucose, -mannose, - galactose, and -xylose have been obtained efficiently from the respective free sugars by use of monochloroacetic anhydride and sodium hydrogen carbonate in DMF.[8] Eight pento- or hexo-aldoses, eight reducing disaccharides and three reducing trisaccharides were per(trifluoro)acetylated with

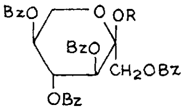
N-methyl-bis(trifluoroacetamide) after mutarotational equilibration in pyridine. See Chapter 21 for n.m.r. studies with these compounds.[9] Their conversion to permonochloroacetylated glycosyl bromides is covered in Chapter 8. The free hydroxyl groups of D-galactose, monacetone-D-glucose, diacetone-D-glucose, and diacetone-D-galactose have been esterified with butyryl chloride in the presence of tri-n-propylamine, the products being required for toxicity and pharmacokinetics studies.[10]



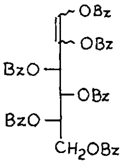
(2)



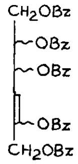
(3)



(4) R = H
(5) R = Bz



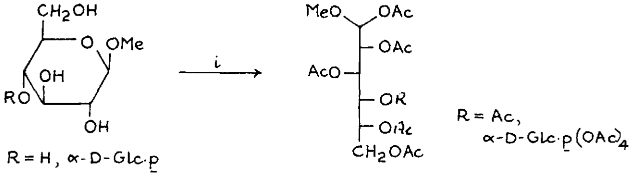
(6)



(7)

The conventional benzoylation (excess of benzoyl chloride in pyridine) of L-sorbose has been examined in detail. In addition to the previously reported products (4) and (6), small quantities of the new pentabenzoates (5) and (7) were isolated.[11]

Methyl α- and β-hexopyranosides reacted differently on exposure to acetic anhydride in the presence of trimethylsilyl triflate. The acetylation of the free hydroxyl groups proceeded with concomitant acetolysis at the anomeric centres of α-configurated derivatives to give α-pentaacetates, whereas the β-anomers suffered ring-opening, as illustrated in Scheme 2.[12] The deacetylation of octa-*O*-acetylcellobiononitrile (8) under standard conditions (MeONa-MeOH) was accompanied by C-1 - C-2 bond cleavage to furnish the disaccharide (9) in high yield (Scheme 3). By careful choice of reaction conditions, disaccharide (9) could be acetylated to give selectively the peracetate with the D-arabinose in the α-D-pyranose-, β-D-pyranose-, or α-D-furanose forms.



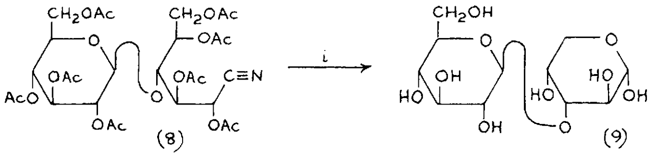
R = H, α-D-Glc-p

R = Ac, α-D-Glc-p(OAc)$_4$

Reagents: i, Ac_2O, TMSOAc

Scheme 2

The 4-, 7-, and 9-mono-, 4,9- and 7,9-di-, and 7,8,9-tri-*O*-acetates of *N*-acetylneuraminic acid [14,15] and partially acetylated derivatives of 1,6-anhydro-β-lactose[16] have been prepared by application of standard protection - deprotection techniques.



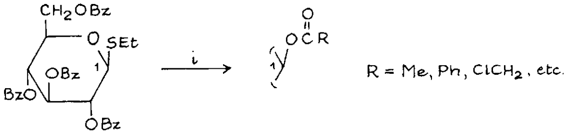
Reagents: i, MeONa, MeOH

Scheme 3

Selective acylations have been used in the synthesis of deoxy analogues of *N*-acetylneuraminic acid; this is covered in Chapter 16.

The synthesis of 2,3-di-*O*-acetyl-1,6-anhydro-*β*-D-glucopyranose is referred to in Chapter 5.

A variety of 1,2-*trans*-glycopyranosyl esters have been prepared in high yields and with excellent selectivity by reaction of alkyl thioglycoside derivatives with carboxylic acids in the presence of *N*-iodosuccinimide. An example is given in Scheme 4.[17] 1,2-*trans*-Glycosyl acetates are available from methyl *α*- or *β*-thioglycopyranosides by treatment with acetic

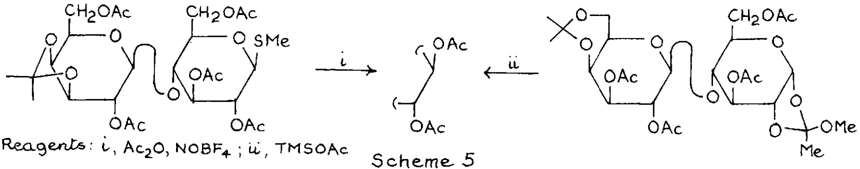


Reagents: i, RCO_2H, NIS

Scheme 4

anhydride and nitrosyl tetrafluoroborate[18] or by heating 1,2-*O*-methoxyethylidene derivatives of hexopyranoses in trimethylsilyl acetate.[19] As the examples in Scheme 5 show, ester and acetal protecting groups and glycosidic bonds are stable under both reaction conditions, as are benzyl ethers. High stereoselectivity was also attained in the novel synthesis of 2,3,4,6-tetra-*O*-acetyl-1-*O*-acyl-*β*-D-glucopyranoses (12) from D-glucose 2,3,4,6-tetraacetate (10) *via* the *α*-glucosyl trifluoroacetate (11) (Scheme 6).[20]

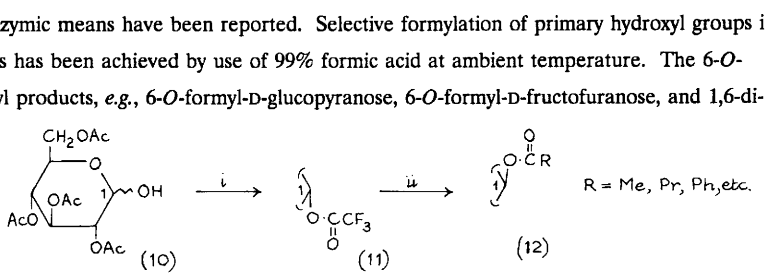
Benzoyl migration from O-4 to O-3 of a 2,6-dideoxy-D-arabino-hexopyranose derivative is referred to in Section 3 of this Chapter.



Reagents: i, Ac_2O, $NOBF_4$; ii, TMSOAc

Scheme 5

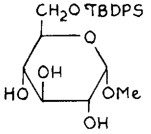
Various new partial and regioselective acylations and deacylations by chemical or by enzymic means have been reported. Selective formylation of primary hydroxyl groups in sugars has been achieved by use of 99% formic acid at ambient temperature. The 6-*O*-formyl products, *e.g.*, 6-*O*-formyl-D-glucopyranose, 6-*O*-formyl-D-fructofuranose, and 1,6-di-*O*-formyl-D-glucitol, were isolated *via* their peracetates or perbenzoates.[21]



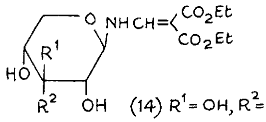
Reagents: i, $(CF_3CO)_2O$; ii, RCO_2H

Scheme 6

Considerable regioselectivity was observed in the partial acetylation of carbohydrate derivatives with acetic anhydride in the presence of $ZnCl_2$, due to initial complexation of the polyhydroxy systems with the divalent metal ions. From the trihydroxy-D-glucose derivative (13), for example, the 2-, 3-, and 4-monoacetates were formed in 41.5, 11, and 4%, respectively.[22] In a comparative study of the benzoylation of the *β*-D-xylo- and *β*-D-ribo-pyranosyl enamines (14) and (15), respectively, with limited amounts of benzoyl chloride all possible mono- and di-benzoates were obtained from the *xylo* starting compound, whereas the *ribo* isomer gave only the 2-mono-, 4-mono- and 2,4-di-esters.[23] The order of esterification of the eight hydroxyl groups of trehalose with pivaloyl chloride in pyridine was found to be HO-6,6′ > HO-2,2′ > HO-3,3′ > HO-4,4′, so that under the appropriate conditions, for example, the heptapivaloate (16) was obtainable in 61% yield.[24]

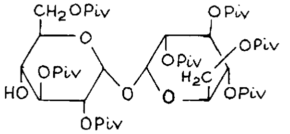


(13)



(14) $R^1 = OH, R^2 = H$

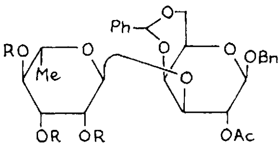
(15) $R^1 = H, R^2 = OH$



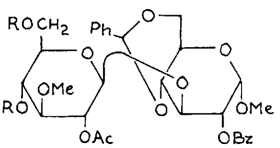
(16)

Allyl 4,6-*O*-benzylidene-*α*-D-glucopyranoside was selectively benzoylated at O-2 by use of l-benzoyloxy-l*H*-benzotriazole, a new benzoylating agent which was found easier to handle than *N*-benzoylimidazole.[25] The selective pivaloation of methyl *α*-L-rhamnoside at O-3 is mentioned in Chapter 12.

Lithium hydroperoxide has been shown to cause preferential deacetylation at O-2 of methyl hexopyranoside peracetates.[22] Selective hydrolysis at O-1 of either anomer of glucose pentaacetate has been effected with ethanolamine,[26] and per(monochloro)acetylated



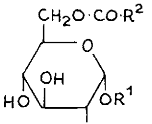
(17) R = Ac
(18) R = H



(19) R = Ac
(20) R = H

glycals were regioselectively deprotected at O-4 by hydrazine acetate (See also Chapter 13).[27]

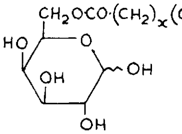
Interesting selectivity has been observed in the Zemplén deacetylation of certain disaccharide derivatives, in that acetyl groups at either O-2 or O-2′ proved quite stable under the standard conditions of this method (catalytic MeONa, ambient temperature). The monoacetates (18) and (20) were thus available in good yields from the tetraacetate (17) and the triacetate (19), respectively.[28]



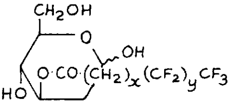
(21) $R^1 = Et$, $R^2 = C_7H_{15}$, $C_{13}H_{27}$, etc

(22) $R^1 = (CH_2)_7Me$, $R^2 = (CH_2)_6Me$, CH_2COMe, $(CH_2)_2CO_2Et$

A study of the deacetylation of methyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside under different conditions of alkaline and enzymatic hydrolysis indicated that the enzyme catalysed processes were far more regioselective than the chemical ones.[29] Several alkyl 6-*O*-acyl-α-D-glucopyranosides with surfactant properties have been synthesised in high yields by lipase mediated acylation. Compounds (21) were produced from ethyl α-D-glucopyranoside and free fatty acids in a solvent-free process on a multi-kg scale,[30] and ethyl esters as acyl donors in a cosolvent were used for the preparation of the octyl α-D-glucoside derivatives (22), some of which have liquid crystal properties.[31] The 6-*O*-fluoroacyl derivatives (23) of D-galactose and 3-*O*-fluoroacyl derivatives (24) of D-glucose, interesting, new, non-ionic



(23) $x = 2, y = 7$; $x = 10, y = 3$; $x = 10, y = 5$

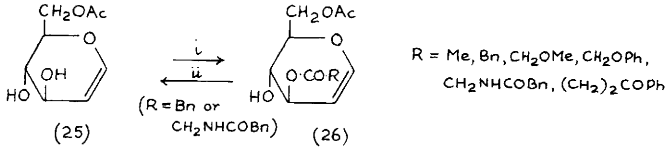


(24)

surfactants for biomedical use, were on the other hand obtained by conventional acylation of selectively protected precursors followed by deprotection.[32]

The regioselectivity of the butanoylation of methyl α-L- and α-D-rhamnoside and -fucoside has been examined. Lipase catalysed transesterification from 2,2,2-trifluoroethyl butanoate in THF gave the 4-monoesters in ≥70% yield from the L-glycosides, while the D-compounds were esterified mainly at O-2; chemical acylation with 1 mol equivalent of butanoyl chloride in pyridine was very unselective, giving mixtures containing not only all three mono- but also di- and tri-esters.[33,34]

Excellent yields were achieved in the selective acylation at O-3 of 6-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (25) by lipase mediated acyltransfer from several vinylesters. As shown in Scheme 7, the starting material (25) could be recovered in 80% yield from two of the products (26) by enzymatic hydrolysis.[35] Reports have been published on the lipase mediated selective synthesis of 2-functionalised 3-monoesters (27) of methyl 5-*O*-decyl-α-D-arabinofuranoside,[36] on the regioselective, lipase-catalysed acylation of methyl α- and β-D-arabino- and -xylo-pyranoside,[37] on the regioselective acylation and deacylation of 2′-deoxynucleoside derivatives by use of a *Pseudomonas fluorescens* lipase and a *Bacillus subtilis* protease, respectively,[38] and on the regioselective acylation of castanospermin with a variety of enzymes in pyridine.



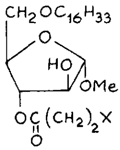
Reagents: i, Lipase (from *Pseudomonas fluorescence*), $RCO_2CH{=}CH_2$,$(MeOCH_2)_2$; ii, Penicillin acylase

Scheme 7

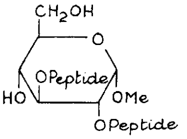
Fatty acid polyesters have been prepared by the well established method of transesterification in the presence of sodium metal from the peracetates of D-glucitol and trehalose,[40] of methyl glucoside, methyl galactoside, octyl glucoside, and stachyose,[41] and of sucrose. The process for formation and purification of sucrose polyesters has been optimised to furnish pure products in >99% yield.[42]

In the course of an investigation into the role of hydrophobicity in the bitter taste of certain peptides, a series of 2,3-di-*O*-aminoacylated derivatives (28) have been synthesised from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and Boc-protected di-, tri-, or tetra-peptides by DCC-CMAP promoted condensation and subsequent acetal hydrolysis,[43] and a similar condensation method was used in the synthesis of the Lipid A subunit analogues (30) from the known precursor (29) to acylate the free hydroxyl group of the ester substituent at C -3.[44,45]

A ^{1}H-n.m.r. spectroscopic method has been developed for the identification of partially acetylated sucroses. It is based on the finding that in the spectrum of sucrose octaacetate, recorded in benzene-d_6-pyridine-d_5 (1:1), the methyl groups are fully resolved

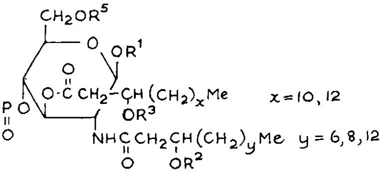


(27) $X = OH, CO_2H, COMe, (CH_2)_3Br$, *etc*



(28)

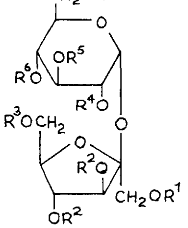
and can therefore be assigned with the help of known, partially acetylated derivatives peracylated with $(CD_3CO)_2O$.[46] By application of this technique the main product formed in the selective deacetylation of sucrose octaacetate with n-propylamine was readily identified as the hexaacetate (31).[47] A similar n.m.r.-based method has been established for the characterisation of partially benzoylated sucroses.[48]



(29) $R^1 = (CH_2)_2TMS, R^2 = CH_2O(CH_2)_2TMS, R^3 = H, R^4 = Ph, R^5 = TBDMS$

(30) $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CO(CH_2)_nMe$, $n = 0, 6, 8, 9, 11, 13$

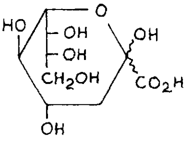
1.2 Isolation from Natural Sources.- β-D-Glucose 1-benzoate and smaller quantities of the 2- and 6-benzoates have been identified as components of cranberries and whortleberries.[49] The phenolic esters 6-*O*-caffeoyl-D-glucopyranose and 1,6-di-*O*-caffeoyl-β-D-glucopyranose were found in extracts of *Prunus serulata*, the diester being a new natural product.[50] Partially acylated sucroses have been isolated from a number of plant sources: 1,2′3′6′-, 1,3′,4′,6′-, and 2′,3′,4′,6′-tetra-, and 1,3′,6′-tri-*O*-acetyl-3-*O*-coumarylsucrose from the bark of *Prunus padus*,[51] 3′6-di-*O*-acetyl-2,3,4-tri-*O*-(3-methylpentanoyl)sucrose [together with 2,3,4-tri-*O*-(e-methylpentanoyl)glucose] from Chilean *Salpiglossis sinuata*,[52] 2,4,1′-tri-*O*-(3-methylbutanoyl)-3-*O*-(2-methylbutanoyl)sucrose and similar 2,3,4,1′-tetra- and 2,3,4-tri-esters from the glandular trichomes of tomato leaves,[53] and 6-*O*-decanoyl-3,4-di-*O*-isobutanoylsucrose (32) and the closely related triesters (33)-(35) from the wild potato



	R^1	R^2	R^3	R^4	R^5	R^6	R^7
(31)	Ac	H	Ac	Ac	Ac	Ac	Ac
(32)	H	H	H	H	$COPr^i$	$COPr^i$	COC_9H_{19}
(33)	H	H	H	H	$COPr^i$	$CO\text{-}CH(Me)Et$	COC_9H_{19}
(34)	H	H	H	H	$CO\text{-}CH(Me)Et$	$COPr^i$	COC_9H_{19}
(35)	H	H	H	H	$CO\text{-}CH(Me)Et$	$CO\text{-}CH(Me)Et$	COC_9H_{19}
(36)	Bn	Bn	Bn	Bn	All	$\underbrace{\qquad\qquad}_{>CHC_6H_4OMe(p)}$	

Solanum berthaultii. Compounds (32)-(35) have been synthesised from sucrose *via* the intermediate (36).[54]

A new sialic acid derivative, 9-*O*-acetyl-3-deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (9-*O*-acetyldeaminated neuraminic acid) (37) was a minor component of a new polysialoglycoprotein found in unfertilised salmon eggs.[55]



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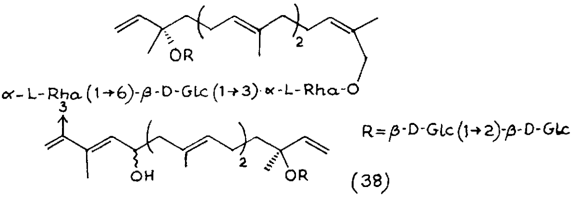
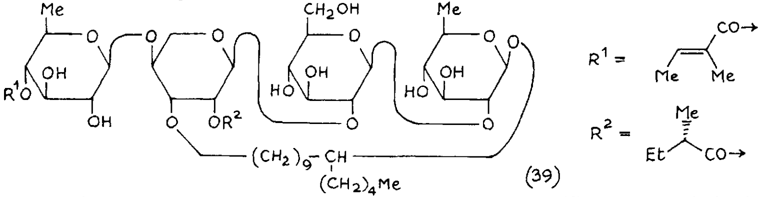


(38)

A new dimeric plant tannin named woodfruticosin A, which is active as an inhibitor of DNA topoisomerase II, has been isolated from a Nepalese medicinal plant.[56] Chelation with the ester groups at O-1 and O-6 of penta-*O*-galloyl-β-D-glucose has been suggested as the mode of its complexation with various aromatic substrates (*e.g.*, caffeine, daunomycin, methylene blue).[57] β-Pentagalloylglucose has also been reported to specifically inhibit two NADH reductases from *E. coli.*[58] Two-dimensional ^{1}H- and ^{13}C-n.m.r. studies of natural polyphenols, with emphasis on the ester linkages between the phenolic acids and glucose, have been reported.[59]



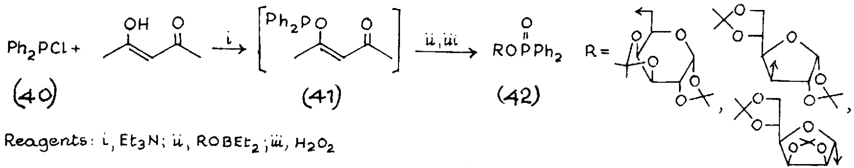
(39)

A number of new complex natural products with esterified sugar moieties have been described: Ternatin B-1, isolated from the flowers of *Clitoria ternatea* is an anthocyanin derivative bearing three side chains which contain six glucose units; of these, four are esterified at O-6 by E-*p*-coumaric acid and one by malonic acid.[60] The capsianosides, found in the red pepper *Capsicum annuum*, are dimeric ester-linked or monomeric diterpene glycosides, such as compound (38) which inhibits angiotensin-converting enzymes.[61] An ether extract from the roots of *Convolvulus scammonia* contained the resin glycoside scammonin I (39); this linear tetrasaccharide carried a tigloyl group at O-4'''', an isobutanoyl group at O-2''', and at O-3''' a jalapinolyl [(11*S*)-11-hydroxyhexadecanoyl] group which is β-glycosidically linked to the reducing end unit by its hydroxyl group.[62]

2 Phosphates and Related Esters

Recommended values for the thermodynamic and transport properties of pentoses, hexoses, and their phosphates, in both the condensed and aqueous phase, have been presented and critically evaluated.[63]

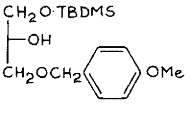
A comprehensive paper has been published on the self condensation of glycolaldehyde phosphate and the condensation of glycolaldehyde phosphate - formaldehyde mixtures in aqueous NaOH. The major products (*ca.* 50% of the total) were DL-allose 2,4,6-triphosphate and DL-ribose 2,4-phosphate, respectively, indicating that *erythro*-aldolisation predominates.[64]



Reagents: i, Et_3N; ii, $ROBEt_2$; iii, H_2O_2

Scheme 8

In an efficient new one-pot phosphorylation method, *O*-diethylboryl derivatives of carbohydrates were treated sequentially with phosphine enolate (41), prepared *in situ* from acetyl acetone and diphenylchlorophosphine (40), and hydrogen peroxide, to give sugar diphenylphosphinates (42), as illustrated in Scheme 8. Use of diethylchlorophosphite in place of chlorophosphine (40) furnished sugar diethylphosphates.[65]



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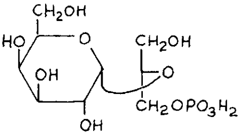
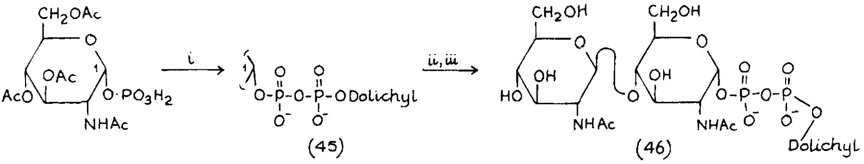


(44)

The repeating unit (44) of the capsular antigen of *Neisseria meningitidis* serogroup H was synthesised by α-galactosylation of the D-mannitol-derived, chiral glycerol derivative (43) with perbenzylgalactosyl chloride, followed by oxidative removal of the *p*-methoxybenzyl group, phosphorylation by use of phosphite methodology, debenzylation and desilylation.[66]

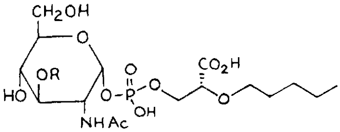


Reagents: i, Dolichyl phosphoryl dichloride; ii, NaOMe,MeOH; iii, UDP-NAG, porcine liver microsomal preparation

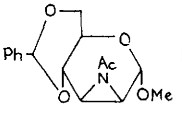
Scheme 9

The synthesis of the biosynthetic chitobiosyl donor (46) by a mixed chemical/enzymic process involved attachment of 3,4,6-tri-*O*-acetyl-2-deoxy-2-acetamido-α-D-glucose to dolichol *via* a pyrophosphate bridge by chemical means as shown in Scheme 9. The monosaccharide pyrophosphate (45) then served, after deprotection, in an enzymic formation of the disaccharide (46).[67] Derivatives (47) of 2-deoxy-2-acetamido-α-D-glucose 1-phosphate were prepared as simple analogues of moenomycin, a complex pentasaccharide which inhibits bacterial cell wall transglycosidation.[68]

Examples of phosphorylated Lipid A subunit analogues have been mentioned above (refs. 40 and 40a) and a further one, an acylated thyminyl-D-glucosamine, is referred to in Part 4 of this Chapter.



(47) $R = CONH_2$ or $[CH(Me)CONH]_2CH\begin{smallmatrix}CO_2H\\ CH_2CH_2Me\end{smallmatrix}$



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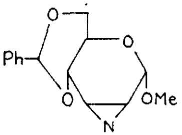

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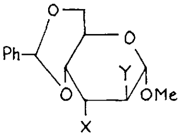
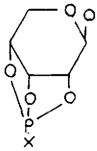


(50) $X = S{\cdot}\overset{\overset{S}{\|}}{P}(OR)_2, Y = NHAc$

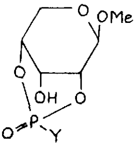
(51) $X = NHAc, Y = S{\cdot}\underset{\underset{S}{\|}}{P}(OR)_2$

$R = Bu^t$ or $RR = {>}CMe_2$

The ring opening of aziridines (48) and (49) with *O*,*O*-dialkylphosphorodithioic acids gave in almost quantitative, stereo- and regio-specific reactions the amino sugars (50) and (51), respectively, carrying dithiophosphate groups vicinal to the amino functions.[69] Phosphorylation of methyl β-D-ribopyranoside with $P(NMe_2)_3$ in dioxane gave, in 90% yield, the bicyclic phosphite derivative (52) which was further transformed by exposure to sulphur or selenium to the bicyclic thio- and seleno-phosphates (53) and (54), respectively;



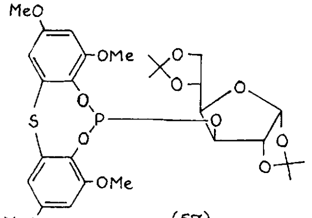
(52) X = –
(53) X = S
(54) X = Se



(55) Y = OH
(56) Y = H

oxidation by H_2O_2 furnished the cyclic phosphate (55), and hydrolysis in aqueous dioxane gave the cyclic phosphonate (56).[70]

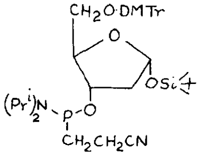
The conversion of glycerophosphoinositols to phosphoinositol has been optimised and the reaction has been exploited for the preparation of D-*myo*-inositol-1,4-bis- and 1,4,5-tris-phosphate in mg quantities from readily available preparations of mixed phosphoinositides.[71] The pyridinium salt of the 1,4,5-trisphosphate, on treatment with DCC in aqueous pyridine, gave the 1,2-cyclic 4,5-trisphosphate.[72]



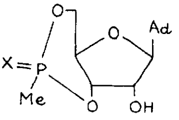
(57)

The synthesis and characterisation of compound (57), the first carbohydrate derivative of a dibenzodioxathiaphosphocin, has been reported; preliminary studies of its use as a ligand in the Au(I)-catalyzed reaction of benzaldehyde with ethyl cyanoacetate are included.[73] Rhodium complexes with chiral carbohydrate phosphinite ligands are referred to in Chapter 17.

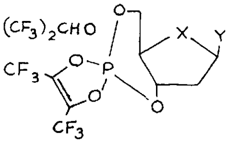
The phosphorylated 2-deoxy-D-*erythro*-pentofuranose derivative (58) has been prepared in three steps from the free sugar for use as a building block in the construction, by automated methods, of oligodeoxynucleotides with apurinic and/or apyrimidinic sites.[74] Facile syntheses of adenosine 3′,5′-cyclic methylphosphonate (59) and



(58)



(59) X = O
(60) X = S



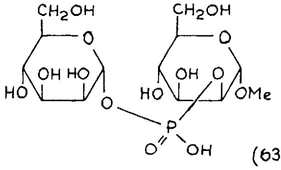
(61) X = O, Y = H or thyminyl
(62) X = CH_2, Y = H

methylphosphonothioate (60) have been published, which involve treatment of a 2′-protected adenosine with *O,O*-bis(1-benzotriazolyl)methylphosphonate (or the corresponding thioate) under mild conditions, followed by deprotection.[75] Various nucleoside cyclic P(V) derivatives such as compounds (61) and (62) have been prepared as models for the proposed activated state of cyclic adenosine 3′,5′-monophosphate.[76,77]

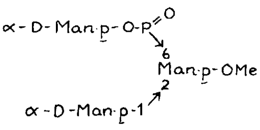
The use of *N*-morpholino-*O,O*-bis[(6-trifluoromethyl)benzotriazolyl] phosphate and 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one as phosphorylating and phosphitylating agents, respectively, and the activation of nucleoside 3′-phosphonates by tris(2,4,6-tribromophenoxy)dichlorophosphorane are covered in Chapter 20, as is the synthesis of cytidine diphosphate 3,6-dideoxyhexoses (synthetic nucleosides).

L-Ascorbate 2-triphosphate has been obtained in 86% yield by phosphorylation of L-ascorbic acid with sodium trimetaphosphate. The phosphorylated product appears to be much more stable towards oxidation by oxygen than is the parent compound.[78]

Several papers by Kochetkov's group have appeared on the application of the hydrogenphosphonate approach to the synthesis of glycosyl phosphosugars linked through primary or secondary hydroxyl groups (see Vol.20, p.77, ref.58). Methyl 2-*O*-(α-mannopyranosylphospho)-α-D-mannopyranoside (63) and its 3-O- and 4-O-isomers, for example, were obtained by condensation of suitable monohydroxy derivatives of methyl α-D-mannopyranoside with tetra-*O*-benzyl-α-D-mannopyranosyl H phosphonate, initiated by pivaloyl chloride, and subsequent iodine oxidation and deprotection.[79] In analogous manner, methyl 2-*O*- and 4-*O*-(α-D-mannopyranosylphospho)-β-D-galactopyranoside,[80] 6-*O*-(α-D-glucopyranosylphospho)- and 6-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosylphospho)-α-D-mannopyranoside were produced,[81] as well as the related trisaccharide (64) which constitutes the immunodominant fragment of the phosphomannan from *Kloeckera brevis*.[82,83]

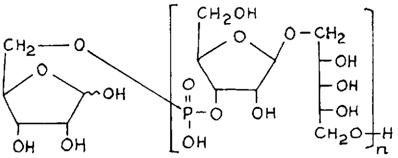


(63)



(64)

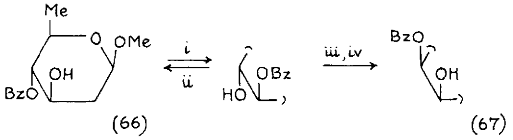
Full details have become available on the synthesis of oligomeric fragments (65) of the *Haemophilus influenza* type 6 capsular polysaccharide (see Vol.22, p.30 and p.80). The presence of a reducing ribose unit allowed coupling to an immunogenic protein by reductive amination.[84] The solid-phase synthesis of a related, aminohexosyl-containing ribosyl ribitolphosphate hexamer has been reported.[85]



(65) n = 1-5

3 Sulphonates

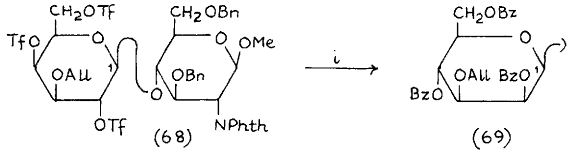
Sugar triflates have been employed as intermediate in various multistep syntheses. As shown in Scheme 10, the conversion of methyl 4-*O*-benzoyl-2,6-dideoxy-β-D-*arabino*-pyranoside (66) to its *lyxo*-isomer (67) (required for model studies relating to the synthesis of mithramycin, see Chapter 3) involved a 4→3 benzoyl migration and a triflate displacement with neighbouring group participation.[86] The triple triflate displacement (with inversions at the secondary centres) outlined in Scheme 11 was a crucial step in the synthesis of the disaccharide (69) from monosaccharide precursors *via* the lactosamine intermediate (68). This procedure avoided the need for direct 1,2-*cis*-glycoside formation.[87] Similar triflate substitutions have been used to effect inversion at C-4 of (1→3)-linked disaccharides.[88]



Reagents: i, Et$_3$N; ii, heat; iii, Tf$_2$O, Py; iv, H$_2$O

Scheme 10

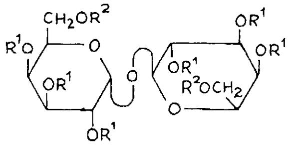
The cord factor analogues 6,6′-di-*O*-mycolyl- and 6,6′-di-*O*-corynomycolyl-α-D-glucopyranosyl α-D-galactopyranosides (71) and (72), respectively, were obtained from the ditriflate (70) with potassium mycolate or potassium corynomycolate.[89] In an attempt to prepare 3-deoxyfucose by Bu$_3$SnH- reduction of a 3-iodide [*e.g.*, compound (75)], the triflate



Reagent: i, Bu$_4$NOBz

Scheme 11

(74) was prepared from methyl α-D-fucoside by standard methods (Scheme 12). All efforts to effect a nucleophilic displacement by iodide [(74)→(75)] failed, however. (See Chapter 12 for a successful deoxygenation route).[90]

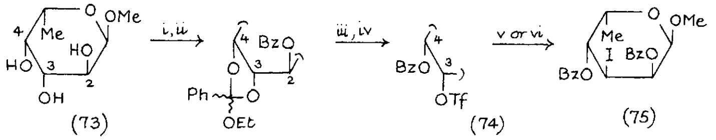


(70) R^1=Bn, R^2=Tf

(71) R^1= H, R^2= mycolyl

(72) R^1 = H, R^2= corynomycolyl

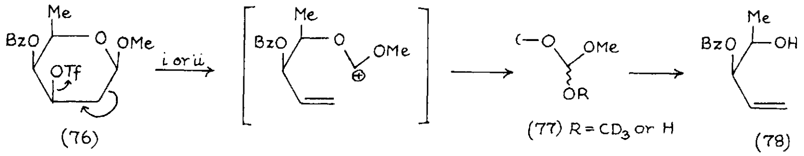
The first Grob fragmentation of a sugar triflate has been observed and is shown in Scheme 13. On heating methyl 2,6-dideoxy-3-*O*-triflyl-β-D-*lyxo*-pyranoside (76) in toluene-pyridine-water, the triflyloxy group was eliminated with concomitant rupture of the C-1 - C-2 bond to give the disubstituted pent-l-ene (78). Participation of solvent in the ring-opening step was excluded, since on replacement of water by CD_3OD the diastereomeric orthoesters (77, R=CD_3) were isolated.[91]



Reagents: i, PhC(OEt)$_3$, H$^+$; ii, BzCl, Py; iii, HOAc, H_2O; iv, Tf_2O, Py; v, NaI; vi, ZnI_2, DEAD, PPh_3

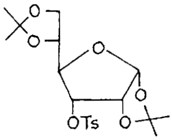
Scheme 12

The conversion of epoxy triflates to cyclic sulphates is covered in Part 4 of this Chapter. Sugar tosylates, *e.g.* compounds (79) and (80), were hydrolysed to the parent alcohols in 65-84% yield by photolysis at 330nm in water-acetonitrile in the presence of hydrazine and a sensitiser (4,8-dimethoxynaphthyl propionic acid).[92]



Reagents; i, Toluene, Py, H_2O; ii, Toluene, Py, CD_3OH

Scheme 13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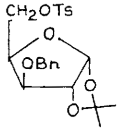
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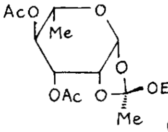
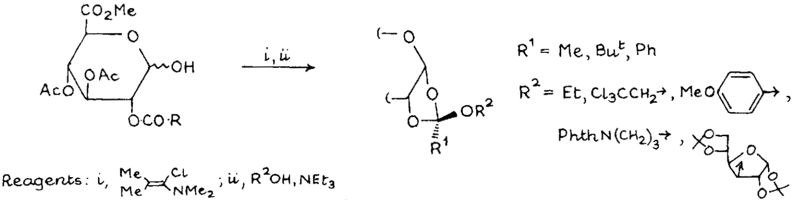

(81)

4 Other Esters

On exposure to ethanolic triethylamine 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide afforded the orthoester (81) rather than the 1,4-anhydride as previously reported (F. Micheel and H. Micheel, *Ber.*, 1930, *63*, 2862).[93] Carbohydrate 1,2-orthoesters are obtained rapidly and efficiently from 2-*O*-acetylated precursors by use of 1-chloro-2,*N*,*N*-trimethylpropenylamine. Examples are given in Scheme 14.[94]

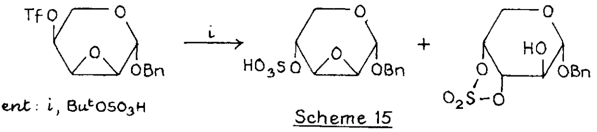


Scheme 14

In the course of an investigation into the effect of pressure on glycosylation a variety of glycosyl halides were treated in dichloromethane at 15 kbar with primary, secondary and tertiary alcohols (including, for example, cholesterol and diacetoneglucose) in the presence of a base and either AgOTf or Et_4NBr as catalyst. It was concluded that, on the whole, high pressure favours orthoester formation.[95,96]

The autocatalytic glycosidation of orthoesters with 2,3-dihydroxy-1,4-naphthaquinone is covered in Chapter 3, and the use of 1,2-orthoesters in the synthesis of 1,2-*trans*-glycosyl esters is referred to in Part 1.1 of this Chapter (ref 16).

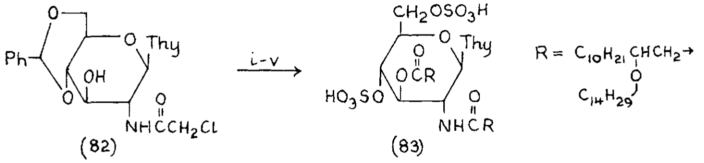
The 2-, 3-, 4-, and 6-monosulphates of methyl α-D-galactopyranoside [97] and the 2- and 3-monosulphates of methyl α- and β-D-glucopyranosiduronic acid[98] have been prepared by standard methods. Sulphates or mixtures of sulphates and cyclic sulphates were produced when benzyl 2,3-anhydro-4-*O*-triflylpentopyranosides were treated with t-$BuOSO_3H$. An example is presented in Scheme 15.[99] The conversion of cyclic sulphates to epoxides is covered in Chapter 5.



Reagent: i, Bu^tOSO_3H

Scheme 15

The disulphated Lipid A subunit analogue (83) was obtained in five steps from the selectively protected derivative (82) of 2-amino-2-deoxy-D-glucose as outlined in Scheme 16; a very similar approach was also used to prepare the 6-hydroxy-4-phosphate corresponding to the 4,6-disulphate (83).[100]



Reagents: i, $(NH_2)_2CS$, $(Pr^i)_2NEt$, THF; ii, RCO_2H, DCC, DMAP; iii, HOAc, H_2O; iv, Me_3NSO_3, DMF; v, TFA

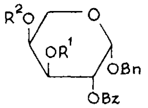
Scheme 16

The synthesis of a linear acidic glycan fragment of keratan I, the trisulphated tetrose (84), from monosaccharide building blocks has been reported. The sulphate groups were introduced simultaneously, by use of $Et_3N\text{-}SO_3$, in the last reaction step before final deprotection.[101] Sulphated 2-*O*-α-D-fucopyranosyl α-DL-fucopyranosides and polysulphated bis-lactobionic acid amide derivatives are referred to in Chapters 3 and 4 respectively.

β-D-Glc*p*NAc6SO$_3$-(1→3)-β-D-Gal*p*6SO$_3$-(1→4)-β-D-Glc*p*NAc6SO$_3$-(1→3)β-D-Gal

(84)

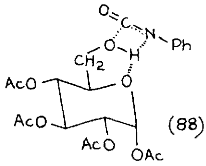
Nitration of benzyl 2-*O*-benzoyl-arabinopyranoside (85) with fuming nitric acid in acetic anhydride gave, as the main product, the dinitrate (86), accompanied by minor quantities of the mononitrate (87). Denitration of compound (86) to give the monoester (87) in reasonable yield was achieved by means of sodium iodide in acetone.[102] Azidonitration of D-glycal triacetates was the first step in a synthesis of *C*-glycosyl derivatives of 2-amino-2-deoxy sugars which is covered in Chapter 9. β-D-Glucopyranoside tetranitrate and β-cellobiose octanitrate are referred to in Chapter 21.



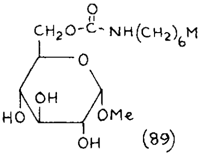
(85) $R^1 = R^2 = H$

(86) $R^1 = R^2 = NO_2$

(87) $R^1 = H, R^2 = NO_2$



(88)



(89)

A mechanistic investigation has been undertaken of the reaction of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside with phenyl isocyanate. The reactivity of the hydroxy sugar appears to be qualitatively similar to that of simple alcohols, and a concerted bond reorganisation *via* a highly ordered cyclic transition state (88), possibly involving hydrogen bonding to the ring oxygen atom, is proposed.[103]

The 3,5-dimethylphenylcarbamates of several cello- and malto-oligosaccharides have been assessed as chiral stationary phases for h.p.l.c. resolution of racemates.[104] 6-*N*-Alkylcarbamate derivatives of D-glucose, D-galactose, and methyl α-D-glucoside [*e.g.*, compound (89)] were synthesised in good yields by reaction of alkyl isocyanates with 1.5 molar equivalents of sugar. Similarly, *N*-glycosyl *N'*-alkyl-ureas and thioureas were obtained from glycosylamines (see Chapter 10). These sugar derivatives are non-ionic detergents.[105]

M.S. studies on carbohydrate 1,2-orthocarbonates are referred to in Chapter 22.

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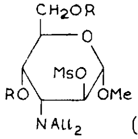
8

Halogeno-sugars

1 Fluoro-sugars

The synthesis of fluorinated carbohydrates by selective fluorination has been reviewed (in Chinese),[1] and a review on the reactions of carbohydrates in anhydrous liquid HF is noted in Chapter 1. The selective synthesis of β-glycosyl fluorides has been achieved by heating acylated glycosyl bromides with $Et_3N.3HF$ in CCl_4.[2]

When the 2-*O*-mesylate (1) was treated with $Et_3N.3HF$ in CH_3CN containing additional Et_3N (effectively giving the reagent $Et_3N.2HF$), the 3-deoxy-3-fluoroglucosamine derivative (2) was the predominant product with the reaction going *via* an aziridinium ion intermediate. Similarly, the trimesylate (3), under the same conditions, afforded the 3,6-difluoro compound (4), whereas with $Et_3N.3HF$ the predominant product was the monofluorinated compound (5).[3,4] Both the 4-deoxy-4-fluoro- and 4,6-dideoxy-4,6-difluoro-derivatives of 2-acetamido-2-deoxy-D-galactose have been prepared as well as the 4,4-difluoro-analogue as potential modifiers of tumor cell surface glycoconjugates.[5] The syntheses of methyl 2-*O*-(6-deoxy-6-fluoro-α-D-mannopyranosyl)-α-D-mannopyranoside and methyl 6-deoxy-6-fluoro-2-*O*-α-D-mannopyranosyl-α-D-mannopyranoside have been described as well as that of 4-nitrophenyl 4-*O*-acetyl-6-deoxy-6-fluoro-α-D-mannopyranoside.[6] When the 2-bromo-2-deoxy-aldonolactones (6) and (7) were treated with KF in acetone, the corresponding 2,3-epoxy-derivatives were obtained rather than fluorinated compounds, but in the presence of $Et_3N.3HF$ the epoxides afforded 2-deoxy-2-fluoro-aldonolactones (8) and (9), respectively. These were reduced to give 2-deoxy-2-fluoro-D-xylose and -arabinose.[7]



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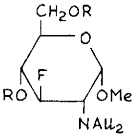
(3) R = Ms



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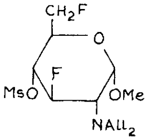
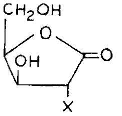


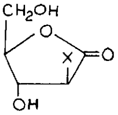
(4)

Studies on the relatively stable, covalent 2-deoxy-2-fluoro-α-D-glucopyranosyl enzyme intermediate produced by reaction of a β-glucosidase with 2-deoxy-2-fluoro-β-D-glucopyranosyl fluoride have demonstrated that the sugar is attached to the enzyme *via* a glutamate residue carboxylate group. Addition of large amounts of a second sugar causes generation of a disaccharide and reactivation of the enzyme as the covalently bound intermediate is removed.[8]

Some deoxyfluoro-D-glucose analogues have been incorporated into glycogen by using rabbit muscle glycogen phosphorylase on the deoxyfluoro-α-D-glucopyranosyl phosphates. It was found that introduction of 4-deoxy-4-fluoro-D-glucose units terminated after the introduction of one unit per non-reducing terminus, and this 4-deoxy-4-fluoro-glycogen acted as an inhibitor of glycogen phosphorylase.[9] D-Glucofuranurono-6,3-lactone has been converted into the 5-azido-6-fluoro derivative (10), from which 1,6-dideoxy-6-fluoro-nojirimycin (11) was obtained.[10] The synthesis of methyl 6-*O*-(*β*-D-galactopyranosyl)-4-deoxy-2-deuterio-4-fluoro-*β*-D-galactopyranoside has been described and the compound has been used to study conformational changes during antibody-antigen complex formation,[11] and four 3,4-dideoxy-3-fluorohexoses (D-lyxo, L-ribo, D-arabino and L-xylo) have been prepared from chiral non-carbohydrate starting materials.[12]



(6) X = Br
(8) X = F



(7) X = Br
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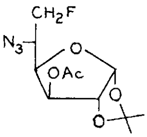
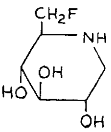


(10)



(11)

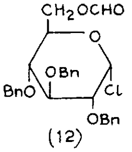
Molecular orbital calculations have been carried out on 2-fluoro- and 2-chloro-tetrahydropyrans as models for examining the anomeric effect in glycosyl halides. The calculated population of the axial conformer decreased as the solvent polarity increased, which indicated a consequent decrease in the anomeric effect.[13] The synthesis of a series of 2-(perfluoroalkyl) ethyl glycosides is mentioned in Chapter 3, and some 3'-fluorinated ribonucleosides are covered in Chapter 20. The syntheses of 2-fluoro-L-daunosamine and 2-fluoro-D-ristosamine are discussed in Chapter 9, while 2'-fluorocarminomycin is described in Chapter 19, and some fluorinated 2-deoxy KDO analogues are covered in Chapter 16.

Procedures for making [^{18}F]-2-deoxy-2-fluoro-D-glucose have been reviewed with emphasis on requirements for routine production.[14] Other reports have also described automated procedures for the same synthesis,[15,16,17] and a further report describes the use of [^{18}F] bound on a quaternary pyridinium anion exchange resin.[18] Radiolabelled 4-deoxy-4-fluoro-D-glucose has been synthesized and used to study its metabolism.[19]

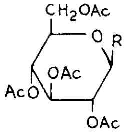
2 Chloro-, Bromo-, and Iodo-sugars

A simplified one-pot protocol for the preparation of acetobromo sugars directly from the unprotected reducing sugars has been outlined.[20] Use of dichloromethyl methyl ether in the presence of $ZnCl_2$ or $BF_3.OEt_2$ has allowed efficient syntheses of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-α and β-D-galactopyranosyl chloride, respectively, from an anomeric mixture of the glycosyl acetates.[21] Similarly, protected 2-(trimethylsilyl)ethyl glycosides and anomerically unprotected sugars are converted into glycosyl chlorides with dichloromethyl methyl ether and $ZnCl_2$ or $SnCl_4$, and these conditions are suitable for use in di- and tri-saccharides.[22,23] However, when 2-(trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside was treated under the above conditions the 6-*O*-formyl glycosyl chloride (12) was produced.[24]

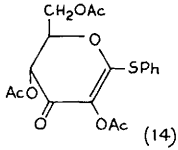
The photochemical bromination of methyl (2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl fluoride)uronate afforded the 5-bromo derivative, which, after Bu_3SnH reduction, gave methyl (2,3,4-tri-*O*-acetyl-β-L-idopyranosyl fluoride)uronate thus effecting overall inversion at C-5.[25] The effects of *S*-oxidation on the radical substitution of thioglycoside derivatives has been studied. While photobromination of thioglycoside (13) furnishes the unsaturated derivative (14), now it has been shown that the sulfoxide (15) under these conditions generates acetobromoglucose, whereas the sulfone (16) gave a mixture of the C-1 and C-5 brominated compounds (17) and (18).[26] Photobromination of the 3,5-*O*-benzylidene derivative (19) has generated the 6-bromo-6-deoxy-L-idofuranose compound (20).[27]



(12)



(13) R = SPh
(15) R = SOPh
(16) R = SO_2Ph



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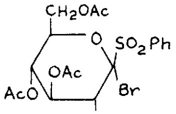

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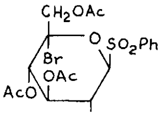

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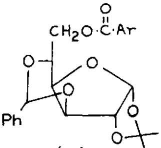

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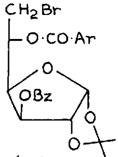
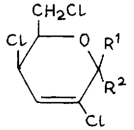


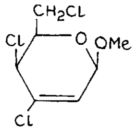
(20)

Specific halogenation reactions (Ph_3P/CX_4/pyr, X=Cl, Br) of derivatives of D-glucose and sucrose have afforded methyl 4,6-*O*-benzylidene-2-bromo- or (chloro-)2-deoxy-α-D-mannopyranoside from methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-β-D-allopyanoside or methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-β-D-glucopyranoside from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside. Methyl α-D-glucopyranoside gave the unsaturated derivative (21) whereas methyl β-D-glucopyranoside afforded a mixture of the chlorinated derivatives (22) and (23); while 4,6-*O*-isopropylidene-sucrose afforded mainly the tetrachloro compound (24) after acetylation.[28] The iodide (25) has been obtained from methyl 4-*O*-

acetyl-2-*O*-benzoyl-α-L-fucopyranoside ($Ph_3P/DEAD/ZnI_2$),[29] a *C*-4-chlorodeoxy derivative of trehalose, was reported,[30] and methyl β-cellobioside has been converted into 3-bromo-3-deoxy derivatives with the *allo*-configuration.[31] The use of NIS glycosylations in the construction of kijanimicin oligosaccharides is mentioned in Chapter 4, and further studies on the *trans*-iodoalkoxylation of some glycals with NIS and an alcohol are covered in Chapter 3.



(21) $R^1 = H, R^2 = OMe$
(23) $R^1 = OMe, R^2 = H$



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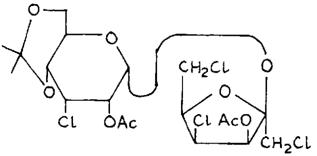

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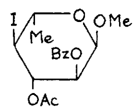

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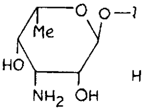
9
Amino-sugars

1 Natural Products

The 4-*epi*-mycosamine unit (1)[1] and the branched-chain 4-*epi*-vancosamine unit (2) (of assumed L-configuration)[2] have been found as glycosidic components of antibiotics.

2 Synthesis

The protected *N*-(1-deoxy-D-fructopyranos-1-yl)valine (3) was obtained from D-glucose and valine by Amadori rearrangement; the dodecapeptide terminal partial sequence of the β-chains of HbA_{1c} haemoglobin was then constructed from this by peptide chain extension and deprotection.[3]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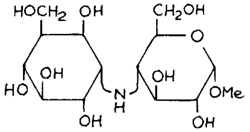
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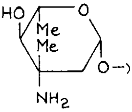
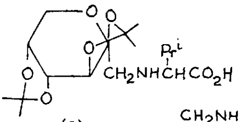
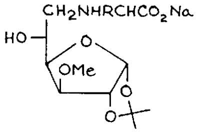
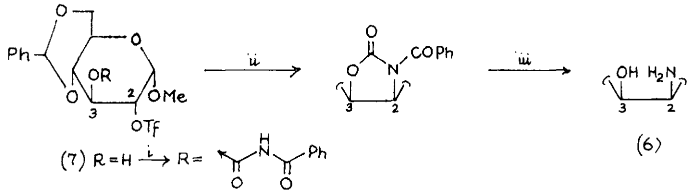

(2)


(3)


(5) R = H, Me, Pr^i,  , etc.

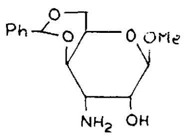
New synthetic routes to amino-sugars and sugar amino-acids from epoxy- and aziridino-pyranoses have been covered in a review (with 33 refs.).[4] Details have been published on the synthesis and cation binding abilities of aza-15-crown-5 and aza-18-crown-6 derivatives incorporating an amino-sugar moiety (*cf.* Vol. 23, p.95).[5] The reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-D-allopyranoside with 3-aminopropyl-silica, followed by acid catalysed hydrolytic debenzylidenation, was used in an attempt to prepare a chromatographic material with a hydrophilic surface; although the product was reasonably stable at high pH, it was not considered sufficiently inert. An alternative product formed by reductive amination ($NaBH_3CN$) of glucose with 3-aminopropyl-silica was even less stable.[6] The synthesis of a 6-*O*-(2-amino-2-deoxy-α-D-altropyranosyl)-D-galactose derivative, which is further detailed in Chapter 10, involved iodo-glycosidation of a D-allal derivative, followed by formation and opening of 2,3-epoxide with azide.[7] The 4-amino-*carba*-disaccharide derivative (4) was synthesized following coupling of an amino-cyclitol derivative (see Chapter 18) with 1,6:3,4-dianhydro-β-D-galactopyranose.[8] The synthesis of methyl oligobiosaminide, an *N*-linked pseudodisaccharide, and several deoxy-sugar analogues is discussed in Chapter 12. 6-Deoxy-D-gluco-6-ylaminocarboxylates (5), synthesized by reaction of the corresponding 5,6-epoxides with amino-acid salts, displayed unusually strong binding of alkali metal ions[9] and bound transition metals ions *via* hydrogen-bonded dimers.[10] 6-Amino-6-deoxy-derivatives of ascorbic and isoascorbic acids were prepared by way of nucleophilic substitutions at C-6 or opening of a 5,6-epoxide derivative of isoascorbic acid, respectively.[11]

The scope of a novel approach to the synthesis of amino-sugars, involving intramolecular displacement of a triflate by a benzoylcarbamate group, has been investigated. 1,2- and 1,3-Diol monotriflates were *N*-benzoylcarbamoylated, then treated with sodium hydride. The 2-amino-2-deoxy-α-D-mannoside (6) was thus obtained from the D-glucoside (7) (Scheme 1), and the 3-amino-3-deoxy-D-guloside (8) was similarly obtained from methyl 4,6-*O*-benzylidene-β-D-galactoside. The 4-amino-4-deoxy-D-taloside (9) resulted from application of the procedure to the 2-unsubstituted α-D-mannoside 4-triflate (10) (Scheme 2). The reaction was highly substrate dependent, however, since in a number of other cases reaction resulted from displacement by the carbonyl oxygen of the carbamate moiety rather than by its nitrogen atom.[12]

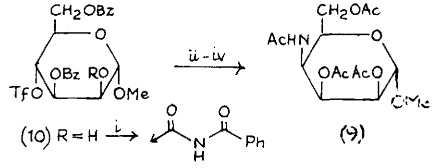


Reagents: i, PhCO·NCO; ii, NaH; iii, ⁻OH

Scheme 1



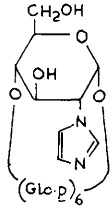
(8)



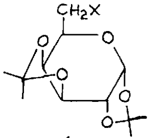
Reagents: i, PhCO·NCO; ii, NaH; iii, ⁻OH; iv, Ac_2O, Et_3N

Scheme 2

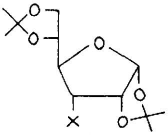
A number of other amino-sugar syntheses have involved intermolecular displacement of sugar sulphonyloxy groups with azide or amine nucleophiles. 2-Deoxy-2-imidazolyl-β-cyclodextrin (11), which has the imidazolyl group on the open face of the cyclodextrin, was obtained in 12% yield from the corresponding 2-monotosylate *via in situ* formation and opening of a 2,3-epoxide. As a chymotrypsin enzyme model, it was 70-fold more active as a catalyst of *p*-nitrophenylacetate hydrolysis than 6-deoxy-6-imidazolyl-β-cyclodextrin with the imidazolyl group on the closed face.[13] The quaternary ammonium salts (12) and (13) were synthesized in 33-70% yields by reactions of the sugar triflates with the corresponding tertiary amines in DMF.[14]



(11)



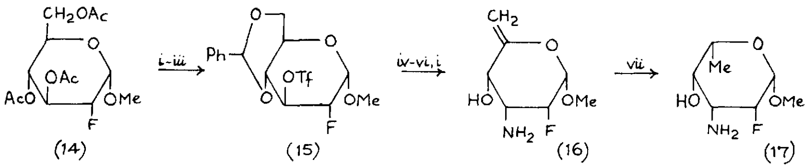
(12)



(13)

X = $\overset{+}{N}Me_3$, $\overset{+}{N}Et_3$, $\overset{+}{N}Me_2Ph$,

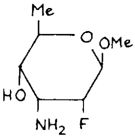
6-Bis(2-chloroethyl)amino-6-deoxy-D-galactose hydrochloride was synthesised *via* the product of reaction of 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose with bis(2-hydroxyethyl)amine, and shown to have good antitumour activity with reduced bone marrow toxicity compared to related materials.[15] The methyl glycoside (17) of (R)-2-fluoro-L-daunosamine was synthesized from the 2-deoxy-2-fluoro-α-D-glucoside (14), key steps being the introduction of the amino-function by reaction of 3-triflate (15) with lithium azide, and formation and stereoselective reduction (H_2-Pd/$BaSO_4$) of 5,6-ene (16) (Scheme 3). The methyl glycoside (18) of (R)-2-fluoro-D-ristosamine was synthesized by an identical sequence from the β-anomer of (14).[16]

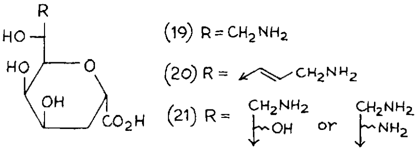


Reagents: i, NaOMe, MeOH; ii, PhCH(OMe)$_2$, H$^+$; iii, Tf_2O, Py; iv, LiN_3, DMF; v, NBS, $BaCO_3$; vi, DBU; vii, Pd(OH)$_2$/$BaSO_4$, H_2

Scheme 3

Amino-analogues (19) - (21) of the potent CMP-KDO synthetase inhibitor 2,6-anhydro-3-deoxy-D-*glycero*-D-*talo*-octonic acid have been synthesized and their inhibitory properties determined. An aldehyde precursor was converted into the 8-amino-analogue (19) by reductive amination ($NaBH_3CN$-NH_4OAc) or into the allylic amine (20) by Wittig chain extension ($Ph_3PCHCHO$), reduction, and amination (i,LiN_3-Ph_3P-CBr_4; ii,Ph_3P then H_2O). The epimeric mixtures (21) were synthesized following reaction of sugar sulphonate derivatives with azide ion. These and other analogues are detailed further in Chapter 16.[17]

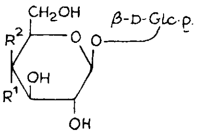

(18)



(19) R = CH_2NH_2

(20) R =

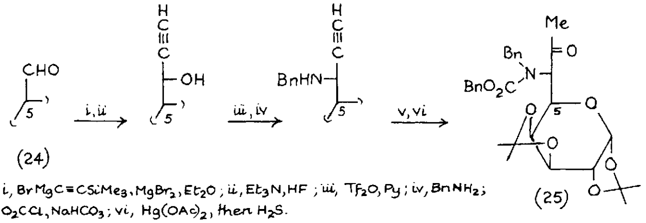
(21) R =



(22) $R^1 = NH_2, R^2 = H$

(23) $R^1 = H, R^2 = NH_2$

4-Amino-4-deoxy-β,β-trehalose (22) was synthesized from a trehalose heptapivalate with a free 4-hydroxy-group, by a double inversion sequence (i,SO_2Cl_2;ii,NaN_3-HMPA). Its 4-epimer (23) was obtained from the same hepta-ester by mesylation and azide displacement;[18] for related trehalosamine syntheses see ref. 32. The lincosamine precursor (25) was constructed by chain extension of the galactodialdose derivative (24), the amino-function being introduced by sulphonate displacement (Scheme 4).[19] The 2-amino-2,3,5-trideoxy-D-*erythro* and -*threo*-pentonic acids, (27) and (29),

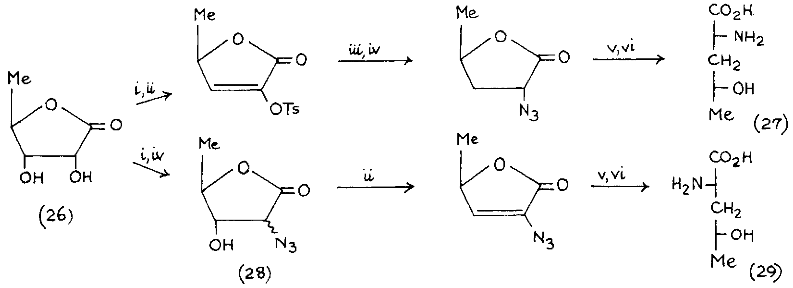


(24)

(25)

Reagents: i, $BrMgC{\equiv}CSiMe_3$, $MgBr_2$, Et_2O; ii, Et_3N, HF; iii, Tf_2O, Py; iv, $BnNH_2$; v, BnO_2CCl, $NaHCO_3$; vi, $Hg(OAc)_2$, then H_2S.

Scheme 4



(26)

(28)

(27)

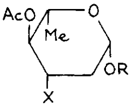
(29)

Reagents: i, TsCl, Py; ii, Ac_2O, Py; iii, H_2, Pd/C; iv, NaN_3, DMF; v, H_2, Raney Ni; vi, Resin (H^+form), with NH_4OH eluant.

Scheme 5

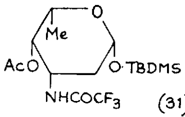
respectively, were synthesized from D-ribonolactone *via* its known 5-deoxy-analogue (26) (Scheme 5). The epimeric azido-lactone intermediates (28) were chromatographically separable, and were converted into 2-amino-2,5-dideoxy-D-ribonic and -arabinonic acid 1,4-lactones upon reduction.[20]

Amino-sugars are frequently obtained from sugar azide precursors. A reagent system (KSAc-HSAc) that can reduce sugar azides directly to the corresponding acetamido-derivatives has been reported.[21] 3′-Azido-3′-deoxy-thymidine (AZT) and 3′-azido-3′-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose were reduced to the corresponding amines in high yield by hydrogenation over a homogeneous catalyst ($Ph_2P.PdCl_2$) immobilized on montmorillonite; this catalyst system was shown not to effect benzyl ether or alkene moieties in non-carbohydrate examples.[22] The 3-amino-2,3,6-trideoxy-L-*arabino*-hexopyranosyl donor (30) and the C-4 epimeric L-daunosamine derivative (31) were synthesized from the known azide precursor (32), the inversion at C-4 required in the case of the latter being effected by displacement of triflate with acetate.[23] The application of



(30) X = $NHCOCF_3$, R = TBDMS

(32) X = N_3, R = H (α,β)

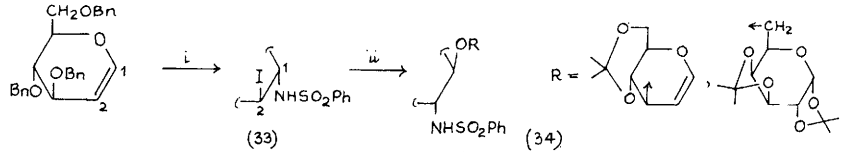


(31)

these and related glycosyl donors in the synthesis of anthracycline antibiotic analogues is covered in Chapter 19. The conversion of a 3-azido-3-deoxy-D-glucose derivative to methyl 3-amino-3,4-dideoxy-α- and β-D-*xylo*-hexopyranosides is detailed in Chapter 12, and the application of 2-azido-2-deoxy-glycosyl halides in the construction of heparin oligosaccharide analogues in Chapter 4.

Syntheses of imino-alditols and imino-aldonic acids are covered in Chapters 18 and 16, respectively.

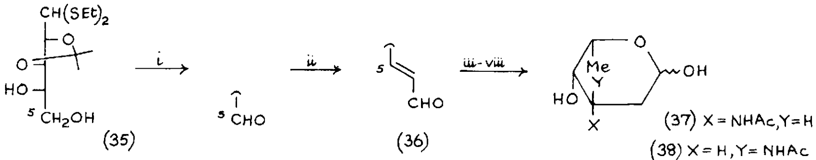
Several amino-sugar syntheses have relied upon the addition of nitrogen nucleophiles to unsaturated sugars. 2-Deoxy-2-iodo-α-D-glycosyl sulphonamides, *e.g.* (33), formed from D-glucal, D-galactal and D-allal derivatives, were converted into 2-amino-2-deoxy-β-D-glycosides, *e.g.* (34), by reaction with various glycosyl acceptors in the presence of



Reagents: i, $PhSO_2NH_2$, $I(sym\text{-}collidine)_2ClO_4$; ii, ROH, LiN

Scheme 6

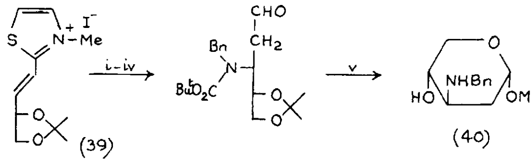
excess of base (Scheme 6). The reaction probably proceeds *via* a 1,2-aziridine intermediate.[24] 1,4-Addition of a nitrogen nucleophile to an enal was the key step in a number of syntheses. *N*-Acetyl-L-daunosamine (37) and its L-*xylo*-isomer (38) were synthesized from the L-arabinose derivative (35) by 1,4-addition of azide to enal (36) (Scheme 7). The enantiomeric amino-sugars were synthesized from D-arabinose.[25]



Reagents: i, $Pb(OAc)_4$; ii, $Ph_3PCHCHO$; iii, NaN_3, HOAc; iv, MeOH, H^+; v, LAH; vi, Ac_2O; vii, Raney Ni; viii, H^+

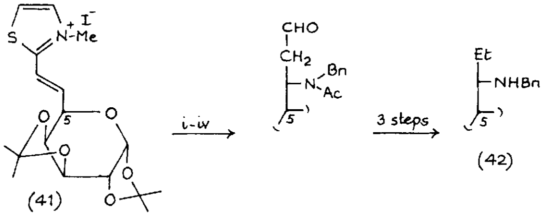
Scheme 7

Similarly, 1,4-addition of azide to L-*erythro*-hex-2-enopyranose provided a stereoselective route to the methyl and benzyl glycosides of L-acosamine (3-amino-2,3,6-trideoxy-L-*arabino*-hexose). Inversion at C-4 yielded the L-daunosamine analogues, in the same manner as detailed above (ref. 23).[26] Sugar aldehydes have been chain extended to unsaturated *N*-methylthiazolium salts such as (39) and (41), which were converted through Michael addition of benzylamine, to the 3-amino-2,3-dideoxy-α-D-*threo*-pentopyranoside (40) and the 7-deoxy-6-*epi*-lincosamine derivative (42) as shown in Schemes 8 and 9, respectively. 3-*epi*-



Reagents: i, $BnNH_2$; ii, $NaBH_4$; iii, $(Bu^tO_2C)_2O$; iv, H_2O, Hg^{2+}; v, MeOH, HCl

Scheme 8



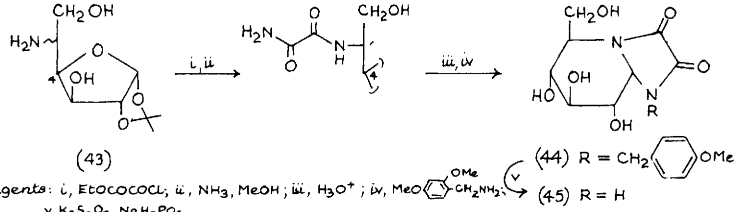
Reagents: i, $BnNH_2$; ii, $NaBH_4$; iii, Ac_2O, Py; iv, Hg^{2+}, H_2O

Scheme 9

Daunosamine was similarly obtained from 4-deoxy-2,3-O-isopropylidene-D-threose.[27] Further anomalously coupled nucleosides, such as methyl 2,3-dideoxy-3-(7-theophyllyl)-α-

threo- and *β-erythro*-pentopyranoside, have been synthesized by Michael-like addition of purines to α,β-unsaturated sugar aldehydes.[28-30]

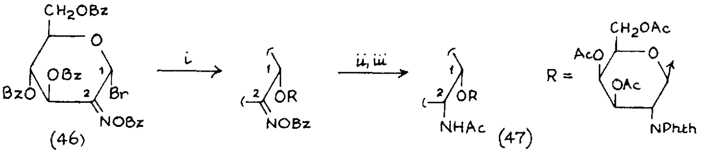
8-*epi*-Kifunensine (45), was synthesized (Scheme 10) from D-glucose *via* the C-5 epimeric amines (43) which were prepared by Tsuda's method from a 5-keto-precursor (Vol.22, p.97). The C-5 epimers were separated chromatographically after acylation (step i). The key cyclization (step iv) gave the *N*-protected derivative (44) as a single isomer, but in a modest (25%) yield. 8-*epi*-Kifunensine (45) showed modest α-glucosidase inhibitory activity.[31]



Reagents: i, EtOCOCOCl; ii, NH$_3$, MeOH; iii, H$_3$O$^+$; iv, MeOC$_6$H$_3$(OMe)CH$_2$NH$_2$; v K$_2$S$_2$O$_8$, NaH$_2$PO$_4$

Scheme 10

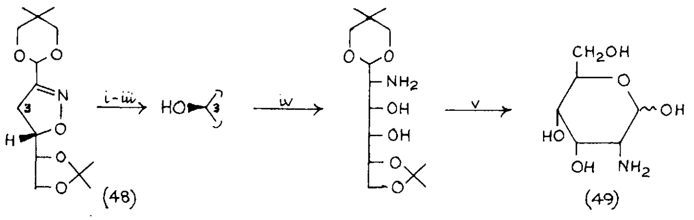
Neotrehalosamine derivatives composed of two different amino-sugars, such as α,β-(1→1)-linked disaccharide (47), have been synthesized using the 2-hexosulosyl bromide (46) as the glycosylating agent (Scheme 11).[32] The synthesis of an *N*-formyl-kansosamine glycosyl donor (a branched-chain sugar) is discussed in Chapter 14.



Reagents: i, ROH, AgOTf, sym-collidine; ii, LiBH$_4$, Me$_3$SiCl; iii, Ac$_2$O

Scheme 11

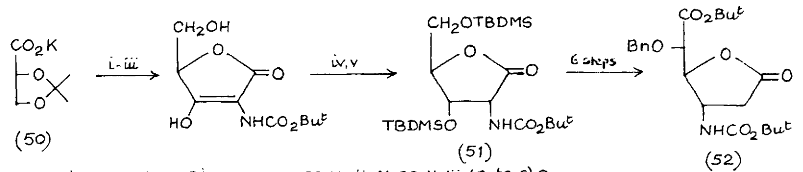
Chiral non-carbohydrate starting materials again feature in a number of amino-sugar syntheses. D-Allosamine (49) was prepared from the cycloadduct (48), the



Reagents: i, LiNPr$^i_2$; ii, B(OMe)$_3$; iii, H$_2$O$_2$; iv, LAH; v, H$_3$O$^+$

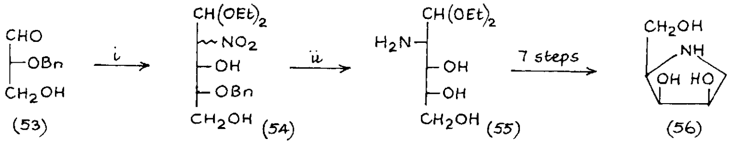
Scheme 12

chiral portion of which originated from 2,3-*O*-isopropylidene-D-glyceraldehyde (Vol.18, p.94), by an oxygenation-reduction sequence (Scheme 12).[33] The hydroxyamino acid moiety of the *Bacillus pumilus* metabolite A1-77-B has been synthesized as its derivative (52) from the D-glyceric acid salt (50) *via* the 2-amino-2-deoxy-D-ribonolactone derivative (51) which was elaborated into the desired product, by two alternative procedures involving Wittig chain-extension methodology (Scheme 13). This same report gave full details on the syntheses of L-daunosamine and L-vancosamine (Vol.18, p.94) and of D-ristosamine (Vol.20, p.97) from L-lactic acid.[34] The diethyl acetal derivative (55) of 2-amino-2-deoxy-D-arabinose was synthesized from diethyl tartrate *via* the D-glyceraldehyde derivative (53), and was converted into 1,4-dideoxy-1,4-imino-D-lyxitol (56) (Scheme 14). The adduct (54) was obtained as a mixture of *arabino-* and *ribo*-isomers in the ratio 88:12 in 90% yield. Compounds of the enantiomeric series were obtained from the other tartrate enantiomer.[35] Full details have been published of the synthesis of a 3-amino-2,3-dideoxy-L-*xylo*-hexose derivative from L-tartaric acid (Vol.17, p.96).[36] Galactostatin (58) has also been synthesized from L-tartaric acid *via* the allylic alcohol (57) (Scheme 15).[37]



Reagents: i, $(PhO)_2P(O)N_3$, Pr^i_2NEt, $NCCH_2CO_2Et$; ii, $MeSO_3H$; iii, $(Bu^tO_2C)_2O$; iv, $[Rh(NBD)(DIPHOS\text{-}4)]^+BF_4^-$, H_2; v, Bu^tPh_2SiCl, Im, DMF

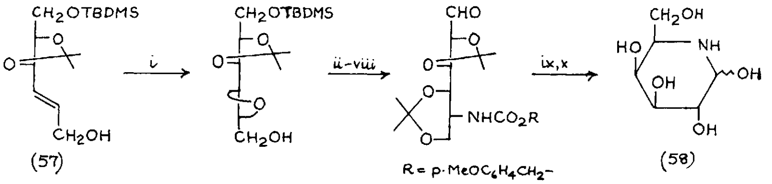
Scheme 13



Reagents: i, $(EtO)_2CHCH_2NO_2$, $Bu_4NF.3H_2O$; ii, H_2, Pd/C, MeOH

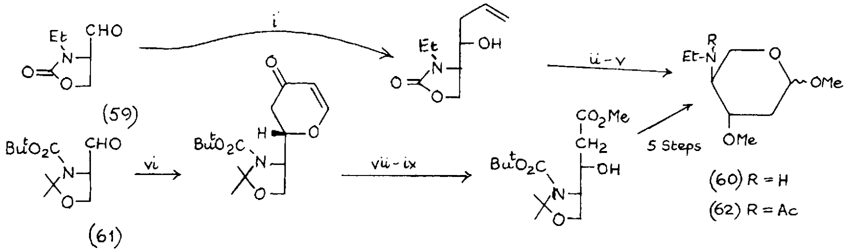
Scheme 14

Two groups have synthesized the E-ring moiety of calicheamicin as its methyl glycoside (60) or the *N*-acetyl-derivative (62) from L-serine *via* serinal derivatives (59) and (61), respectively (Scheme 16).[38,39] The same serinal derivative (61) was converted into the 4-amino-4-deoxy-L-ribose derivative (63) by an iterative one carbon chain-extension reaction sequence (Scheme 17),[40] and into 3-deoxy-L-mannojirimycin and 3-deoxy-L-



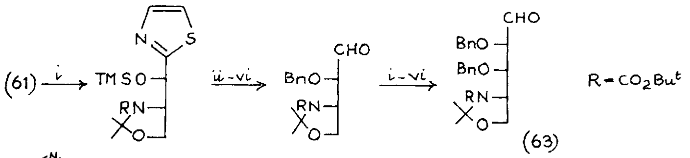
Reagents: i, MCPBA ; ii, Li_2NiBr_4 ; iii, $(MeO)_2CMe_2$, H^+ ; iv, Bu_4NF ; v, NaN_3, DMSO ; vi, H_2, Pd/C ; vii, RO_2CS N Me N Me, Et_3N ; viii, $(COCl)_2$, DMSO, Et_3N ; ix, H_2O, SO_2 ; x, Resin (HO^-- form)

Scheme 15



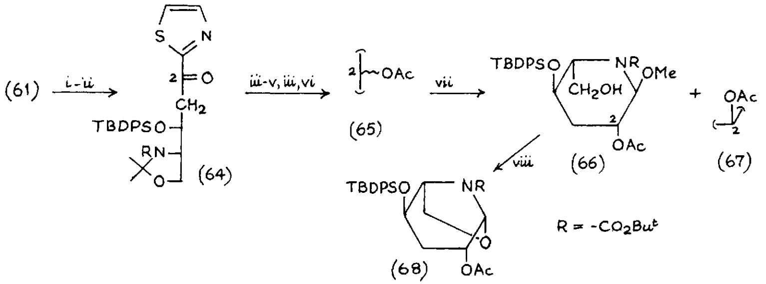
Reagents: i, MgBr, (−)-β-methoxydiisopinocampheylborane ; ii, Ag_2O, MeI ; iii, O_3, then $P(OMe)_3$; iv, NaOH ; v, HCl, MeOH ; vi, MeO $OSiMe_3$, $ZnCl_2$; vii, $NaIO_4$, RuO_4 ; viii, MeOH, K_2CO_3, then HCl ; ix, CH_2N_2

Scheme 16



Reagents: i, N S TMS ; ii, Bu_4NF ; iii, BnBr ; iv, MeI ; v, $NaBH_4$; vi, Hg^{2+}, H_2O

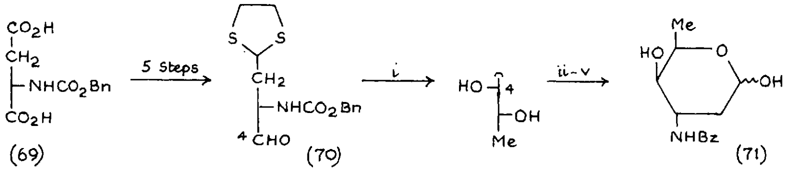
Scheme 17



Reagents: i, Bu^tOLi, N S Me ; ii, TBDPSCl, Im, DMF ; iii, $NaBH_4$; iv, Ac_2O, Py ; v, MeI ; vi, $HgCl_2$, H_2O ; vii, MeOH, TsOH ; viii, TsOH, PhMe, Δ

Scheme 18

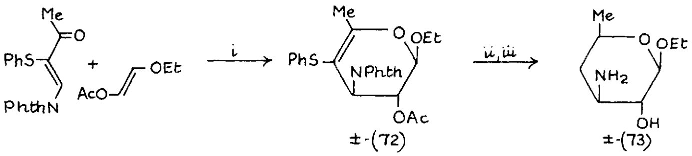
nojirimycin derivatives (66) and (67), respectively, by using 2-acetylthiazole as a masked α-hydroxypropanal β-anion synthon (Scheme 18). The initial adduct (64) and its C-4 epimer were obtained as a separable mixture (75% yield) in a ratio of 4:1, while the reduction product (65) was a 7:3 mixture of C-2 epimers. The bicyclic anhydro-derivative (68) was formed on treatment of the glycoside (66) under acidic conditions.[41] The 3-*epi*-D-daunosamine compound (71) was synthesized from the L-aspartic acid derivative (69), the key step being pinacol-type cross-coupling between the chelating aldehyde (70) and the non-chelating acetaldehyde (Scheme 19).[42]



Reagents: i, CH_3CHO, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$; ii, Hg^{2+}, MeOH; iii, LiOH, H_2O; iv, BzCl, K_2CO_3; v, AcOH, H_2O

Scheme 19

The racemic desosamine glycoside (73) has been synthesized from the hetero-Diels-Alder adduct (72) (Scheme 20). Several related syntheses were also reported.[43]



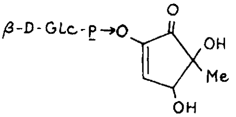
Reagents: i, 125°, 90h; ii, Raney Ni; iii, $NaBH_4$, then HOAc

Scheme 20

3 Reactions

1-Deoxy-1-piperidino-maltulose, the Amadori product derived from maltose and piperidine, decomposes in warm water, the glucosylated cyclopentenone (74) being one of the products.[44]

Syntheses and applications as chromogenic substrates of *N*-acetyl-β-D-hexosaminidase of 4-[(3,5-dichloro-4-hydroxyphenyl)amino]phenyl, indophenyl,[45] and the water soluble 3,4-dinitrophenyl[46] 2-acetamido-2-deoxy-β-D-glucopyranosides have been reported. Methyl, allyl and benzyl 1-amino-1-deoxy-α-D-fructofuranosides were synthesized from 1-amino-1-deoxy-D-fructose by Fischer glycosidation of the *N*-protected derivatives (75) to yield α,β-furanoside mixtures in which the α-anomer predominated, followed by base catalysed hydrolysis.[47] 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl fluoride and *O*-trichloroacetimidate, and the partially protected derivatives (76) and (77) of 2-amino-2-deoxy-D-glucose and -galactose were prepared as standardised intermediates for oligosaccharide synthesis.[48] Reaction of 2-acetamido-2-deoxy-β-D-glucopyranose tetraacetate with alcohols in the presence of zirconium(IV) chloride gave the corresponding β-glycosides in 72-82% yield, whereas the gluco[1,2]oxazoline was the product in the absence of the alcohol.[49] The *N*-alkoxycarbonyl derivatives (78) and (79) have been synthesized and used as donors in the synthesis of 2-amino-2-deoxy-β-D-glucosides. The oxazolidinone (80) was formed as a byproduct of glycosidation using bromide (79; R = allyl, benzyl, or *p*-nitrobenzyl).[50] Other amino-sugar *O*- and *C*-glycosides are discussed in Chapter 3.



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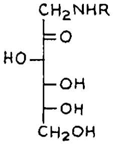

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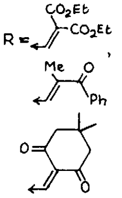

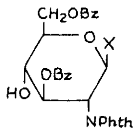

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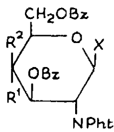
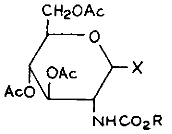


(77) $R^1 = OH, R^2 = H$ or $R^1 = H, R^2 = OH$

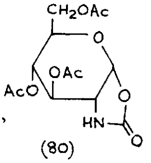
X = OBn, SEt, O



(78) X = β-OAc

(79) X = α-Br

R = Me, Et, , Bn, CH_2CCl_3, $CH_2C_6H_3$-4-NO_2, Bu^t



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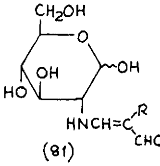
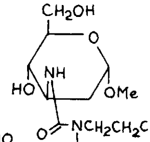


(81)

R = H or Me



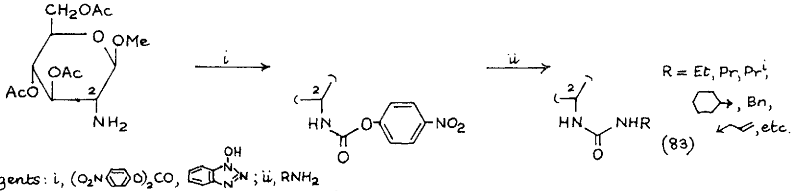
(82)

The enamines (81) were obtained by reaction of 2-amino-2-deoxy-D-glucose with the sodium salts of malondialdehyde or its α-methyl equivalent.[51] Visible light-induced mono-de-*N*-methylation of a dimethylamino-sugar containing anthracyclinone is discussed in Chapter 19.

A review on the chemistry of acetic formic anhydride has covered several carbohydrate applications including to the synthesis of *N*-formyl-derivatives.[52] Rapid, one-pot productions of 2-deoxy-2-[^{18}F]fluoroacetamido-D-glucopyranose,[53] -mannopyranose, and -galactopyranose[54] as potential diagnostic imaging agents involved acylation ($^{18}FCH_2CO_2H$ -

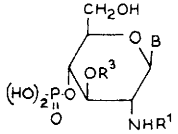
DCC) of the corresponding aminosugars. 2-Amino-2-deoxy-D-galactosamine and adriamycin residues have been incorporated into *N*-(2-hydroxypropyl)methacrylamide copolymers, the sugar moieties being included to promote conjugate targeting to L1210 cells and hepatocytes.[55]

The antitumour nitrosourea CY233 (82) has been synthesized labelled on the urea carbonyl (using $^{14}COCl_2$), the chloroethyl group (using [^{14}C]ethanolamine), and the aglycon (using $^{14}CH_3OH$ or $^{13}CH_3OH$) for mechanistic studies of its antitumour activity.[56] Ureido-sugars (83), precursors of nitrosoureido-sugars, have been synthesized by the new route shown in Scheme 21.[57]

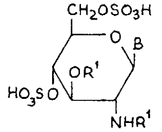


Scheme 21

The Lipid A analogues (84) - (88) have been synthesized. The 4,6-disulphated 1-thyminyl-analogue (85) had anti-HIV activity,[58] while the analogues (86) and (87), in which the natural α-glycosyl phosphate moiety is substituted by a phosphono-oxyethyl group, had anti-tumour activity.[59]



(84) B = Thyminyl
$R^1 = C_{14}OC_{14}$, $R^2 = C_{14}OC_{12}$
$R^3 = CO(CH_2)_{12}Me$



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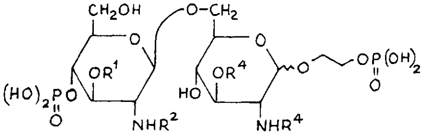
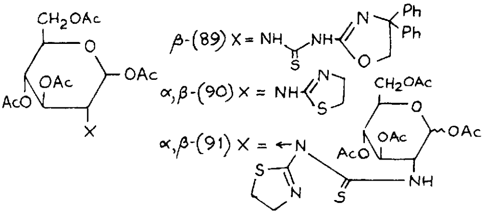
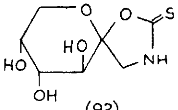


α-(86) $R^4 =$ (R)-$COCH_2CH(OH)(CH_2)_{10}Me$
α-(87) $R^4 = R^3$
β-(88) $R^4 = R^3$

The *N*-heteroarylthiourea derivative (89) was obtained from the corresponding 2-deoxy-2-isothiocyanato-derivative, and its tautomeric equilibrium in solution was studied by i.r. and ^{1}H-n.m.r. spectroscopy.[60] Condensation of 2-chloroethylamine with the 2-deoxy-2-isothiocyanato derivative gave either the thiazoline (90) or the thiourea (91) depending upon the solvent.[61] Related thiourea-linked disaccharides are discussed in Chapter 10. Reaction of the acetic acid salt of 1-amino-1-deoxy-D-fructose with carbon disulphide at 75°C gave the spirocyclic derivative (92) in 49% yield.[62]





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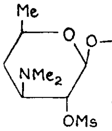

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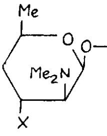
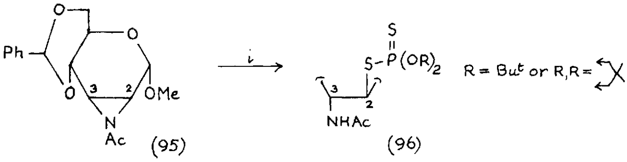


(94) X = OCHO, N_3, NH_2, OMe, F, etc. (13 examples)

The kinetics of base-catalysed solvolysis of the Schiff base adducts formed from benzaldehydes with 2-amino-2-deoxy-D-glucose were determined, and the mechanism of decomposition was discussed.[63] 2-Amino-2-deoxy-D-glucose was transported across a supported liquid membrane by use of 4-octadecyloxybenzaldehyde as carrier, the transport being by way of the derived Schiff base.[64]

Various amino-sugars and their derivatives have been obtained by interconversion from amino-sugar starting materials. The 2-*O*-methanesulphonate derivative (93) of the desosamine unit in erythromycin underwent displacement with participation by the 3-dimethylamino-group with a variety of nucleophiles to give the rearranged products (94), except in the case of reaction with lithium chloride by which the 2-chloro-2-deoxy-derivative was obtained with retained D-*xylo*- configuration.[65] The synthesis of 2-acetamido-2,3-dideoxy-3-fluoro-D-glucose derivatives and related difluorides, involving similar neighbouring group participation reactions, is discussed in Chapter 8. Amino-thiosugars such as (96) have been obtained by *trans*-diaxial ring opening of *N*-acetylated aziridino-sugars such as (95) (Scheme 22).[66] Syntheses of the 3- and 4-deoxy-analogues of 2-acetamido-2-deoxy-D-galactose are discussed in Chapter 12.

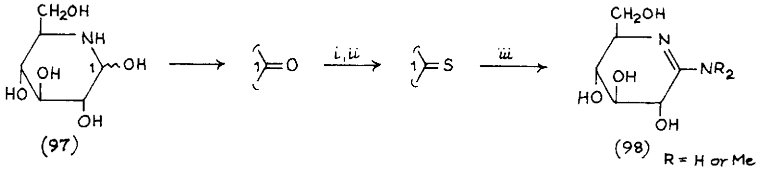


Reagent i, $(RO)_2P(S)SH$

Scheme 22

Syntheses of uronic acid derivatives of *N*-acetylmuramic acid and of 4-*epi*- and 8-*epi*-*N*-acetylneuraminic acid, and the deamination of *N*-acetylneuraminic acid are discussed in Chapter 16, and the syntheses of carbocyclic analogues of muramyl dipeptide are detailed in Chapter 18.

The amidines (98) have been synthesized from nojirimycin (97) as shown in Scheme 23, and isolated as their stable hydrochloride salts. These amidines are analogues of the presumed oxonium ion intermediates in enzymic hydrolysis of glycosides; compound (98; R = H) was found to be a potent competitive inhibitor of sweet almond β-glucosidase and mannose- and galactose-processing enzymes.[67]



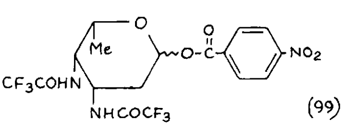
Reagents: i, O-trimethylsilylation; ii, Lawesson's reagent ; iii, R_2NH,MeOH

Scheme 23

Chelation of copper(II) ions by amino-sugars and conformational studies of amino-sugars derivatives and disaccharides are discussed in Chapters 17 and 21, respectively.

4 Diamino-sugars

The 3,4-diamino-2,3,4,6-tetradeoxy-L-*lyxo*-hexose derivative (99) was synthesized from benzyl 3-azido-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (Vol.21, p.86) by displacement of a 4-triflate with ammonia, and then used in the glycosidation of an anthracyclinone derivative (see Chapter 19).[68] The dideoxygenation of a 2,6-diaminohexosyl residue is covered in Chapter 12, and platinum(II) complexes of various diaminosugars are discussed in Chapter 17. Syntheses of diamino-derivatives of 2-deoxy-KDO and of the desosamine unit in erythromicin have been mentioned earlier in this Chapter (see ref. 17 and 65, respectively).



(99)

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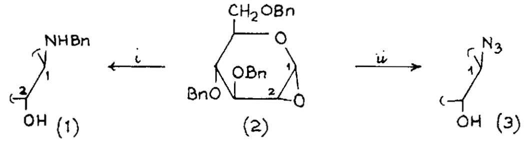
10
Miscellaneous Nitrogen Derivatives

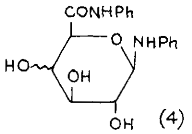
1 Glycosylamines

The 1,2-anhydro-sugar (2), prepared by reaction of the corresponding glucal derivative with 3,3-dimethyl-dioxirane, has been used in the preparation of the *N*-benzyl-*β*-D-glucosylamine (1) and the *β*-azide (3) (Scheme 1).[1] *N*-(2-Hydroxyethyl)glycosylamines were formed in 73-91% yield on reaction of five aldoses (D-Glc, D-Man, D-Gal, D-Xyl and L-Ara) with ethanolamine in ethanol (2-6 h, 40-55°C), and were shown to be present in solution predominantly as *α,β*-pyranose mixtures.[2] The direct carbodiimide-induced formation of the D-gluc- and -galact-uronosylamine amides (4) from the free uronic acids, and the selective hydrolysis of their *N*-glycosidic linkages, has been reported.[3]



Reagents: i, $BnNH_2$, $ZnCl_2$; ii, $Bu_4\overset{+}{N}\overset{-}{N_3}$

Scheme 1



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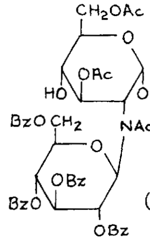

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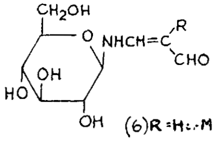
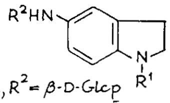
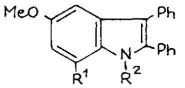


(6) R = H, Me



(7) R^1 = Ac, R^2 = *β*-D-Glc*p*

(8) R^1 = *β*-D-Glc*p*$(Ac)_4$, R^2 = *α,β*-D-Glc*p*$(Ac)_4$

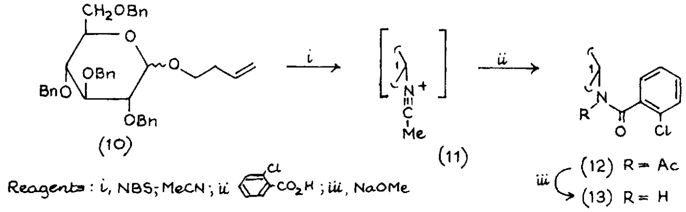


(9) R^1,R^2 = H, *α,β*-Glc*p*$(Ac)_4$

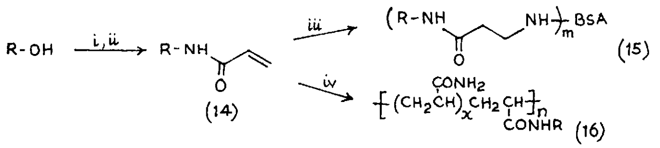
The *N*-linked disaccharide (5) was obtained in 38% yield during an attempted *O*-glycosylation (with tetra-*O*-benzoyl-*α*-D-glucopyranoyl bromide -AgOTf-collidine).[4] The *N*-glucosyl-enamines (6) were prepared by reaction of D-glucosylamine with the sodium salts of malondialdehyde or its *α*-methyl analogue.[5] Several 2,N^3-disubstituted 5-chloro-4-(*β*-Dglycopyranosylamino)-pyrimidine peracetates have been subjected to thermochemical and spectral studies.[6] Conformational studies of the model glycosylamine, 2-methylaminotetrahydropyran, and discussed in Chapter 21.

The N^5-glucosyl derivative (7) of 5-aminoindoline was synthesised by reaction of D-glucose with N^1-acetyl-5-aminoindoline, while the N^1,N^5-diglucosyl derivative (8) was similarly obtained from D-glucose and 5-aminoindoline followed by acetylation. Bisglucosides of 5-aminoindole were obtained by dehydrogenation and deacetylation of the mixture (8).[7] Koenigs-Knorr conditions were used for an alternative synthesis of the N^5- and N^6-glucosides of 5- and 6-aminoindole, respectively,[8] and the N^1-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucuronide) of sulfadimidine.[9] Reaction of *O*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-trichloroacetimidate with 5-methoxy-2,3-diphenylindole gave a mixture (9) of anomeric *C*- and *N*-glycosides.[10]

The α-glucosyl nitrilium species (11) was formed from the pent-4-enyl glycoside (10) and trapped as the adduct (12) (Scheme 2). Contrary to assumptions by previous workers, it was shown to have the α- rather than the β- configuration suggesting that it is formed under kinetic rather than thermodynamic control. Were the latter operative, the reverse anomeric effect would favour the equatorial (β) product. The adduct (12) has an unusually large le,2a proton coupling constant of 7.3 Hz, which was ascribed to flattening of the pyranose ring near C-1,C-2. For comparison, the β-anomer of the *N*-deacetylation product (13) was prepared from the β-azide.[11] Sialyloligosaccharide protein conjugates (15) and water-soluble polyacrylamides (16) have been synthesized via *N*-acryloyl-glycosylamines (14) as serologically useful antigens (Scheme 3).[12] *N*-(2-Hydroxypropyl)methacrylamide copolymers containing both adriamicin and fucosylamine residues have also been prepared, the sugar residues being included to promote conjugate targeting to L1210 cells and hepatocytes.[13]



Scheme 2



R = α-D-Neu*p*5Ac-(2→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-1→
or α-D-Neu*p*5Ac-(2→8)-α-D-Neu*p*5Ac-(2→3)-β-D-Gal*p*-(1→4)-β-D-Glc-1→

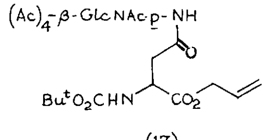
Reagents: i, NH_4HCO_3; ii ⫽\COCl, Na_2CO_3; iii, pH 10, Na_2CO_3 buffer, BSA; iv, ⫽\$CONH_2$, $(NH_4)_2S_2O_8$

Scheme 3

The construction of *N*-linked glycopeptides and related model compounds continues to be investigated. Crystalline 2-acetamido-2-deoxy-β-D-glucopyranosylamine was obtained directly from *N*-acetylglucosamine [with NH_3-$(NH_4)_2CO_3$-EtOH] and condensed with *N*-benxyloxycarbonyl-L-aspartic acid to give a mixture of the *N*-1- and *N*-4-glycosylated asparagine derivatives.[14] The *N*-4-glycosylated asparagine derivative (17) was synthesized by coupling 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosylamine with a suitably protected aspartic acid derivative and could be incorporated into a peptide using normal coupling processes after deprotection either at the ester site, with Wilkinson's catalyst, or at the amine group (with HCl in CH_2Cl_2).[15] A similar derivative, differing in the asparagine protecting groups (Fmoc on amine, pentafluorophenyl ester), was synthesised in the same way by another group and incorporated into an 11-residue peptide fragment of the enzyme glucoamylase.[16] The per-*O*-acetylated derivative of the β-mannosyl-chitobiosyl-asparagine conjugate (18), a central core of the *N*-glycoproteins, was constructed by reaction of a trisaccharide β-glycosyl isothiocyanate with an *O*,*N*¹-protected aspartic acid derivative, a condensation reaction used previously for the preparation of similar products (Vol.14, p.83).[17] The action of an oligosaccharide transferase was studied by examination of the coupling product obtained from a labelled oligosaccharide and a chemically synthesized peptide acceptor. A glycopeptide fragment generated from this coupling product was shown to be identical to a chemically synthesized 4-*N*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)asparagine-containing tripeptide rather than its 1-*N*-(glycosyl)isoasparagine isomer.[18] The adduct formed between the glycopeptide antibiotic teicoplanin and glucose in aqueous solution has been studied.[19] Galactosyl transferase has been used to transfer a β-D-galactopyranosyl unit onto the 4-position of a β-GlcNAc- or β-GlcNAc*p*(1→4)-β-GlcNAc*p*(1→4)-asparagine derivative; the acceptors were synthesized from the corresponding peracetylated glycosyl azides.[20] Glycosylation of a β-D-glucosyl dipeptide derivative resulted in two anomeric *N*-triglycosyl dipeptides, which are models for a new glycopeptide found in rat glomerular basement membrane (see Chapter 4).[21]

Glycosylurea and thiourea derivatives, *e.g.* (19), were synthesized by condensation of alkyl isocyanates and isothiocyanates respectively, with β-D-glucopyranosylamine and β-lactosylamine, as non-ionic detergents of particular interest for extraction of membrane proteins.[22] Various 1-(β-D-glycosyl)-derivatives of diphenylhydantoin and hydrochlorothiazide were synthesized in an attempt to enhance the hydrophilicity and biological activity of these materials.[23] Conformation analysis and X-ray structures of some 1,2- and 1,3-fused glycosylamine derivatives are included in Chapters 21 and 22.

Reaction of 2-amino-2-deoxy-D-glucose hydrochloride with potassium cyanate yields a mixture from which, after acetylation, the fused urea derivative (20) and the heterocycle (21) were isolated; 2-deoxy-2-ureido-D-glucose is postulated as an intermediate in the formation of both products.[24] Reaction of 2-amino-2-deoxy-D-*glycero*-L-*gluco*-heptose with cyanamide gave the fused guanidine salt (22); acetylation of the crude reaction product provided both the fused urea derivative (23) and the heterocycle (24).[25]



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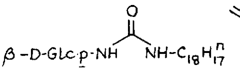

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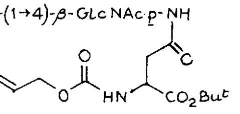

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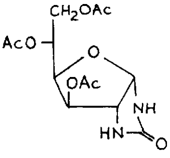

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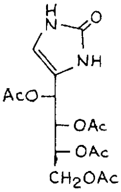

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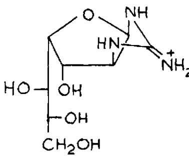

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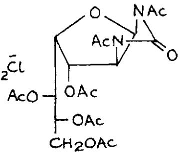

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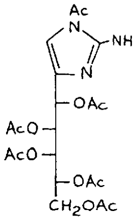
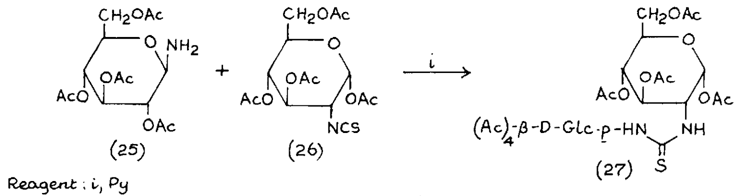


(24)

Peracetylated glycosyl isothiocyanates have been prepared in 48-86% yield by reaction of amino-sugar glycosyl bromides or neutral sugar glycosyl chlorides with ammonium thiocyanate (in MeCN or Me_2CO at 40-50°C), the reaction proceeding *via* intermediate thiocyanate derivatives.[26] A number of so called 'thioureylene' disaccharides, *e.g.* (27), with a thiourea bridge between the two sugar moieties, have been synthesized by condensation of an amino-sugar or glycosylamine, *e.g.* (25), with a deoxy-isothiocyanato-sugar or glycosyl isothiocyanate, *e.g.* (26) (Scheme 4).[27] Condensation of the glucosyl or xylosyl isothiocyanate (28) with 2-chloroethylamine led to the thiazoline salt (29) which gave the bis(glucosylated) thiourea derivative (30) in the presence of excess of the isothiocyanate (28). The free base form of the glucosyl derivative (29) appears to be the same as the compound claimed earlier (H. Ogura et al, *J. Carbohydr., Nucleosides,*

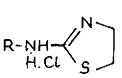


Scheme 4

Nucleotides, 1981, *8*, 437) as having structure [31, R=β-D-Glc(Ac)$_4$].[28] Peracylated β-D-glucopyranosyl, β-D-galactopyranosyl, and α-L-rhamnopyranosyl isothiocyanates have been condensed with a variety of heterocyclic amines to yield *N*-glycosyl-thiourea derivatives.[29,30]

R-NCS

(28)



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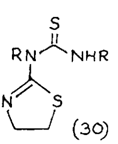

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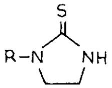
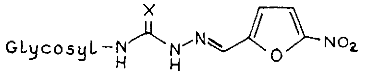


(31)

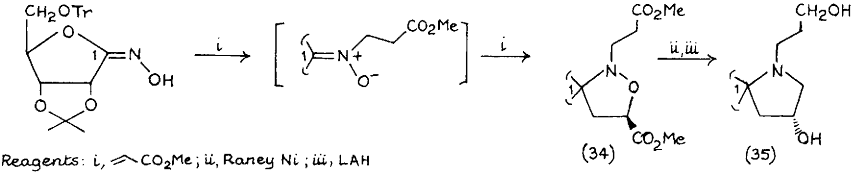
R = β-D-Glc-p(Ac)$_4$ or β-D-Xyl-p(Ac)$_3$

The *N*-glycosylated analogues (32) and (33) of furacilin and benzazon VII were prepared by condensation of glycosyl isocyanates and isothiocyanates, respectively, with 5-nitrofurfural hydrazone followed by deacetylation.[31]

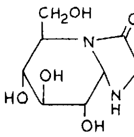


(32) X=O
(33) X=S

Spirocyclic sugar isoxazolidinones such as (34) have been synthesized by tandem Michael addition - 1,3-dipolar cycloaddition reactions as shown in Scheme 5. Reduction of adduct (34) yielded the spirocyclic glycosylamine derivative (35).[32] The syntheses of 8-*epi*-kifunensine (36)[33] and the amidines (37)[34] are detailed in Chapter 9.



Scheme 5



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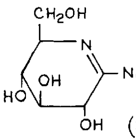
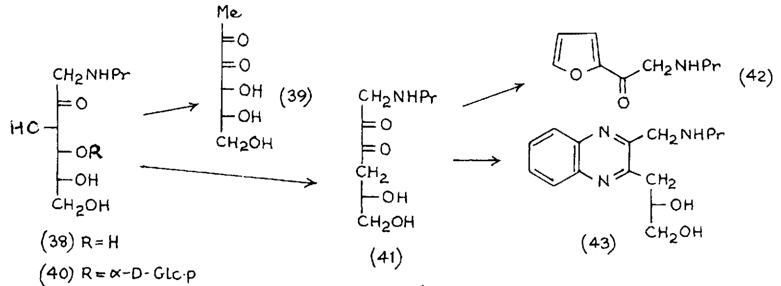


(37) R = H or Me

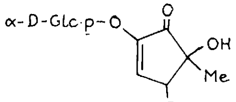
The Maillard reaction, whereby sugars and amines or amino-acids condense, rearrange and degrade, often during the cooking or preservation of foods, has been reviewed.[35] This reaction of D-glucose with propylamine gave mainly the 1-deoxy-2,3-hexodiulose (39) *via* the Amadori product (38) (Scheme 6). Maltose, on the other hand, gave the Amadori product (40) with a better leaving group at C-4 (*O*-α-D-Glc*p* *cf* OH), and this yielded mainly the 1,4-dideoxy-1-propylamino-2,3-hexodiulose (41) which degraded to the 2-aminoacetylfuran (42) or could be trapped as the adduct (43) on reaction with *o*-phenylenediamine.[36] The formation of acids, lactones, and esters in a model Maillard reaction between glucose and glycine heated at 45°C for 45 minutes has been studied. Sugar degradation products were determined as benzimidazole derivatives after reaction with *o*-phenylenediamine.[37] More than 120 amino-acid specific Maillard products have been isolated and identified from the reaction of L-proline, hydroxyproline, cysteine and methionine with monosaccharides at 150° for 1-1.5 h, in connection with studies of thermally generated aromas. Proline derived components were important constituents of bread, malt and beer, and cysteine and methionine derived components were predominant in roasted coffee and meat flavours.[38] The effects of temperature, pH, and the relative concentration of rhamnose and proline on the quantity of specific volatiles produced in the Maillard reaction of these substrates have been studied, and the data have been analysed by computer methodology.[39] The glucosylated cyclopentenone (44) was one of the products of decomposition of the Amadori product 1-deoxy-1-piperidino-maltulose in warm water.[40]



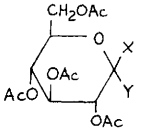
Scheme 6

2 Azido-, Azi-, and Diazo-sugars

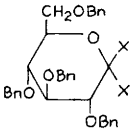
Glycosylidene diazides (45) and (46) have been synthesized from *gem*-dihalide (47) (with AgN_3-$MeNO_2$) or lactone (48) (with Me_3SiN_3-$BF_3.OEt_2$), respectively.[41] The synthesis of tetra-*O*-acetyl-β-D-glucopyranosyl azide from the corresponding α-bromide, and its reduction to the corresponding glucosylamine derivative, has been reported.[42]



(44)

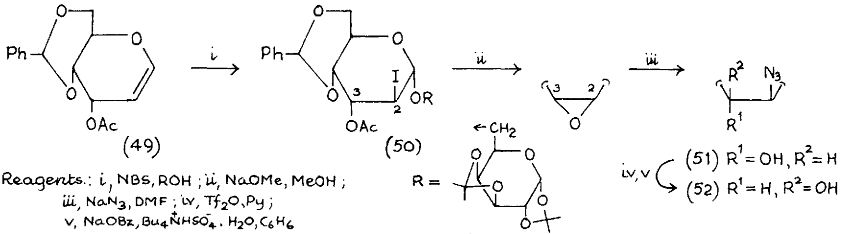


(45) $X = Y = N_3$
(47) $X = Cl, Y = Br$



(46) $X = N_3$
(48) $X,X = O$

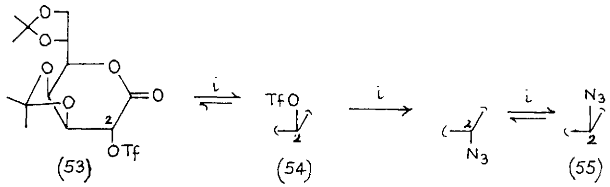
The 2-azido-2-deoxy-α-D-altrosyl and -mannosyl-(1→6)-D-galactose derivatives (51) and (52), respectively, were synthesized from the D-allal derivative (49) initially by an iodo-glycosidation reaction (Scheme 7). This reaction sequence demonstrated an approach to



Reagents.: i, NBS, ROH ; ii, NaOMe, MeOH ; iii, NaN_3, DMF ; iv, Tf_2O, Py ; v, NaOBz, $Bu_4\overset{+}{N}HSO_4^-$, H_2O, C_6H_6

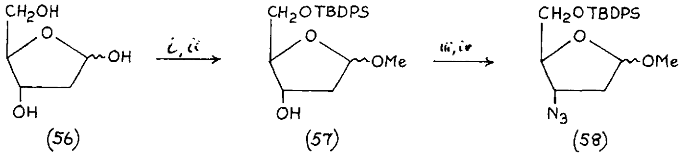
Scheme 7

replacing the 2′-iodo-substituent in disaccharides such as (50) with a heteroatom.[43] The epimeric lactone 2-triflates (53) and (54) both give the same azide (55) at equilibrium due to facile epimerization under the reaction conditions of both the D-*glycero*-D-*galacto*-heptonic acid 2-triflate and 2-azide to their more stable D-*glycero*-D-*talo*-isomers, (Scheme 8).[44] The methyl 3-azido-2,3-dideoxy-α,β-D-*erythro*-pentofuranoside (58) has been synthesized in 26% overall yield from 2-deoxy-D-ribose (56) as shown in Scheme 9.



Reagents: i, NaN_3, DMF

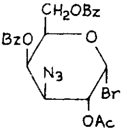
Scheme 8



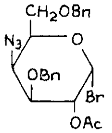
Reagents: i, MeOH,HCl; ii, TBDPSCl,Im,DMF; iii, Ph_3P, DEAD, MeI; iv, NaN_3, DMF

Scheme 9

Introduction of the azido-function was achieved by a double inversion sequence applied to intermediate (57), the anomers of which were separable.[45] The 3-azido-3-deoxy- and 4-azido-4-deoxy-D-galactosyl bromides (59) and (60), respectively, were synthesized from D-glucose derivatives, displacement of sulphonate ester groups from C-4 being used to effect the required inversions. These glycosyl donors were utilized in the construction of amino-sugar analogues of a Lewis b blood group-related tetrasaccharide.[46] The 5-azido-5-deoxy-D-gluconontrile derivative (61) and its 5-deoxy-5-trifluoroacetamido-analogue (62) were synthesized in multi-step procedures from a 5-azido-5-deoxy-D-glucose derivative, but attempts to convert them into the corresponding 5-amino-5-deoxy-D-glucononitrile derivatives, and thence into amidines such as (37), were unsuccessful.[47]



(59)



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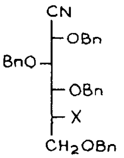
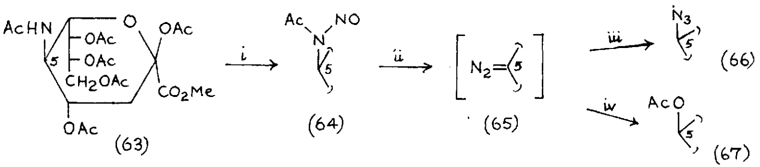


(61) $X = N_3$

(62) $X = NHCOCF_3$

Sugar azides can be reduced directly to the corresponding acetamido-sugars with a mixture of thiolacetic acid and its potassium salt.[48] A heterogenized homogeneous catalyst, interlamellar montmorillonite diphenylphosphine palladium(II), has been reported (two carbohydrate examples) to reduce azides selectively to amines without affecting benzyl ether or alkene moieties.[49]

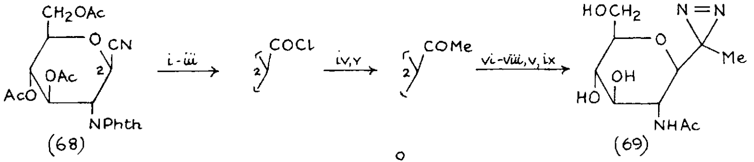


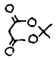
Reagents: i, NO^+OAc^-; ii, CF_3CH_2ONa; iii, NaN_3; iv, Bu_4NOAc, HOAc

Scheme 10

The *N*-acetylneuraminic acid derivative (63) was converted *via* the *N*-nitroso-derivatives (64) into the diazo-intermediate (65) which was then captured with nucleophilic reagents to give the azide (66) or the KDN (3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid) derivative (67), the stereoselectivity implying the operation of neighbouring group participation during the addition process (Scheme 10).[50]

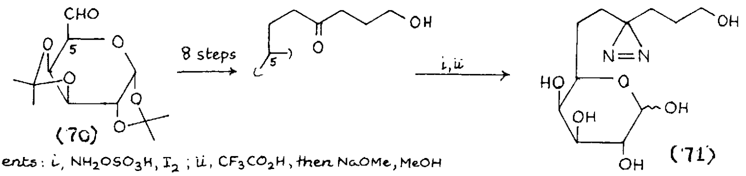
4-Acetamido-3,7-anhydro-2-azi-1,2,4-trideoxy-D-*glycero*-D-*gulo*-octitol (69) was synthesized from the glycosyl nitrile (68) (Scheme 11) as a potential photo affinity reagent



Reagents: i, HBr, HOAc; ii, NO$_2$, CH$_2$Cl$_2$; iii, PCl$_5$; iv , Py; v, AcOH, H$_2$O; vi, MeOH, NH$_3$; vii, H$_2$NOSO$_3$H; viii, I$_2$, Et$_3$N; ix, NaOMe, MeOH

Scheme 11

with good affinity for human *β*-hexosaminidase.[51] The D-*galacto*-undecose derivative (71) with the diazirino-photoaffinity group was synthesized from the D-galactodialdose (70) (Scheme 12).[52]

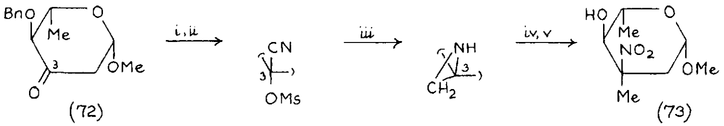


Reagents: i, NH$_2$OSO$_3$H, I$_2$; ii, CF$_3$CO$_2$H, then NaOMe, MeOH

Scheme 12

3 Nitro-sugars

The identity of the decilonitrose residue in the antibiotic decilorubicin has been confirmed as 2,3,4-trideoxy-3-*C*-methyl-3-nitro-L-*ribo*-hexopyranose by an unambiguous synthesis of its glycoside (73) from L-rhamnose *via* the 3-ulose (72) (Scheme 13).[53] Potassium fluoride (in



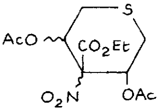
Reagents: i, HCN; ii, MsCl, Py; iii, LAH; iv, Raney Ni, H$_2$; v, MCPBA

Scheme 13

Pr^{i}OH with dibenzo-18-crown-6) has been used as a catalyst for the condensation of dialdehydes with nitroalkanes, products such as compounds (74) and (75) having been described.[54]

4 Nitriles, Oximes and Hydroxylamines

Glycosyl nitriles have been synthesized as precursors of *C*-glycosyl derivatives. The 2-azido-2-deoxy-hexosyl bromides (76) and (77), obtained as a separable mixture from D-glucal triacetate (i,NaN_3-$Ce(NH_4)_2(NO_3)_6$; ii, LiBr) were converted [$Hg(CN)_2$-$PhNO_2$] into the nitriles (78; α:β, 2:1) and (79), respectively. Similar results were achieved starting from D-galactal triacetate.[55] 2,5-Anhydro-3-deoxy-mannononitrile (82), a known precursor of 2′-deoxy-*C*-nucleosides, was synthesized from 2-amino-2-deoxy-D-glucose (80) (Scheme 14).



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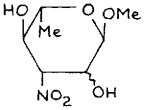
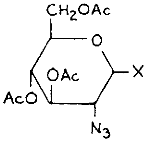
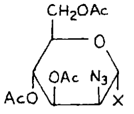


(75)



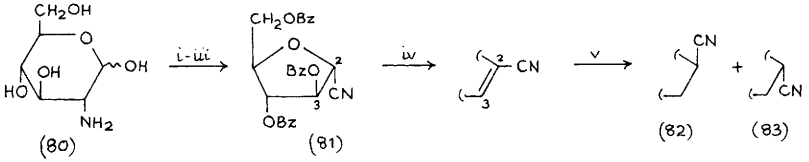
(76) X = α-Br

(78) X = α,β-CN



(77) X = Br

(79) X = CN



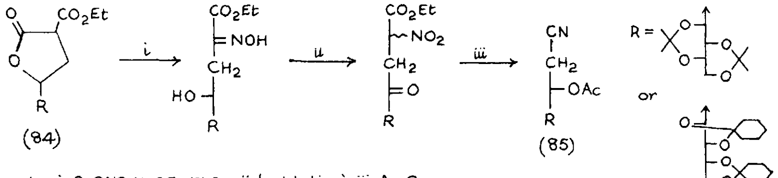
Reagents: i, $NaNO_2$, HOAc, H_2O; ii, NH_2OH, MeOH; iii, BzCl, Py; iv, DBU; v, H_2, Pd/$BaSO_4$

Scheme 14

Nitrile (81) was obtained in >70% yield in one-pot *via* a deamination - ring contraction reaction. β-Elimination of benzoic acid and hydrogenation gave a separable 2:1 mixture of nitriles (82) and (83); equilibration ($LiNPr^i_2$) of the α-anomer (83) gave a 1:1 mixture of α- and β-anomers. The nitrile moiety of compound (82) was converted sequentially into amide, acid then ester groups.[56]

2-Deoxy-hexononitriles (85) were obtained from the lactones (84) *via* oxime and nitro-sugar intermediates as shown in Scheme 15.[57]

The *N*-phenylcarbamates (86), derived from 2-acetamido-2-deoxy-gluconohydroximino-lactone, and its chitobiono-lactone equivalent were synthesized as potential inhibitors of *N*-acetylglucosaminidases.[58]

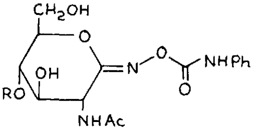


Reagents: i, PrONO, NaOEt, EtOH; ii, 'oxidation'; iii, Ac_2O

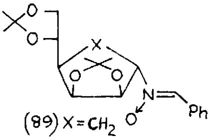
Scheme 15

Disaccharides such as (87), linked by an *N*-hydroxyamino-bridge, have been obtained by condensation of deoxy-*N*-hydroxyamino-sugars with aldehydro-sugars and reduction of the resulting nitrones, and the nitroxyl free radicals produced from them have been studied by e.s.r. spectroscopy.[59] The products (88) of conjugate addition of *N*-substituted hydroxylamines to a 2-deoxy-hex-2-enos-4-ulose derivative have now been found to have the D-*arabino*-configuration shown rather than the D-*xylo*-configuration originally proposed (*cf.* Vol.21, p.108).[60] The substantially reduced diastereoselectivity observed in addition and dipolar cycloaddition reactions of *N*-pseudoglycosyl nitrones such as (89) (see Chapter 18 for products), compared to that achieved for *N*-glycosyl nitrones such as (90), revealed the role of a kinetic anomeric effect in the latter cases.[61]

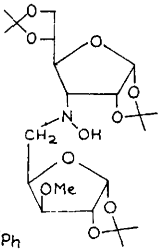
O-Glycosylhydroxylamines [*e.g.* (91)][62,63] or analogues linked through carbons other than the anomeric [*e.g.* (92)][63] have been prepared by reaction (Ph_3P-DEAD) of partially protected aldoses with *N*-hydroxyphthalimide followed by treatment with hydrazine to remove the phthalimido-protecting group. Various oximes have been prepared from hydroxylamine (92), and in some cases these were reducible to the corresponding *N*-alkylhydroxylamine derivatives.[63] Nicolaou and co-workers have reported syntheses of the model



(86) R = H
or β-D-GlcNAcp



(89) X = CH_2
(90) X = O



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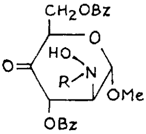
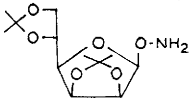


(88) R = Me, Ph, etc.



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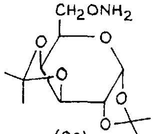
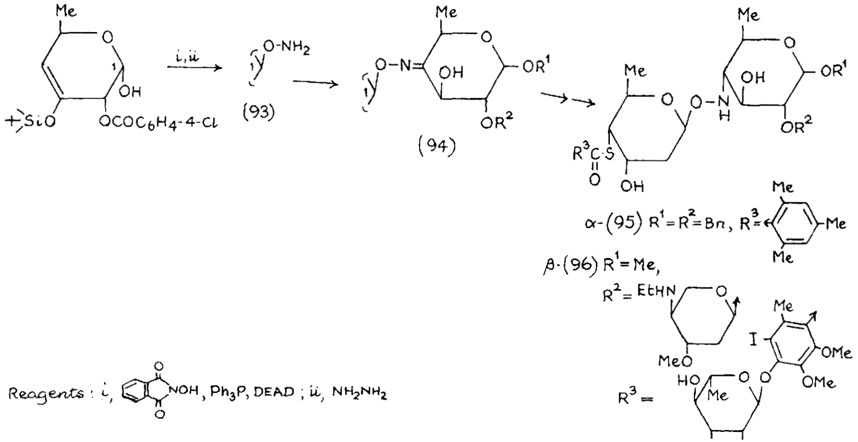


(92)

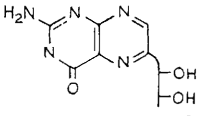
oligosaccharide (95)[64] and the full oligosaccharide fragment (96)[65] of the calicheamycins. In both cases the *O*-glycosylhydroxylamine (93) was coupled with a 4-keto-sugar derivative, and the oxime moiety in the resulting adduct (94) was subsequently reduced stereoselectively to establish the characteristic hydroxylamine interresidue linkage (Scheme 16).



Scheme 16

5 Hydrazones and Related Heterocycles

[3′-^{2}H]-Biopterin (97), required for metabolism studies, was synthesised by reaction of the phenylhydrazone of 5-deoxy-[5-^{2}H]-L-arabinose (see chapter 12) with 2,5,6-triaminopyrimidin-4-one.[66] The same reaction applied to the semicarbazones of pentoses proceeded regiospecifically to yield D-anapterin (98) and L-primapterin (99), which have the polyhydroxyalkyl substituent in a different position on the pteridinone ring.[67] Condensation of 2-methylthio-4,5,6-triamino-pyrimidine with pentose phenylhydrazones yielded tricyclic adducts such as the crystalline product (100) obtained from D-arabinose[68].



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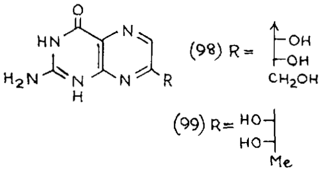
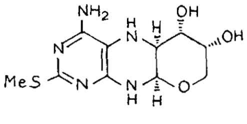
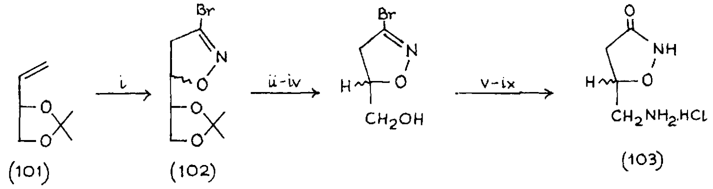




(100)

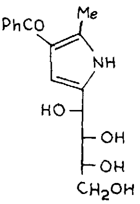
6 Other Heterocycles

The adducts (102) were obtained as a mixture of *anti*- and *syn*-isomers in a 76:24 ratio by cycloaddition of bromonitrile oxide to the alkene (101). After separation they were converted into the two enantiomers of dihydromuscimol (103) (Scheme 17).[69] The pyrrole (104) was obtained by condensation of 2-amino-2-deoxy-D-glucose with 1-phenyl-1,3-butanedione in the presence of triethylamine.[70] Oxadiazole derivatives, *e.g.* (105), were prepared by reaction of tetrazole derivatives, *e.g.* (106), with acetic anhydride or benzoyl chloride in pyridine.[71]



Reagents: i, $Br_2C{=}NOH$, $NaHCO_3$; ii, Resin (H^+-form), H_2O; iii, $NaIO_4$; iv, $NaBH_4$; v, BnOLi, DMSO; vi, MsCl, Et_3N; vii, NaN_3, DMSO; viii, Ph_3P, H_2O; ix, H_2, Pd/C, then HCl

Scheme 17



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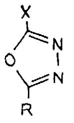

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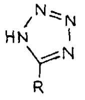

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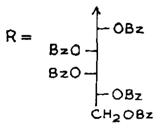

, X = Me or Ph

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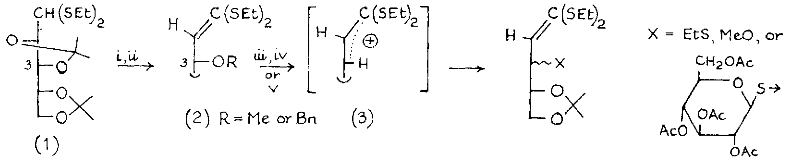
11
Thio- and Seleno-sugars

A review has appeared, in Japanese, on the use of PhS-, PhSe-, and PhSO-groups in highly stereoselective glycosidation reactions.[1] Part of the reviewed material has also been published in English and is referred to in Chapter 3, as are thioglycoside derivatives of sialic acid.

A series of mesogenic 1-alkylthio-1-deoxy-D-glucitols (hexyl to decyl) have been synthesised by reduction of the corresponding alkyl 2,3,4,6-tetra-*O*-diethylboryl 1-thio-D-glucopyranosides with diethyl borane, followed by deprotection.[1a] It has been shown that aldose dialkyl dithioacetals form a columnar hexagonal liquid crystalline mesophase, whereas their 6-deoxy analogues do not, indicating the essential nature of the terminal hydroxyl group for this molecular arrangement.[2]

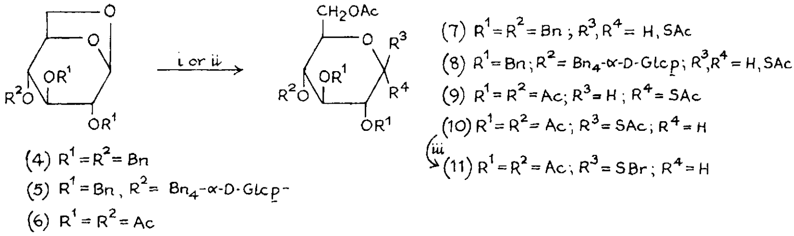
Ketene dithioacetal derivatives (2) are available from 2,3:4,5-di-*O*-isopropylidene-D-arabinose diethyl dithioacetal (1) by treatment with ^{t}BuOK followed by an alkyl halide to cause *in situ* alkylation. On exposure to nucleophiles in the presence of a Lewis acid they undergo substitution at C-3 (rather than addition to the double bond) presumably *via* the carbocation (3) as shown in Scheme 1. This reaction has been used, with moderate success, to introduce a thio sugar residue and hence afford a sulphur-linked disaccharide derivative.[3]



Reagents: i, Bu^{t}OK, DMSO, THF ; ii, MeI or BnCl ; iii, EtSH, ZnCl$_2$; iv, TMSCN, MeOH ; v, Ac$_4$-Glc*p*SH, ZnCl$_2$, MeOH

Scheme 1

Lewis acid catalysed thioacetolysis of the benzyl protected 1,6-anhydro-*β*-D-glucopyranose derivatives (4) and (5) gave 9:1 mixtures (7) and (8), respectively, of *α*- and *β*-1-thioacetates in reasonable yields (Scheme 2). From the peracetylated starting compound (6), on the other hand, the *α*- and *β*-products (9) and (10) were formed in a high yield and in 1:9 ratio.[4] The *α*-anomer (9) has also been prepared by ^{t}butylhydroperoxide catalysed addition of thioacetic acid to tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol,[5] and the *β*-anomer (10) was obtained from acetobromoglucose by treatment with KSAc. On shaking with excess of bromine in carbon tetrachloride at low temperature the thioacetate (10) was converted to the unstable, crystalline sulphenyl bromide derivative (11).[6]



(4) $R^1 = R^2 = Bn$

(5) $R^1 = Bn$, $R^2 = Bn_4$-α-D-Glc*p*-

(6) $R^1 = R^2 = Ac$

(7) $R^1 = R^2 = Bn$; $R^3, R^4 = H, SAc$

(8) $R^1 = Bn$; $R^2 = Bn_4$-α-D-Glc*p*; $R^3, R^4 = H, SAc$

(9) $R^1 = R^2 = Ac$; $R^3 = H$; $R^4 = SAc$

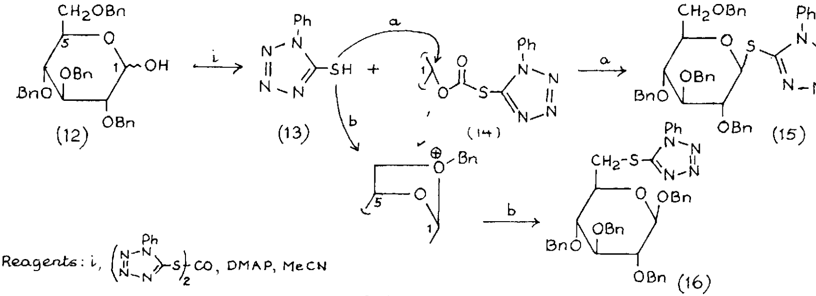
(10) $R^1 = R^2 = Ac$; $R^3 = SAc$; $R^4 = H$

(11) $R^1 = R^2 = Ac$; $R^3 = SBr$; $R^4 = H$

Reagents: i, Ac_2S, $ZnCl_2$; ii, Ac_2S, $BF_3 \cdot OEt_2$; iii, Br_2, CCl_4

Scheme 2

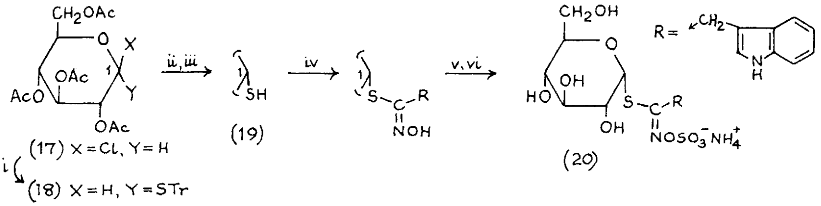
The 1-thio-D-glucose derivative (15) has been synthesised from the corresponding free sugar (12) by treatment with *S,S'*-bis(1-phenyl-1*H*-tetrazol-5-yl)dithiocarbonate. As indicated in Scheme 3, a thiocarbonate derivative (14) was formed initially with concomitant liberation of thiol (13). Direct attack by this thiol at C-1 (path a) gave the main product (15) in 63% yield, whereas benzyloxy participation in the displacement at C-1 with attack by the nucleophile at C-6 (path b) gave its regio-isomer (16) which was isolated in 33% yield.[7] The use of compound (15) in silver triflate promoted glycosylations is referred to in Chapter 3.



Reagents: i, $(\text{1-phenyltetrazol-5-yl-S})_2CO$, DMAP, MeCN

Scheme 3

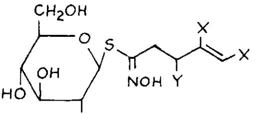
Addition of tetra-*O*-acetyl-1-thio-α-D-glucose (19) to a nitrile oxide was the key step in the first synthesis of an unnatural α-glucosinolate, (20), which is outlined in Scheme 4. Included in the Scheme is a new, high-yielding procedure for the preparation of compound (19) from its *S*-trityl derivative (18),[8] which in turn was available from the *β*-chloride (17).[9] The *galacto* analogue of the trityl thioether (18) has also been prepared.[8]



Reagents: i, $Bu_4\overset{+}{N}STr^-$, PhMe; ii, PhHgOAc; iii, H_2S; iv, $R\text{-}C{\equiv}\overset{+}{N}\text{-}O^-$; v, $ClSO_3H$, Py; vi, NH_3, MeOH

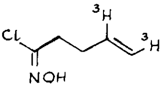
Scheme 4

The degradation of glucosinolates by ammonia in aqueous methanol has been investigated with simple hydroxamic acid derivatives (21) as model substrates. Nitriles or hydroxynitriles and thioglucose and its dimer, bis-(D-glucopyranosyl)disulphide, were the major products.[10] In a similar study, use was made of the [4′, 5′-^{3}H] labelled derivative (22), prepared by reaction of the chloride (23) with 1-thioglucose 2,3,4,6-tetraacetate and subsequent deacetylation.[11]

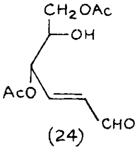


(21) X = H, Y = H or OH

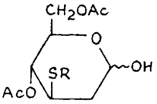
(22) X = ^{3}H, Y = H



(23)



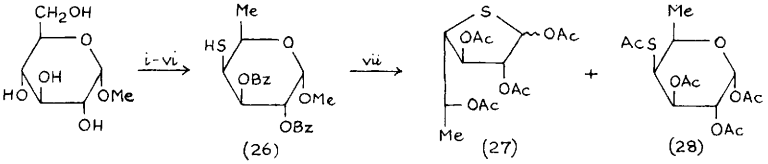
(24)



(25) R = Et or Bu^t

The Michael addition of thiols to enal (24) proceeded with high stereoselectivity to give D-*arabino* configurated 2-deoxy-3-thioethers (25) in excellent yields.[12] The use of sialic acid derived glycosyl donors with participating 3-phenylthio- and 3-phenylseleno-groups is referred to in Chapters 3 and/or 4.

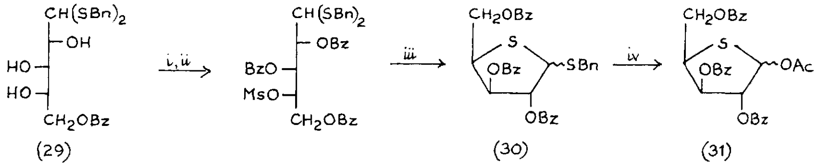
The 4-thio-D-fucopyranose derivative (26) was prepared from methyl α-D-glucopyranoside in six steps (Scheme 5), with introduction of the sulphur substituent by nucleophilic displacement of a 4-mesyloxy group with thiocyanate. On acetolysis, a 3:4



Reagents: i, Ph_3P, CBr_4; ii, N-Bz-imidazole; iii, TsCl, Py; iv, Raney Ni, H_2; v, KSCN, DMF; vi, Zn, HOAc; vii, Ac_2O, H_2SO_4, HOAc

Scheme 5

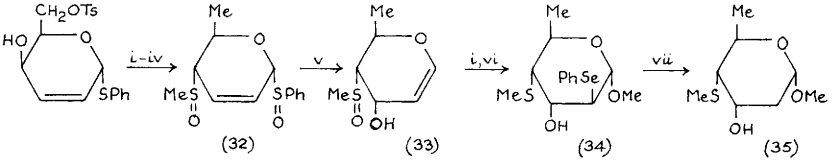
mixture of the furanoid and pyranoid peracetates (27) and (28), respectively, was obtained.[13] In the synthesis of the D-*xylo* thionucleoside precursor (31) from the L-*arabino*-configurated dithioacetal (29), the leaving group at C-4 was displaced intramolecularly, as shown in Scheme 6, and mercury(II) acetate was employed to convert the intermediate benzyl *S*-glycosides (30) to the 1-*O*-acetates (31).[14]



Reagents: i, Bu_2SnO, MsCl; ii, BzCl, Py; iii, Bu_4NI, $BaCO_3$; iv, $Hg(OAc)_2$, HOAc

Scheme 6

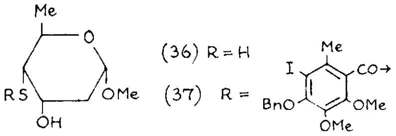
A further 4-thiosugar derivative, methyl 2,6-dideoxy-4-methylthio-α-D-*ribo*-hexopyranoside (35), was synthesised to establish the absolute configuration of the antibiotic esperamicin. The synthesis, which is outlined in Scheme 7, included introduction of a sulphur substituent at C-4 by nucleophilic displacement of a mesyloxy group, a selective [2,3]sigmatropic rearrangement to form the glycal derivative (33) from the allylic phenylsulphoxide (32), methoxyselenation of the glycal double bond and reduction of the resulting seleno-sugar (34) with triphenyltin hydride.[15] Further examples of allylic sugar sulphoxides undergoing [2,3]sigmatropic shifts are given in Chapter 13.



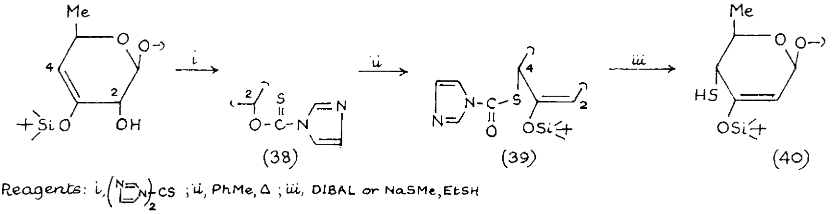
Reagents: i, LAH; ii, MsCl, Et_3N; iii, MeSNa; iv, MCPBA; v, Et_2NH; vi, PhSeCl, MeOH; vii, Ph_3SnH, AIBN

Scheme 7

The subunit (37) of the calicheamicins has been prepared by acylation of the thio-sugar (36) with the appropriately substituted benzoyl chloride.[16] The total synthesis of the oligosaccharide moiety of calicheamicin γ_1^I has been completed by Nicolaou's group, and details relevant to this Chapter are given in Scheme 8. Key features were the use of thiocarbonyldiimidazole as the sulphur source to prepare the sugar thionocarbamate (38), which underwent a [3,3]sigmatropic shift to give the 4-thiosugar derivative (39). Exposure



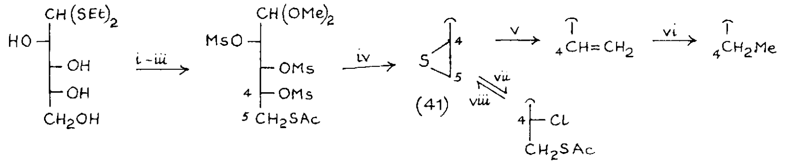
to catalytic NaSMe in EtSH or to DIBAL generated the free thiol (40) ready for coupling to the adjoining aromatic unit [*cf.*, (37)].[17,18] Other aspects of this work are found in Chapters 4, 9, and 15 and the x-ray analysis of a derivative of compound (35) is referred to in Chapter 22.



Reagents: i, $(\mathrm{N{=}N})_2\mathrm{CS}$; ii, PhMe, Δ ; iii, DIBAL or NaSMe, EtSH

Scheme 8

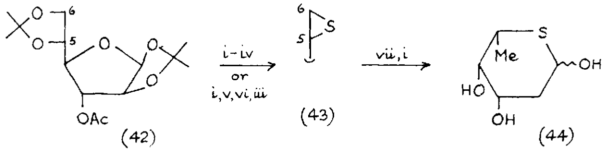
The conformational preferences of the 4-thiohexofuranoses with α- and β-D-*galacto*- and -D-*manno*, and α-D-*talo*- configurations have been assessed from $^3J_{H,H}$ values on the basis of a Karplus equation, the parameters for which were obtained by molecular mechanics calculations for tetrahydrofuran and tetrahydrothiophene.[19]



Reagents: i, MsCl, Et$_3$N ; ii, NBS, MeOH ; iii, KSAc, MeOH ; iv, HCl, MeOH ; v, Ph$_3$P, C$_6$H$_6$; vi, PtO$_2$, H$_2$; vii, AcCl ; viii, (NaHCO$_3$ or HCl), MeOH

Scheme 9

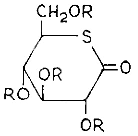
The synthesis and some reactions of 4,5-epithio-2,3-di-*O*-methanesulphonyl-L-xylose dimethyl acetal (41) are summarised in Scheme 9,[20] and Scheme 10 shows the preparation of 3-*O*-acetyl-5,6-epithio-1,2-*O*-isopropylidene-α-L-galactofuranose (43) from the D-altrose compound (42) - itself available in ten steps from D-glucose - and its conversion to 5-thio-L-fucose (44), an inhibitor of α-fucosidases.[21]



Reagents: i, HOAc(aq); ii, TsCl(1·4 eq), Py; iii, MeONa, MeOH; iv, $(NH_2)_2CS$; v, TsCl(2·8 eq), Py; vi, KSAc; vii, LAH

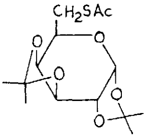
Scheme 10

Several peralkylated 5-thio-D-glucono-1,5-lactone derivatives, *e.g.*, compounds (45) and (46), have been synthesised by hydrolysis of the corresponding methyl glycosides, followed by Moffatt oxidation.[22] Oxidation of the permethylated 5-thioglucopyranoside (47) with MCPBA gave an 85:15 mixture of diastereomeric axial and equatorial sulphoxides (49) and (50). As indicated in Scheme 11, introduction of an α-acetoxy group at C-1 to give (48), achieved by acetolysis of the methyl glycoside, caused a marked change in the diastereomeric product ratio.[23]



(45) R = Me

(46) R = All



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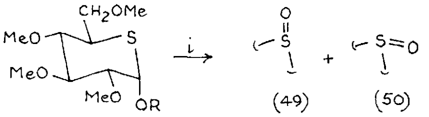


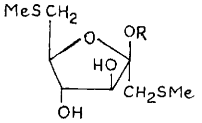
(47) R = Me $\xrightarrow{ii}$ (48) R = Ac

Starting Cpd	% Yield (49)	% Yield (50)
(47)	73	13
(48)	30	55

Reagents: i, MCPBA; ii, Ac_2O, CF_3CO_2H, AcOH

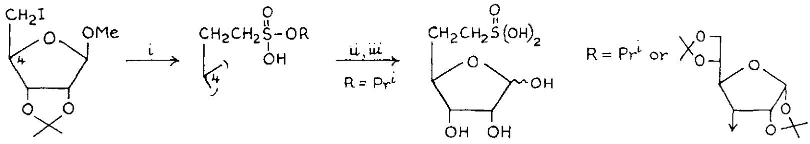
Scheme 11

6-*S*-Acetyl-1,2:3,4-*O*-isopropylidene-6-thio-α-D-galactopyranose (51) has been prepared in one step and in excellent yield from the 6-hydroxy compound by application of Mitsunobu conditions.[24] The synthesis of L-gulose and L-galactose from 6-*S*-phenyl-6-thiohexoses *via* Pummerer rearrangement is covered in Chapter 2, the synthesis of a lincomycin analogue involving a (2-hydroxyalkyl)thio intermediate in Chapter 19, and the reactions of 2-deoxy-3,4:5,6-di-*O*-isopropylidene-2-*C*-(nitromethyl)-1-*S*-phenyl-1-thio-D-glucitol in Chapter 14.



(52) R = H
(53) R = α-D-Glc.p

The di-*S*-methyl-dithio derivatives (52) and (53), respectively, of fructose and sucrose have been obtained by standard methods from the corresponding free sugars. Compound (52) is twenty times sweeter than sucrose, whereas the sucrose analogue (53) is only slightly sweet. Oxidation of the sulphide groups to sulphoxides or sulphones destroys the sweetness in both cases.[25]



Reagents: i, $ROSO_2CH_2Li$ - DMPU ; ii, NH_3 ; iii, H^+

DMPU = Dimethylpropyleneurea

Scheme 12

The reaction of simple α-lithio sulphonate esters with sugar iodides provides a facile route to the sulphonate analogues of important carbohydrate phosphates. When performed with the lithium salts of carbohydrate mesylates, the reaction furnishes sulphonate linked disaccharides. Examples are given in Scheme 12.[26]

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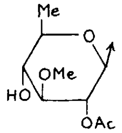
12

Deoxy-sugars

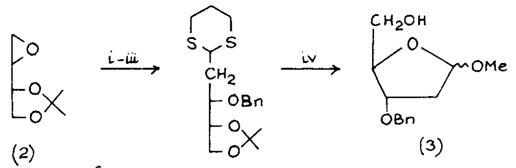
2-*O*-Acetyl-*β*-D-thevetosyl residues (1) and their 4-*O*-*β*-D-glucosylated analogues have been identified as components of steroid glycosides in the plant *Adenium obesum.*[1] Simple heating of cardenolide glycosides above their melting points is sufficient to cleave the glycosidic linkages joining 2,6-dideoxy-sugar moieties to the aglycons, but 6-deoxy-sugar bonds are more resistant to this thermal degradation.[2]

The mechanism for the conversion of GDP-D-mannose to GDP-6-deoxy-D-*lyxo*-hexos-4-ulose by bacterial GDP-mannose dehydratase has been studied using GDP-6(R)-and 6(S)-D-[4-^{2}H,6-^{3}H] mannose. It was concluded that the oxidoreductase caused transfer of H-4 to C-6 by a predominantly intramolecular, stereospecific process in which H-4 replaces HO-6 with inversion of configuration.[3] The mechanism of action of the enzyme which deoxygenates CDP-6-deoxy-D-*xylo*-hexos-4-ulose at C-3 during the formation of 3,6-dideoxyhexoses in nature has also been examined.[4] The incorporation of 3- and 4-deoxy- and deoxyfluoro-D-glucosyl residues into glycogen and maltopentaose by the action of rabbit muscle glycogen phosphorylase upon the corresponding α-D-glycosyl phosphates has been examined. While large numbers of 3-deoxy-residues could be incorporated, 4-deoxy-residues acted to inhibit the enzyme and were thus present only at non-reducing terminii.[5]

The 2-deoxy-D-*erythro*-pentofuranoside (3) was synthesized by one-carbon chain-extension of the epoxide (2) derived from D-isoascorbic acid (Vol. 22, p. 178, ref. 10) (Scheme 1). The isomeric 2-deoxy-L-*threo*-pentofuranoside (4) was likewise obtained from L-ascorbic acid.[6] 2,6-Dideoxy-3- and 5-*O*-methyl-DL-hexose isomers have been synthesized from 2,3-anhydro-4-deoxy-DL-*ribo*-hexose dimethyl acetal which rearranges to the corresponding 3,4-anhydro-*xylo*-hexose derivative faster than it undergoes oxirane ring cleavage.[7]



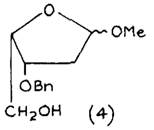
(1)



Reagents : i, Li-$\langle^{S}_{S}\rangle$; ii, BnBr ; iii, MeI-CaCO$_3$; iv, MeOH, H$^+$

Scheme 1

Radical reduction (with Bu_3SnH) of thioacylated sugars continues to be widely applied for the synthesis of deoxy-sugars. 3-Deoxy-D-*erythro*-hexulose (*i.e.* 3-deoxy-D-fructose) was conveniently prepared by acid hydrolysis of the product of Barton C-3 deoxygenation of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose, and its interactions with the enzymes of fructose metabolism were reported.[8] An alternative reducing agent



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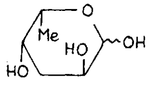

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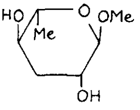

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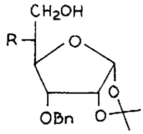
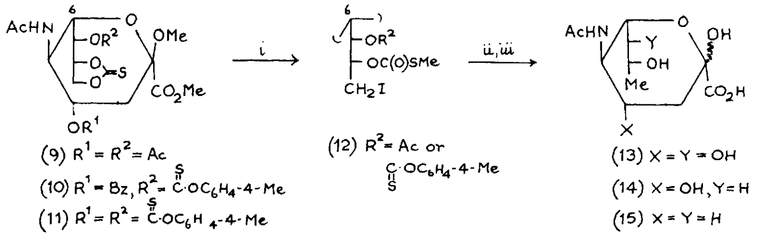


(7) R = OH
(8) R = H

combination [*tert*-dodecanethiol - $Bu^t_2O_2$ - Et_3SiH (2 mol %) in octane] has been developed to avoid the use of organotin species and effected conversion of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose 3-methylxanthate into its 3-deoxy-analogue in 60% yield.[9] 3-Deoxy-L-fucose (5) was synthesized from methyl α-L-fucopyranoside by radical reduction of a 3-*O*-(imidazolylthiocarbonyl)-derivative.[10] The ascaryloside (6) was obtained from methyl α-L-rhamnopyranoside by selective 3-*O*-pivaloylation (Me_3CCOCl-py, -20°C) and photochemical deoxygenation of the product.[11] Selective mono-deoxygenation of a diol, as for the conversion of allofuranoside (7) to its 5-deoxy-analogue (8), has been effected by a variety of methods: (a) Barton radical reduction of a xanthate ester, (b) hydroboration of an alkene, or (c) reduction ($LiAlH_4$) of a 6-benzoate, 5-tosylate.[12] 3- and 4-Deoxy-analogues of 2-acetamido-2-deoxy-D-glucose and -galactose have been synthesized by radical reduction of thiocarbonyl ester derivatives, and a 2-acetamido-2,6-dideoxy-D-glucose derivative was obtained by radical reduction of a 6-iodide. The deoxy-analogues of glucosamine were used in the enzymatic synthesis of deoxygenated oligosaccharides,[13] while the deoxy-analogues of galactosamine were shown not to have the binding affinity to rat and rabbit hepatic lectins that was observed for allyl 2-acetamido-2-deoxy-β-D-galactopyranoside.[14] Radical reduction of a thiocarbonyl ester also featured in a synthesis of 2′,3′-dideoxycytidine discussed in Chapter 20.

2′-,3′-,4′- and 6′-Deoxy-analogues of methyl β-lactoside have been synthesised. Radical reduction of 2′- and 4′-*O*-(phenylthionocarbonate)-derivatives gave the 2′- and 4′-deoxygenated disaccharides, while reduction ($NaBH_4$-$NiCl_2.6H_2O$) of a 6′-bromide gave the 6′-deoxygenated disaccharide. The 3′-deoxygenated disaccharide was constructed by coupling known 3-deoxy-glycosyl bromide donor and galactoside acceptor residues. While the methyl β-lactoside and its 6′-deoxy-analogue were substrates for β-D-galactosidase from *E. coli*, the 2′-deoxy- and 2′-amino-2′-deoxy-analogues were potent inhibitors.[15] The 9-

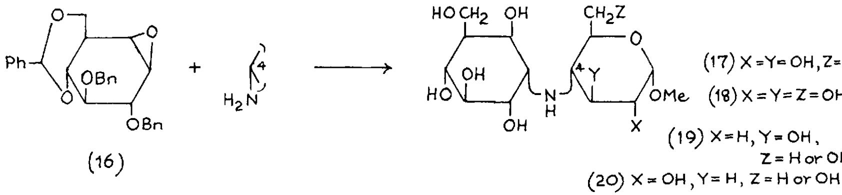
deoxy-, 7,9-dideoxy- and 4,7,9-trideoxy-*N*-acetylneuraminic acids (13) - (15) were synthesized by radical reduction of the 9-iodides (12) obtained from the mono- to tri-thiocarbonate derivatives (9) - (11), respectively (Scheme 2). These deoxy-compounds were activated by CMP-sialidase, but to a lesser extent (30-60%) than *N*-acetylneuraminic acid itself.[16] Syntheses of 7- and 8-*epi*- and 7,8-di-*epi*-2-deoxy-α-*N*-acetylneuraminic acid, and of 2,7- and 2,8-dideoxy-α-*N*-acetylneuraminic acid (by radical reduction of thiocarbonate derivatives) are discussed in Chapter 16.



Reagents: i, MeI ; ii, Bu₃SnH ; iii, hydrolysis

Scheme 2

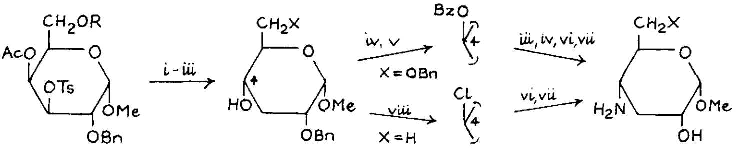
5-Deoxy-[5-^{2}H]-L-arabinose has been synthesized from L-arabinose by reduction (NaBD$_4$-DMSO) of the 5-tosylate of its diethyl dithioacetal, and converted into [3′-^{2}H] biopterin.[17] Methyl oligobiosaminide (17), its 6-hydroxy-derivative (18), and their 2- and 3-deoxy-analogues (19) and (20) have been synthesized by coupling 4-amino-4-deoxy-hexose residues with the pseudo-sugar epoxide (16) (Scheme 3). While almost no glycosidase



Scheme 3

inhibitory activity was evident for compound (17), its 2-deoxy- and 3-deoxy-6-hydroxy-analogues had enhanced activity against α-D-glucosidase and α-D-mannosidase, respectively. The 4-amino-4-deoxy-sugars required for the synthesis of the deoxy-derivatives (19) and (20) were obtained from methyl α-D-galactopyranoside. The 4-amino-2,4-dideoxy- and 4-amino-2,4,6-trideoxy-α-D-*arabino*-pyranosides were synthesized by conventional procedures (2-OCS$_2$Me → 2-H then 4-OMs → 4-N$_3$, and 6-OH → 6-Cl → 6-H). The 4-amino-3,4-dideoxy- and 4-amino-3,4,6-trideoxy-α-D-*ribo*-hexopyranosides (23) were synthesized as shown in

Scheme 4. Reaction of the galactoside mono- or di-tosylates (21) with sodium borohydride



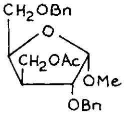
(21) R = Bn or Ts (22) X = OBn or H (23) X = OH or H

Reagents: i, $NaBH_4$; ii, Ac_2O, Py; iii, NaOMe, MeOH; iv, MsCl, Py; v, NaOBz; vi, NaN_3; vii, H_2, Pd/C; viii, SO_2Cl_2, Py.

Scheme 4

in refluxing propan-2-ol yielded predominantly the 3-deoxy- or 3,6-dideoxy-D-*ribo*-hexosides (22), presumably by way of a 3-deoxy-hex-4-uloside. Compound (22, X = H) was isolated in 47% yield from amongst a mixture of products, while compound (22, X = OBn) (63%) was accompanied by its C-4 epimer (7%) and the ring-contraction product (24) (30%).[18]

A new synthesis of 2-deoxy-D-*arabino*-hexose (*i.e.* 2-deoxy-D-glucose) involved the preparation (using Ph_3P-CCl_4-imidazole) of the 2-chloro-2-deoxy-D-mannonate derivative (25) from the D-gluconate (26), and its reduction (i, H_2-Pd/C-NaOAc; ii, Bu^i_2AlH). A variety of facile elimination and reduction reactions applied to (25) yielded various acyclic unsaturated and deoxy-derivatives.[19] Full details have been published on the syntheses of the stereospecifically deuterium-labelled 3,6-dideoxyhexoses ascarylose (Vol. 21, p. 121), abequose (Vol. 22, p. 127) and paratose (Vol. 23, p. 128).[20] Methyl 3-amino-3,4-dideoxy-α-D-*xylo*-hexopyranoside and its β-anomer (27) have been separately synthesized from the known 3-azido-3-deoxy-D-glucose by selective 4-chlorination (SO_2Cl_2-py) of the anomeric 2,4-diols (28) and radical reduction (Bu_3SnH).[21] The formation of 1-deoxyketose derivatives as by-products in the reaction of the corresponding 1-deoxy-1-halo-sugars with metal graphite reagents is discussed in Chapter 6.



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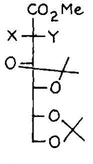
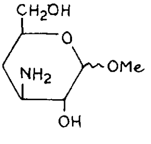


(25) X = Cl, Y = H
(26) X = H, Y = OH



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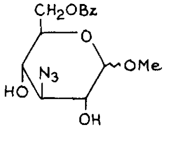
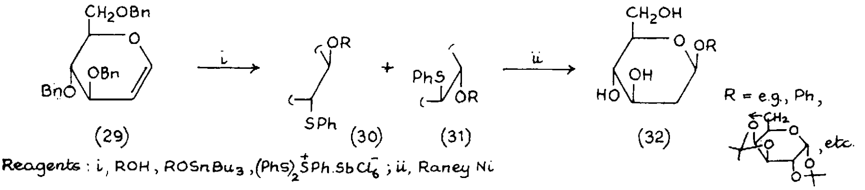


(28)

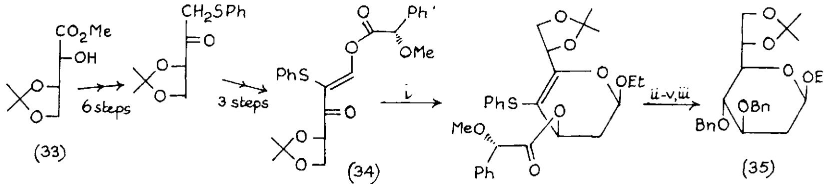
2-Deoxy-β-D-glucopyranosides, *e.g.* (32), can be synthesized by desulphurization of the major adduct (30) obtained along with less amounts of its isomer (31) from the D-glucal derivative (29) (Scheme 5). This procedure was applied to a range of glycals and appears



Reagents: i, ROH, ROSnBu$_3$, (PhS)$_2\overset{+}{S}$Ph.SbCl$_6^-$; ii, Raney Ni

Scheme 5

to be widely applicable.[22] Sterol 2-deoxy-D-glycosides have been synthesized from tri-*O*-acetyl-D-glycals by conversion to the 2-deoxy-glycosyl chlorides (with HCl in C_6H_6) and condensation with sterols (in the presence of $Hg(CN)_2$ and molecular sieves).[23] Syntheses of other 2-deoxy-glycosides are discussed in Chapter 4. The 2-deoxy-L-*galacto*-heptose derivative (35) was synthesized from L-ascorbic acid *via* the known L-threonate derivative (33), a key step being the inverse hetero-Diels-Alder addition of ethyl vinyl ether to enone (34) (Scheme 6).[24] The diamino-disaccharide derivative (36), required for the synthesis of

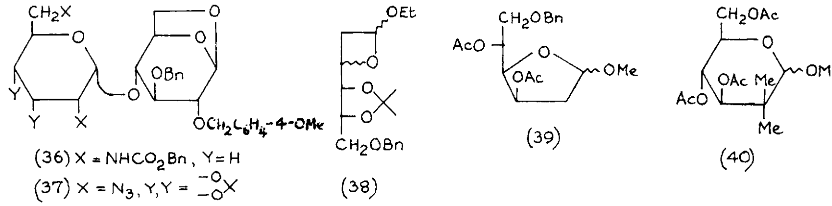


Reagents: i, ⌒OEt, 75°C, 6h; ii, NaOH; iii NaH, BnBr; iv, Raney Ni; v, BH_3·THF; then H_2O_2, NaOH

Scheme 6

an aminoglycoside, was synthesized from maltose *via* the known diazide (37) (Vol. 21, p. 188, ref. 14) by Corey-Winter conversion of the 3′,4′-diol into a 3′,4′-alkene [i, Im_2CS; ii, $P(OMe)_3$] and reduction.[25]

2-Alkoxyoxetanes, *e.g.* (38), have been obtained by formal [2 + 2]cycloadditions between 2,3-*O*-isopropylidene-*aldehydo*-D-erythrose derivatives and vinyl ethers, and have been converted to 2-deoxy-D-hexose derivatives, *e.g.* (39) and (40).[26] Palladium(II)



(36) X = $NHCO_2Bn$, Y = H

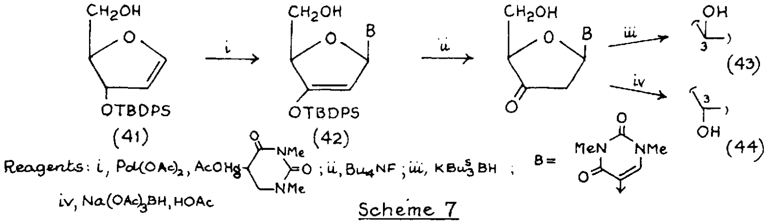
(37) X = N_3, Y,Y = $\begin{smallmatrix}-O\\-O\end{smallmatrix}\!\!>\!\!\times$

(38)

(39)

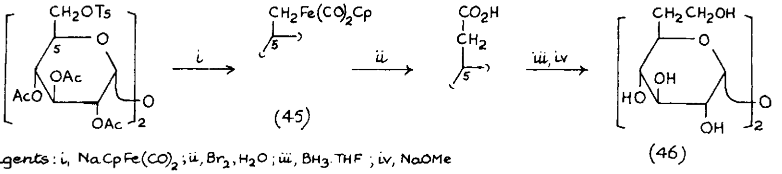
(40)

mediated coupling of mono-protected *erythro*-furanoid glycals with *C*-nucleophiles occurs selectively from the face opposite the substituted hydroxy-group. The 3-silylated glycal (41) thus gave the *β*-adduct (42) which could be converted into either the 2′-deoxy-D-*threo*-pentofuranosyl *C*-nucleoside analogue (43) or its D-*erythro*-isomer (44) (Scheme 7).[27]



Scheme 7

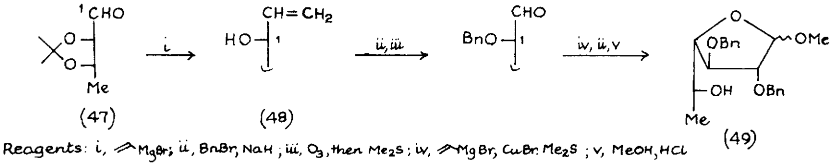
The chain-extended *α*,*α*-trehalose analogue (46) was synthesized *via* the organoiron(II) intermediate (45) which underwent a carbonyl insertion reaction (Scheme 8).



Scheme 8

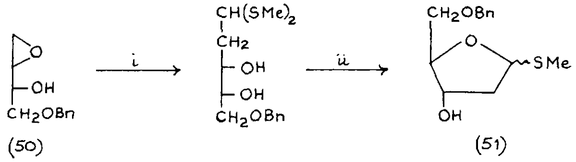
The analogous 6-deoxy-7-uronic acid was also synthesized, *via* a 6-cyanide derivative.[28] The syntheses of 6,7-dideoxy-octadialdose and 9,10-dideoxy-undecadialdose derivatives is discussed in Chapter 2.

Allylic alcohols of use in the synthesis of deoxy sugars have been synthesized by reaction of 4-deoxy-L-erythrose derivative (47) (available from the products of cinnamaldehyde in fermenting bakers' yeast) with various metal-alkenyl reagents; the major isomer (48), formed with vinylmagnesium bromide, was thus converted into the 6-deoxy-L-altrofuranosides (49) (Scheme 9).[29] Full details on the synthesis of 2-deoxy-L-sugars from L-tartaric acid *via* 4-*O*-benyl-2,3-*O*-isopropylidene-L-threose (Vol. 17, p. 122) have been published.[30] Branched-chain deoxy-sugars are discussed in Chapter 14.



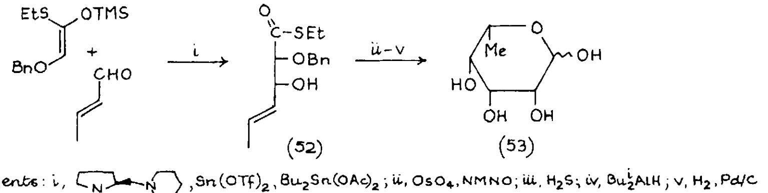
Scheme 9

The chiral epoxide (50), obtained by Sharpless asymmetric eposidation of a racemic alkene, has been converted into the 2-deoxy-thioglycosides (51), which were obtained as a 1:1 anomeric mixture (Scheme 10); the α-thioglycoside was used in the synthesis of 2′-deoxynucleosides.[31] 6-Deoxy-L-talose (53) has been synthesized from the aldol condensation product (52; >97% *ee*) formed using a chiral catalyst (Scheme 11).[32]



Reagents: i, $(Me_2S)_2CH_2$, BuLi ; ii, $AgBF_4$

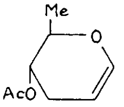
Scheme 10



Reagents: i, , $Sn(OTf)_2$, $Bu_2Sn(OAc)_2$; ii, OsO_4, NMNO; iii, H_2S; iv, Bu^i_2AlH ; v, H_2, Pd/C

Scheme 11

Racemic glycal (54), available from 3-buten-2-one and isobutyl vinyl ether, yielded a separable mixture of diastereomeric disaccharides on acid-catalysed addition of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose. Deprotection and hydrolysis of the separated diastereomers gave enantiomerically pure D- or L-amicetose (2,3,6-trideoxy-*erythro*-hexose).[33]



± (54)

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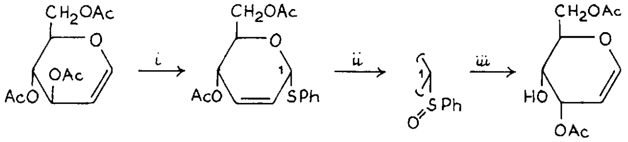
13
Unsaturated Derivatives

A number of carbohydrate examples feature in a review on "stereocontrolled cyclofunctionalization of double bonds through heterocyclic intermediates."[1]

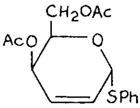
1 Glycals

An ingenious approach to D-allal derivatives is illustrated in Scheme 1, the sulphoxide rearrangement involving either a [2,3]-sigmatropic rearrangement to a sulphenate ester followed by acetyl migration, or neighbouring group participation by the acetoxy group in the displacement of the benzenesulphenyl group. That the D-galactal-derived (1) gave the D-gulal ester (2) suggests the intermediacy of the sulphenate (3).[2]


Reagents : i, PhSH, BF_3 ; ii, MCPBA ; iii, Piperidine

Scheme 1

An improvement in the synthesis of the tri-*O*-acetyl-D-galactal was noted when the reaction of tetra-*O*-acetyl-α-D-galactopyranosyl bromide with zinc–acetic acid was carried out at -15°C at which temperature less hydrolysis and acetolysis of the carbon-bromine bond occurred.[3] Tri-*O*-acetyl-D-glucal may be obtained from 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-D-glucosyl phenylthionocarbonate.[3a] Racemic (4) has been resolved by the acid-catalysed addition of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose and separation of the diastereomeric disaccharides produced. Amicetose, in both enantiomeric forms, was then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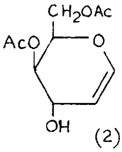
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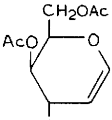
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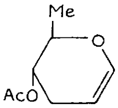
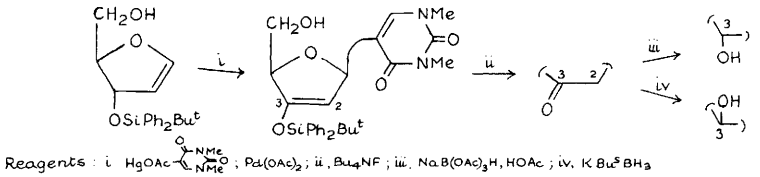

(4)

obtained in this way (Chapter 12).[4]

Sequential, selective silylation of the glycal gave 3-*O*-t-butyldimethylsilyl-6-*O*-t-butyldiphenylsilyl-D-glucal in 80% yield. From this product the 6-substituent could be removed under basic conditions to give the 3-ether. By reversing the initial silylation steps 6-*O*-t-butyldimethylsilyl-D-glucal was obtained.[5]

Regioselective deprotection of per(monochloroacetyl)glycals by hydrazine hydrate occurs at O-4. In this way 4-*O*-unprotected esters were made from D-galactal, D-glucal and L-rhamnal, and 4-acetates were then derived by acetylation followed by dechloroacetylation by use of thiourea.[6]

A review with 57 references has appeared on regio- and stereo-selective syntheses of *C*-glycosides by palladium-mediated glycal—aglycon coupling.[7] A new application, shown in Scheme 2, offers very selective routes to 2-deoxy-*C*-nucleoside compounds.

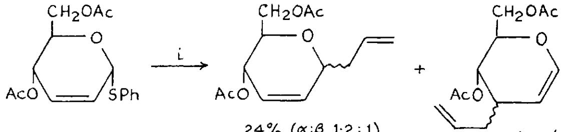


Reagents : i, HgOAc– ; Pd(OAc)$_2$; ii, Bu_4NF ; iii, NaB(OAc)$_3$H, HOAc ; iv, KBu^sBH_3

Scheme 2

When the reaction is applied to the isomeric 5-*O*-t-butyldimethylsilyl glycal, α-*C*-glycosides resulted.[8]

A full report (cf. *J. Org. Chem.*, 1987, *52*, 5691) has appeared on the production of *C*-glycosides by the coupling of glycal esters and alkenes (see Chapter 3). The 3-*C*-allylglycal (5) can be obtained as shown in Scheme 3, but the reaction has poor regio- and stereo-selectivity.[9]



24% (α:β, 1·2 : 1)

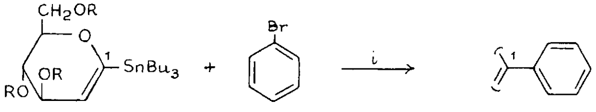
16% (ribo:arabino, 1:2)

(5)

Reagents : i, $CH_2{=}CHCH_2SnBu^n_3$, hν

Scheme 3

Reaction of tetra-*O*-acetyl-1-cyano-α-D-glycopyranosyl bromide with zinc–triethylamine–benzene gave the cyanoglycal (6) in 95% yield,[10] and two groups[11, 12] have used the tributyltinglycals (7) to make 1-arylglycals e.g. (8) (Scheme 4) and related



(7)

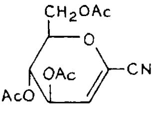
(8)

R = $SnBu_3$ (ref. 11)
= Bn (ref. 12)

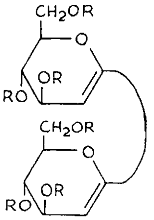
Reagents : i, $Pd(PPh_3)_4$

Scheme 4

compounds. The dimers (9) are present as by-products in the reactions, and the benzyl form can be obtained as main product on treating the tin derivative with $PdCl_2(MeCN)_2$.[12] From it the C-C linked disaccharide (10) is obtainable.

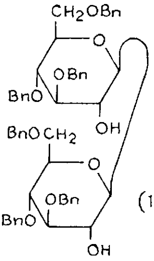


(6)



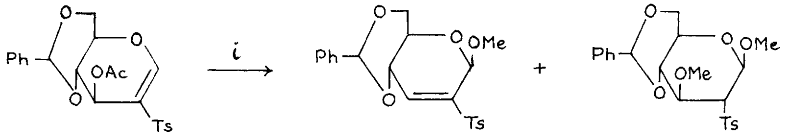
(9) R = $SnBu_3$ (ref. 11)

R = Bn (ref. 12)



(10)

Phenyl glycosyl sulphones can be converted into 1-(phenylsulphonyl)glycals and hence 2,3-unsaturated aldonolactones (see under "Other Unsaturated Derivatives"). The reaction of the 2-(*p*-tolylsulphonyl)glycal (11) with sodium methoxide gives the product (12) of S_N2' displacement together with the methanol adduct (13) (Scheme 5).[13] The use



(11)

(12) (36%)

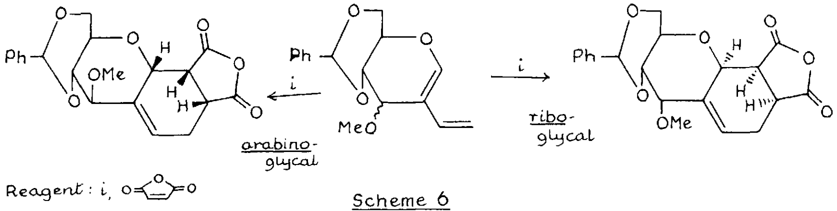
(13) (44%)

Reagent : i, NaOMe

Scheme 5

of a 2-(phensulphinyl)glycal derivative in the synthesis of a *C*-glycosidic antibiotic is noted in Chapter 19.

Results of Diels-Alder reactions applied to 2-*C*-vinylglycals are illustrated in Scheme 6.[14]

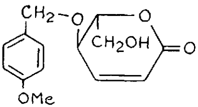


Scheme 6

2 Other Unsaturated Derivatives

Various exocyclic enes, derived from both aldonolactone and ulose derivatives, have been made using unpurified Tebbe reagent.[15] Reference to the generation of 2,6-anhydrohex-1-enitols from 1-halogenoketose derivatives is made in Chapter 6 and an annulated pyranoid derivative with a C-2 *exo*-double bond is noted in Chapter 14.

The conversion of 2,3-ditriflate esters into 2,3-unsaturated sugar derivatives has been reported,[16] and the treatment of the original α-diols with chlorodiphenylphosphine, imidazole and iodine is advocated for the large scale preparation of such compounds. Terminal α-diols give alkenes via iododiphenylphosphinates.[17] A set of 4-*C*-branched 2,3-enopyranosides has been made by application of Claisen-like sigmatropic rearrangements applied to 3,4-unsaturated precursors.[18] Specifically, the lactone (14) has been synthesised from L-serine;[19] more generally, 2,3-unsaturated aldonolactones may be obtained as indicated in Scheme 7.[20] The furan (15) was converted into a 4:1 mixture of the racemic enes (16) and (17).[21] Related compounds can be separated by conversion into diastereomeric disaccharide analogues.[22]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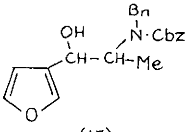
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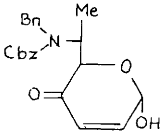
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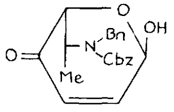
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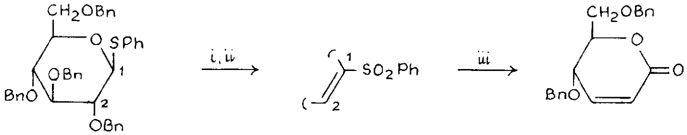


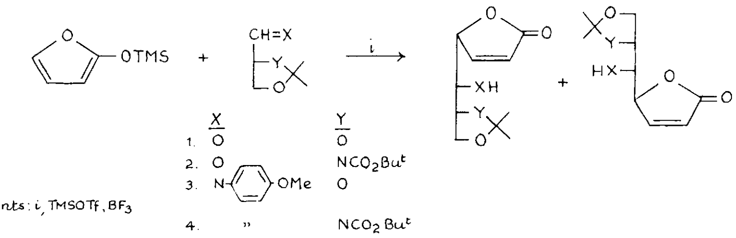
Reagents : i, MCPBA ; ii, LDA ; iii, NaOMe, THF, crown ether

Scheme 7

2,3-Unsaturated glycopyranosyl cyanides may be obtained from acetylated glycals using trimethylsilyl cyanide.[23]

The use of the double bonds of 2,3-unsaturated glycopyranosides to trap carbon radicals intramolecularly and thus provide stereospecific routes to branched-chain sugars is noted in Chapter 14.

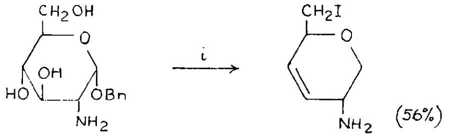
Treatment of 2-chloro-2-deoxynucleoside phenylthionocarbonates with tributyltin hydride and a radical initiator affords the 2-alkenes.[3a] Chapter 16 reports other 2,3-unsaturated furanoid compounds. Some aldonolactones of the series have been made as indicated in Scheme 8.[24]



Reagents: i, TMSOTf, BF3

Scheme 8

In the series of 3-enopyranosides, compound (18), under the Garegg iodinating conditions, gave mainly the 3,4-unsaturated 6-iodide (19) (Scheme 9). Lesser amounts of

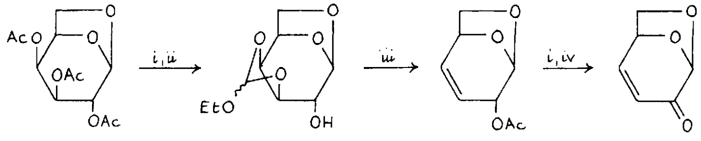


(18) (19)

Reagents : i, PPh3, I2, imidazole

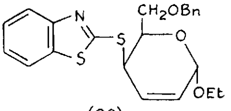
Scheme 9

a di-iodo product and of the β-anomer of (19) were also obtained, the latter having been derived from contaminating β-anomer of (18). Some inconsistencies between this work and previously published data (*J. Carbohydr. Chem.*, 1984, *3*, 189) were explained.[25] By use of a related elimination from a 3,4-orthoester derivative, levoglucosenone has been synthesised from D-galactose (Scheme 10).[26] Allylic rearrangement occurred when the allylic sulphide (20) was treated with BuMgBr–CuI and compound (21) resulted in good yield. The C-4 epimer of compound (20) failed to react — presumably because of the hindering of attack by the axial ethoxy group.[27] Compounds derived from *N*-acetylneuraminic acid with double bonds either in the 3,4- or 4,5-positions (normal ring numbering) are referred to in Chapter 9.

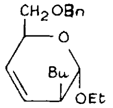


Reagents: i, NaOMe; ii, (EtO)$_3$CH, H$^+$; iii, ZrO$_2$, Ac$_2$O; iv, MnO$_2$

Scheme 10



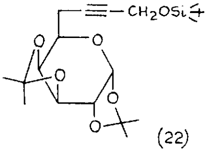
(20)



(21)

A convenient synthesis of hex-5-enopyranosides from 6-deoxy-6-halo-hexopyranosides involves treatment with sodium hydride–DMF with benzyl halide present; simultaneous benzylation of free hydroxy-groups occurs.[28] Reference is made to 5,6-unsaturated hexofuranose derivatives having a dimethoxyphosphinyl group at C-3 in Chapter 17.

Standard Wittig procedures have led to oct-6-enopyranose derivatives of relevance as potential lincomycin precursors.[29] A novel approach to compounds of this series is illustrated in Scheme 11.[30] The 7-yne derivative (22) was made using the lithium acetylide



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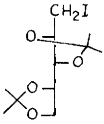

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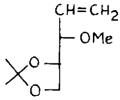
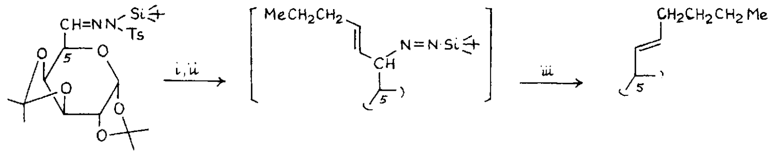


(24)

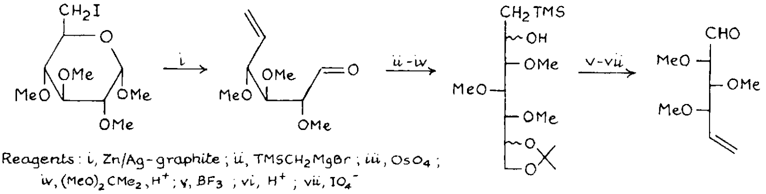
and the carbohydrate 6-triflate.[31]



Reagents: i, $LiCH{=}CHPr^n$; ii, HOAc; iii, Δ

Scheme 11

In the area of acyclic, unsaturated derivatives, the iodide (23) was converted into the ene (24) by use of C_8K followed by methyl iodide, and the reaction was applicable in the *arabino*-series.[32] By the method illustrated in Scheme 12, all of the isomeric

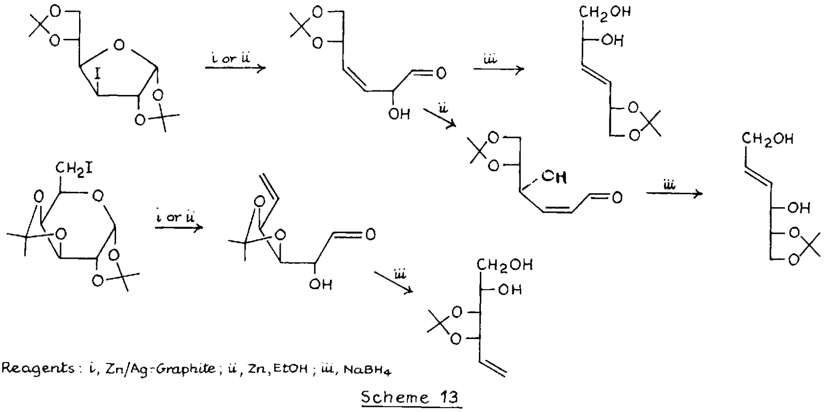


Reagents: i, Zn/Ag-graphite; ii, $TMSCH_2MgBr$; iii, OsO_4; iv, $(MeO)_2CMe_2$, H^+; v, BF_3; vi, H^+; vii, IO_4^-

Scheme 12

5,6-dideoxy-2,3,4-tri-*O*-methyl-hex-5-enoses, which are potentially useful chiral synthons, were prepared.[33] The same group of workers have reported other ring-opening reactions that also result in acyclic alkenes (Scheme 13).[34]

A new reaction of a 2-deoxy-hexopyranosyl 3-triflate that resulted in C-1–C-2 bond cleavage and the formation of a pent-1-enitol derivative is reported in Chapter 7.



Scheme 13

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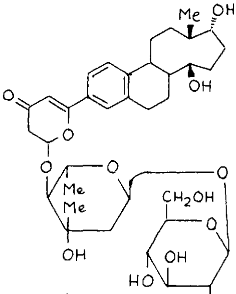
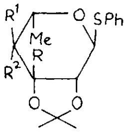
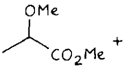
14
Branched-chain Sugars

1 Compounds with an R-C-O Branch

Carolinoside (1), isolated from *Solanum carolinense* as the host plant specific feeding induction factor for *Manduca sexta*, has been further characterised and shown to incorporate a 2,6-dideoxy-3-*C*-methyl-*β*-L-*arabino*-hexopyranose unit.[1] Alkylation (LDA/MeI) of ketone (2) has afforded the 3-*C*-methyl derivative (3) which was converted to the *N*-benzylformamide compound (4), an *N*-formylkanosamine glycosyl donor.[2] Aldol condensation (LDA/THF) of ester (5) with aldehyde (6) produced predominantly the isomer (7) which was converted into L-cladinose (8).[3] An aldol condensation of *trans*-but-2-enal with a ketene thioacetal has been employed with a chiral catalyst in a preparation of 4-*C*-methyl-D-ribose.[4]


(1)


(2) R = H; R^1,R^2 = O
(3) R = Me; R^1,R^2 = O
(4) R = Me; R^1 = N(Bn)CHO; R^2 = H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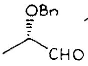
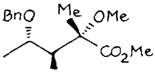
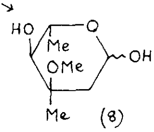
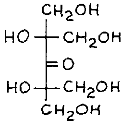

(6)


(7)

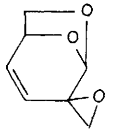

(8)

The addition of tetramethylzirconium to carbohydrate ketones has been used for the preparation of branched-chain derivatives. The methyl group was introduced in the equatorial orientation with pyranosyl ketones in chair conformations, whereas for some enones a 1,2- addition was observed with the methyl group incorporated *cis* to an adjacent hydroxyl group.[5] Oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-glucoseptanose has afforded the corresponding 5-ulose which, on treatment with MeMgI and subsequent hydrolysis, gave 5-*C*-methyl-D-glucose and 5-*C*-methyl-L-idose.[6] The synthesis of 6-*C*-methyl- and 6-*C*-(hydroxymethyl)analogues of *N*-acetylneuraminic acid and of the corresponding branched

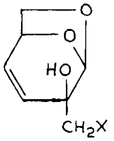
2,3-didehydro-2-deoxy compounds is discussed in Chapter 16 together with the synthesis of some branched KDO analogues as potential inhibitors of CMP-KDO synthetase, and the allylation of ascorbic acid at C-2 using Pd(0) complexes. A 5-*C*-methyl-*C*-pyranoside derivative used in the partial synthesis of Brevetoxin A is mentioned in Chapter 24.



(9)



(10)

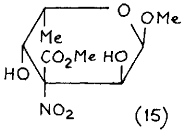


(11) X = OH
(12) X = H
(13) X = N_3
(14) X = NH_2

The bis-branched-chain 3-pentulose (9) was formed in the formose reaction using thiamine HCl as catalyst under controlled conditions.[7] The *spiro*-epoxide (10), synthesized from levoglucosenone by the Corey procedure (NaH/Me_3SI/DMSO-THF), was used to prepare the branched derivatives (11) - (14).[8]

2 Compounds with an R-C-N Branch

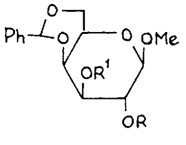
Methyl 3,6-dideoxy-3-*C*-methoxycarbonyl-3-*C*-nitro-α-L-*galacto*-hexopyranoside (15) was prepared by periodate oxidation of methyl α-L-rhamnopyranoside followed by condensation with methyl nitroacetate.[9] The synthesis of 2-*C*-hydroxymethyl derivatives of *N*-acetyl-6-amino-2,6-dideoxyneuraminic acid is covered in Chapter 16.



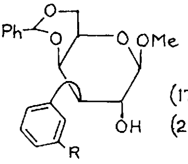
(15)

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

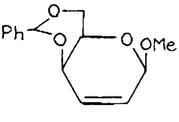
During Tipson-Cohen reaction of ditosylate (16) (NaI/Zn/DMF) a minor by-product (13%) was isolated and identified as the 3-*C*-aryl derivative (17). The mixed sulfonates (18) and (19) were prepared and subjected to the same conditions to give, as well as the expected alkene (20), the by-products (21) and (17) respectively. A C-3 carbanionic intermediate was postulated which attacked the aromatic ring of the C-2 sulfonate expelling SO_2.[10] Syntheses from D-glucose of a triquinane and of an intermediate in the synthesis of the ansa chain of streptovaricin A are covered in Chapter 24, and some branched-chain 2',3'-dideoxy nucleosides are mentioned in Chapter 20.



(16) R = R¹ = Ts
(18) R = SO_2Ph, R¹ = Ts
(19) R = Ts, R¹ = SO_2Ph

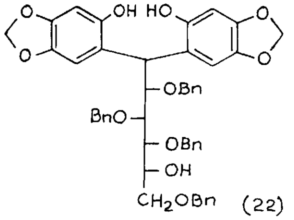


(17) R = Me
(21) R = H

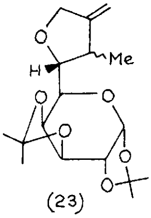


(20)

Bromomagnesium salts of some substituted phenols, when treated with aldose derivatives having unprotected anomeric hydroxyl groups have given bis(hydroxyaryl)-*C*-glycosyl compounds, *e.g.* (22) from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose.[11] A palladium-catalysed reaction which forms methylene tetrahydrofurans from aldehydes has been extended to carbohydrates and has allowed the formation of adduct (23) and other, similar compounds from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,5-dialdopyranose.

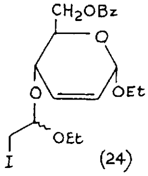


(22)

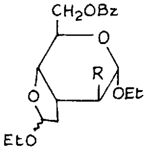


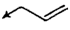
(23)

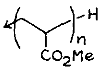
Radical reactions have been further utilised in the construction of branched-chain sugars. Unsaturated iodide (24) with allyltributyltin or Bu_3SnH and methyl acrylate has afforded the doubly-branched derivatives (25) and (26) by way of intra- and then inter-molecular radical processes. Similarly, bromide (27) gave the 3-*C*-allyl derivative (28) which, after transformation into enal (29), underwent a further radical cyclisation (Scheme 1).[13] Free radical addition of *p*-toluenesulfonyl bromide to the 1,6-diene (30) gave rise to bicyclic adduct (31) which could be reductively debrominated with Bu_3SnH.[14] The synthesis



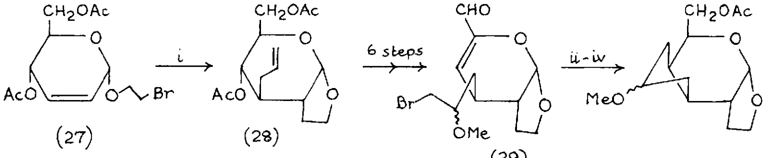
(24)



(25) R = 

(26) R =  n = 1–3

of isoavenaciolide by way of a radical cyclisation of a D-ribose derivative is mentioned in Chapter 24. Treatment of 1,3,4,6-tetra-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranose with allyltributyltin gave, as the predominant product, 1,3,4,6-tetra-*O*-acetyl-2-*C*-allyl-2-deoxy-β-D-glucopyranose.[15] Stork's silylmethylene radical cyclisation ($ClSiMe_2CH_2Br$, then Bu_3SnH) was applied to the annulated sugar allylic alcohol (32) and its epimer at the allylic alcohol

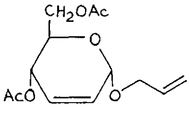


(27) (28) (29)

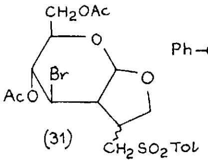
Reagents: i, $\diagup\!\!\diagdown SnBu_3$, AIBN ; ii, Bu_3SnH, AIBN ; iii, $NaBH_4$; iv, Ac_2O, Py

Scheme 1

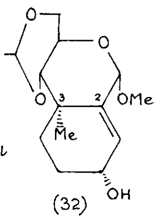
centre. In both cases *trans* addition to the double bond occurred, in the case of (32) to give silyl ether (33) which was transformed into alcohol (34).[16] A new procedure for the replacement of a hydroxyl group by a C-C bond has been described. A mesylate or triflate ester is displaced by $AnTe^-$ to give an anisyl telluride derivative. This is photolysed in the presence of suitable radical acceptors to give branched compounds.[17]



(30)

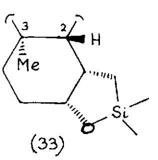


(31)

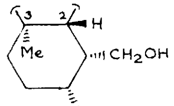


Ph

(32)



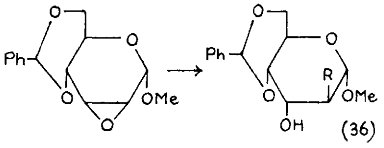
(33)



(34)

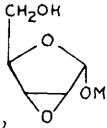
A new route to higher order allylic cyanocuprates that are stable at 0°C has been reported. This allowed the *C*-allyl compound (36) (R = allyl) to be prepared in almost quantitative yield from epoxide (35).[18] The same epoxide has been opened with a number of other organometallic reagents to give the branched derivatives (36).[19] Epoxide (37) was treated with allyl- and isobutenyl-magnesium chloride to give the branched *arabino* derivatives (38), whereas the β-anomer of (37), under the same conditions, afforded the products (39) of opening at C-3.[20] The anhydro-pentopyranosides (40) and (41) with alkynyl aluminates both suffered *trans*-diaxial oxirane ring opening to give branched derivatives (42) and (43), respectively. The regioselectivity was different because the starting epoxides had different conformations.[21]

The *spiro*-cyclopropyl glycoside (44) has been prepared from methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside, and then reduced and deprotected to give triol (45). The free sugar corresponding to glycoside (45) was also prepared.[22] Photolysis of bis-azide (46) in the presence of acrylonitrile afforded, as the major product, the *spiro*-cyclopropyl sugar (47).[23] The oxirane triflates (48) and (49), when treated with lithiated acetonitrile, initially gave products of displacement of the triflate groups which, in the presence of excess of base, suffered intramolecular opening of the oxirane rings to give the cyclopropyl derivatives (50) and (51). By contrast, lithiated t-butyl acetate, with oxirane triflates (48) and (49), gave the products of simple triflate displacement with the oxirane rings intact.[24]

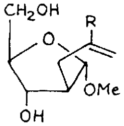


(35) (36)

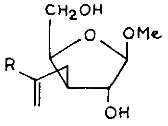
$R = CH_2CH{=}CH_2$,
$CH_2C(Me){=}CH_2$,
$CH_2C{\equiv}C{\cdot}SiMe_3$



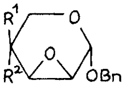
(37)



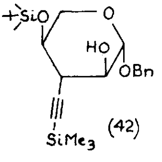
(38) R = H, Me



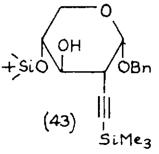
(39) R = H, Me



(40) R^1 = OSi, R^2 = H
(41) R^1 = H, R^2 = OSi



(42)



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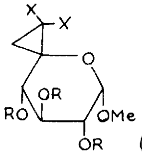
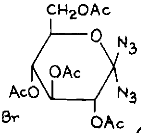


(44) R = Ac, X = Br
(45) R = X = H



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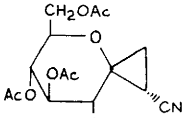

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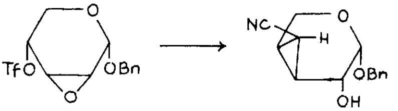
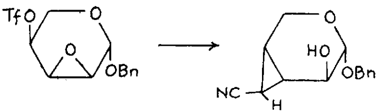
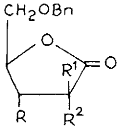


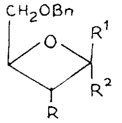
(48) (50)



(49) (51)

The ring contraction (K_2CO_3/MeOH) of 2-*O*-triflates of γ-lactones with a branched chain at *C*-3 has been shown to proceed with inversion of configuration. Thus D-*ribo*-triflate (52) afforded oxetane (53), and *arabino*-triflate (54) gave the epimer (55).[25] The oxetane (53) (R=CH_2OBn) has also been converted into the nucleoside analogue oxetanocin.[26] An improved synthesis of 1-*O*-acetyl-D-oxetanose (56), from epoxy alcohol (57), itself available by Sharpless epoxidation of (Z)-butene-1,4-diol monobenzyl ether, has been elaborated.[27] A further report has been published on the synthesis of 3-*C*-carbamoyl-3-*C*-cyano-3-deoxyhyxopyranosides by the cyclisation of periodate-oxidised methyl glucoside with cyanoacetamide.[28] Selective reductions applied to other similar *gem*-disubstituted carboxethyl-nitrile derivatives have been reported.[29]

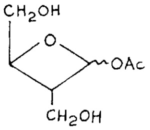




R = Me, CH_2OBn, CH_2CH_2OBn

(52) R^1 = H, R^2 = OTf (53) R^1 = H, R^2 = CO_2Me

(54) R^1 = OTf, R^2 = H (55) R^1 = CO_2Me, R^2 = H



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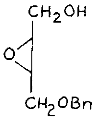
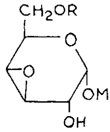
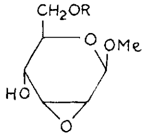


(57)

A number of hexopyranose epoxides have been treated with LiBr to furnish ring-contracted dihydrofuran aldehydes. Epoxides (58) and (59) afforded unsaturated aldehydes (60) and (61), respectively.[30] Conjugate addition of LiMeCuCN to aldehyde (61) with *in situ* trapping of the enolate produced the enol silyl ethers (62).[31] The branched nitro compound (63) has been converted separately into the aldehyde (64) and the thioglycoside (65).[32] Whereas previous applications of the Tebbe reagent have used specially purified material, apparently the crude reagent system can be employed on sugar esters and lactones

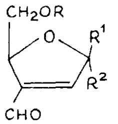


(58)



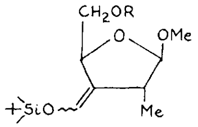
(59)

R = $SiMe_2$Thexyl

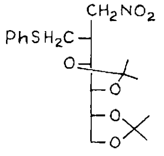


(60) R^1 = H, R^2 = OMe

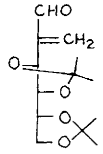
(61) R^1 = OMe, R^2 = H



(62)



(63)



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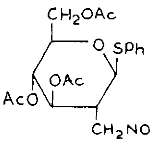
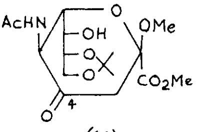
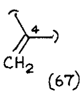


(65)

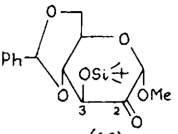
and, in the case of uloses, affords branched alkene derivatives.[33] The diulose derivative (66) with Cp_2ZrCl_2/CH_2I_2 has produced the alkene (67) from which 4-deoxy-4-*C* methyl epimers of neuraminic acid were obtained.[34] Wittig reaction ($Ph_3P{=}CHCO_2Et$) of either the 2-ulose (68) or 3-ulose (69) generated only the alkene (70) because of isomerisation of silyl ether (69). Alternatively, the t-butyldiphenylsilyl ether (71) with $Ph_3P{=}CHCO_2Me$ gave the unisomerised product (72), which was converted into lactone (73). Methylation ($LiN(TMS)_2$/MeI) of this afforded stereospecifically the *exo*-derivative (74).[35] 2,3:4,6-Di-*O*-isopropylidene-D-arabinose has been converted into 2-deoxy-2-*C*-phenyl-D-mannose which was utilised as a substrate for an immobilised *N*-acetylneuraminate pyruvate lyase to produce a 5-*C*-phenyl KDN analogue.[36] Bis-annulated pyranosides (75) and (76) have been prepared by intramolecular Diels-Alder cycloadditions,[37] and other thermal Diels-Alder reactions of pyranose diene derivatives are covered in Chapter 13. The synthesis, from D-glucose, of (+)-meroquinene, a branched iminocyclitol, is discussed in Chapter 24.



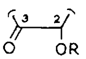
(66)



(67)

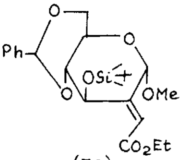


(68)

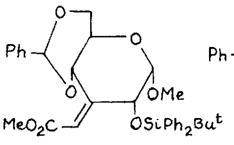


(69) R = Si

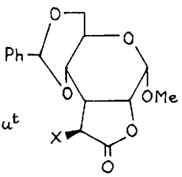
(71) R = $SiPh_2Bu^t$



(70)

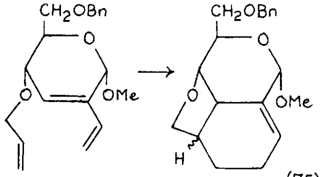


(72)



(73) X = H

(74) X = Me



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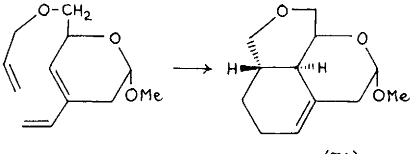

(76)

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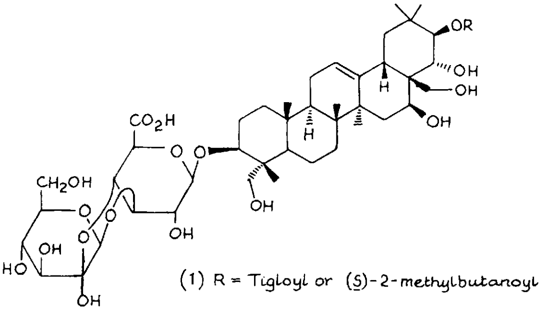
15

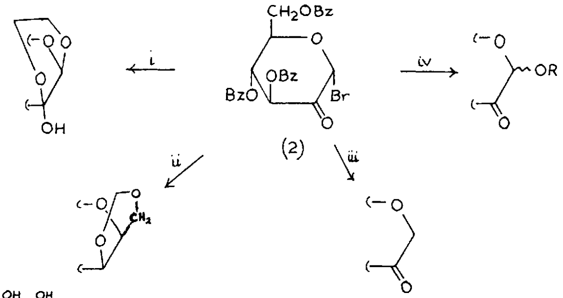
Aldosuloses, Dialdoses, and Diuloses

1 Aldosuloses

Two new gymnemic acid congeners (1) have been isolated from the leaves of *Gymnema sylvestre*[1]. A review of the Maillard reaction - in which oxidised derivatives of carbohydrates are proposed as important intermediates - has been published.[2] Carbohydrate alcohols with other hydroxyl groups appropriately protected as acetals, ethers or benzoates are oxidised by "active" RuO_2 - $NaIO_4$ under phase-transfer conditions to ketones, aldehydes or to carboxylic acids.[3] The glyculosyl bromide (2), readily prepared from the corresponding hydroxyglycal tetrabenzoate, has been utilised in a number of reactions (Scheme 1).[4] Both 3-deoxy-L-*glycero*-pentos-2-ulose and L-*threo*-pentos-2-ulose have been identified as intermediates in the acid or neutral degradation of L-ascorbic acid in water at 100°C.[5] The syntheses of D-*erythro*-pentos-2-ulose and its D-*threo* isomer by the oxidation of D-arabinose



(1) R = Tigloyl or (S)-2-methylbutanoyl

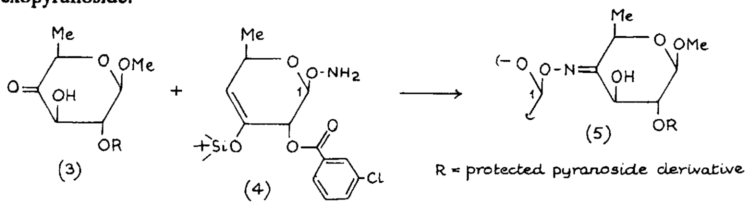


Reagents: i, OH OH; ii, CH_2O, Zn; iii, Bu_3SnH, AIBN; iv, ROH

Scheme 1

and D-xylose, respectively, with cupric acetate followed by ion-exchange chromatography have been reported. The 1-^{13}C- and 2-^{13}C- substituted derivatives were also prepared by oxidation of the appropriate ^{13}C-substituted sugars.[6]

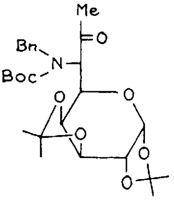
During the total sysnthesis of the oligosaccharide fragment of calicheamycin γ, the hexulose derivative (3) was treated with the glycosyloxyamino-sugar (4) to form the oxime derivative (5) (Scheme 2). In a later step the oxime was reduced to give a product having a saturated O-N-saccharide linkage.[7] The lincosamine precursor (6) has been reported in a synthesis from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-dialdohexopyranoside.[8]

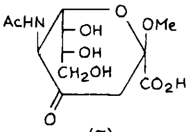


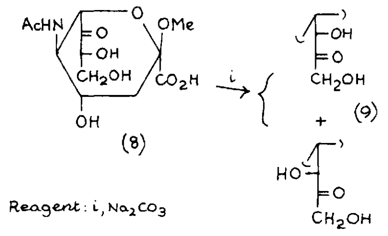
Scheme 2

2 Oxa-dialdoses

A fast and reliable HPLC method has been developed to follow the course of the periodate oxidation of sucrose as a function of periodate used. Two intermediate sucrose dialdehydes were formed as well as the final tetra-aldehyde compound.[9]


(6)


(7)



Scheme 3

3 Diuloses

The 4- and 7-oxo-*N*-acetylneuraminic acid derivatives (7) and (8) have been synthesized. Treatment of the latter with Na_2CO_3 afforded a 1:1 mixture of 8-oxo-neuraminic acid derivatives (9) and (10) (Scheme 3).[10]

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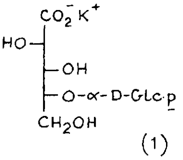
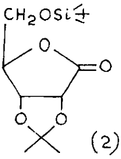
16
Sugar Acids and Lactones

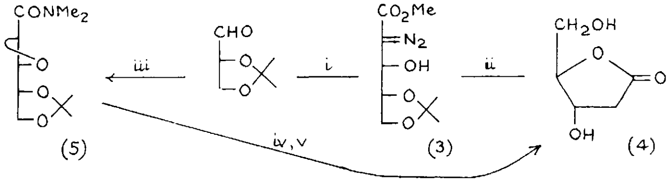
1 Aldonic Acids

Gluconic and galactonic acids can be obtained from lactose in ultrafiltrates of whey by microbiological hydrolysis and oxidation.[1] An investigation has been reported into the effects of bismuth salts on the oxidation of lactose to lactobionic acid using molecular oxygen and palladium catalysts,[2] and controlled oxidation of the ketodisaccharide leucrose gave 4-*O*-(α-D-glucopyranosyl)-D-arabinonate (1), convertible into various esters and amides.[3] The ribonolactone derivative (2) can be prepared from the corresponding hemiacetal in high yield by permanganate oxidation.[4]


(1)


(2)

Reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde with methyl diazoacetate gives predominantly (ca. 5:1) the D-*erythro*-isomer (3) (Scheme 1), convertible on hydrogenolysis to lactone (4).[5] The same product (4) could also be obtained via the epoxyamide (5), which was produced in a 6:1 predominance over the alternative *trans*-epoxide when isopropylidene glyceraldehyde was treated with a sulphur ylid (Scheme 1).[6] A full account



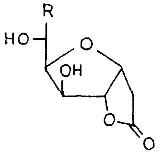
Reagents: i, N_2CHCO_2Me; ii, H_2, Pd/C, MeOH; iii, $Me_2\overset{+}{S}\text{-}\overset{-}{C}HCONMe_2$; iv, $NaBH_4$, EtOH; v, TFA, H_2O

Scheme 1

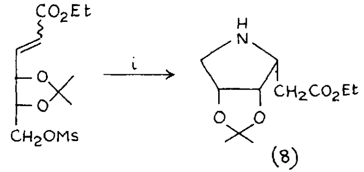
has been given of the interaction of isopropylidene-D-glyceraldehyde with 2-trimethylsilyloxyfuran to give 2,3-dideoxy-hept-2-enono-1,4-lactones (see

Vol. 23, p. 158), and the use of imines and derivatives of D-serinal in similar reactions led to analogous 4- and 5-aminodeoxy derivatives.[7] A synthesis of pyranoid enonolactones is mentioned in Chapter 13.

Reaction of D-xylose and D-glucose with Meldrum's acid gave lactones (6) and (7), respectively, in reasonable yield.[8] The iminoester (8) is produced in good yield by a stereoselective Michael addition reaction, as indicated in Scheme 2, and a more complex case involving the α,β-unsaturated ester derived from 2,3:5,6-di-*O*-isopropylidene D-mannofuranose was also reported.[9]



(6) R = H
(7) R = CH_2OH

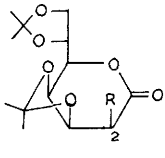


(8)

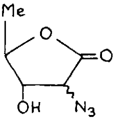
Reagents: i, NH_3, EtOH

Scheme 2

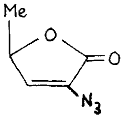
Interesting results have been published concerning the reactions of 2-*O*-sulphonyl derivatives of aldonolactones. The triflate (9) was converted using sodium azide in DMF into the azide (10) with overall retention of configuration, although this reaction was shown to proceed by displacement with inversion followed by epimerization of the initial azide. The C-2 epimer of (9) also gave (10) with azide in DMF, and in this case it was shown that this apparently simple inversion occurred by a sequence of epimerization to (9), displacement, and epimerization of the azide.[10] A mixture of epimers (11), with the D-*arabino*-isomer predominating (7:3), was formed when 2-*O*-tosyl - 5-deoxy-D-ribonolactone was treated with sodium azide in DMF. Treatment



(9) R = OTf
(10) R = N_3



(11)



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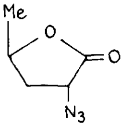
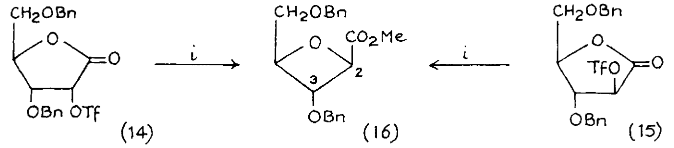


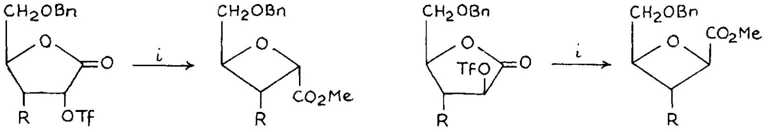
(13)

of (11) with Ac_2O-pyridine formed the unsaturated azidolactone (12), whilst the 3-deoxy analogue (13) was formed via a clean inversion of configuration from the 2-*O*-tosyl derivative. These azidolactones were used to prepare *erythro*- and *threo*-γ-hydroxynorvaline.[11] Ring contraction of 2-*O*-triflyl derivatives of aldono-1,4-lactones gives oxetane-2-carboxylic esters such that the product has *trans*-stereochemistry at C-2 and C-3. Thus for example both the D-ribonolactone derivative (14) and its D-arabinono analogue (15) gave the same D-*ribo*- product (16) (Scheme 3).[12] On the other hand, similar systems in which the 3-alkoxy group is replaced either by hydrogen (i.e. a 3-deoxy system) or a carbon chain, undergo ring contraction with predictable inversion of configuration, as in the cases in Scheme 4.[13] The application of such chemistry for the synthesis of oxetanocin is discussed in Chapter 19. Related triflates derived from 3-azido-3-deoxy- and 3-deoxy-3-fluoro-1,4-lactones give only small amounts of oxetane products, with elimination products predominating.[14]



Reagents: i, K_2CO_3, MeOH

Scheme 3

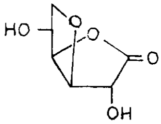


Reagents; i, K_2CO_3, MeOH

R = Me, $-CH_2OBn$, $-CH_2CH_2OBn$

Scheme 4

3,6-Anhydro-D-glucono-1,4-lactone (17) is formed from D-glucono-1,5-lactone by treatment with formic acid in anhydrous HF, and D-mannono-1,4-lactone gives the C-2 epimer of (17) under the same conditions.[15] 2,3-Epoxyaldonolactones, as a mixture of 1,4- and 1,5- isomers, can be formed as indicated in Scheme 5; these can be used as precursors for 2-deoxy-2-fluoro-aldonolactones.[16] A reference to a derivative of 2-chloro-2-deoxymannonic acid is given in Chapter 11.



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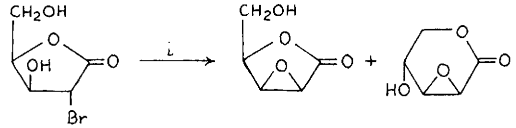
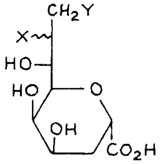


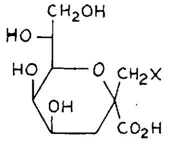
Reagents : i, KF, Me_2CO

Scheme 5

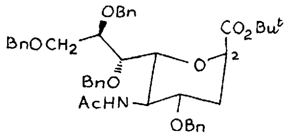
Analogues of 2-deoxy-β-KDO and 2-deoxy-α-Neu*N*Ac continue to attract attention. A range of compounds has been reported which involve modification of 2-deoxy-β-KDO at C-8, including the chain extended analogues of type (18),[17] and the same group has also prepared the *C*-glycosidic analogues (19) by methods complementary to those used earlier by other



(18) X,Y = NH_2,OH

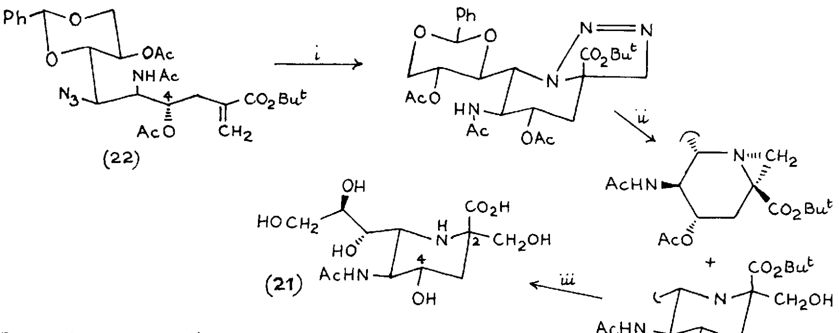


(19) X = NH_2,OH,-PO_3H_2



(20)

workers (Vol. 21, p.159) for similar compounds.[18] The Swedish group has also reported further extensions of their route to analogues of type (19).[19] The derivative (20) can be obtained from its C-2 epimer by formation of the anion and kinetic protonation; deprotection then yields 2-deoxy-α-Neu*N*Ac.[20] Zbiral's group have reported the synthesis of the 7-epi-, and 8-epi-, and 7,8-bis-epi- analogues of 2-deoxy-α-Neu*N*Ac, together with the 2,7- and 2,8-dideoxycompounds, by manipulation of previously known intermediates; this paper also describes an improved synthesis of 2-deoxy-α-Neu*N*Ac methyl ester.[21] The hydroxymethyl derivative (21) has been prepared from the previously reported intermediate (22) (Vol. 22, p.160) as outlined in Scheme 6; similar chemistry involving the C-4 epimer of (22) and the C-4 ketone was used for the synthesis of the 2-epimer and 2,4-bis-epimer of (21).[22]



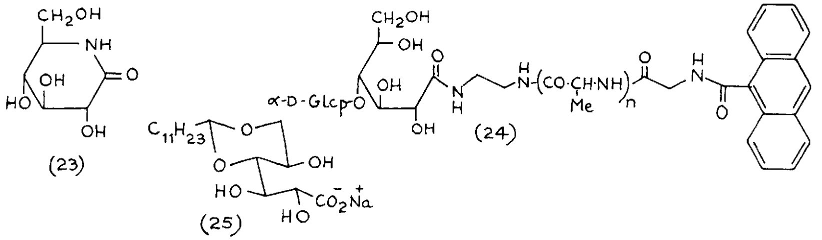
Reagents: i, C_6H_6, Δ; ii, AcOH; iii, deprotection

Scheme 6

A full account has been given of the preparation of anomeric ortholactones from 1,1-dihalogeno-1-deoxypyranoses (see Vol. 22, p.160).[23]

Nojirimycin δ-lactam (23) has been prepared from 1.2:5,6-di-*O*-isopropylidene glucose by a sequence involving two inversions at C-5.[24] Structures of type (24), in which an oligopeptide is attached to a carbohydrate at one end and to a 9-anthracenecarbonyl group at the other, have been synthesized to study their interaction with lipid bilayers.[25]

Aqueous gels containing 1% *N*-octylgluconamide crystallize and remain stable for long periods in the presence of small amounts of sodium dodecylsulphate. The physical structure of these gels has been studied, and comparisons made with the analogous gulonamide and mannonamide compounds.[26] The thermotropic liquid crystal properties of *N*-n-undecyl-D-gluconamide have been studied.[27] Gluconolactone has been converted into trihydroxycarboxylates containing a long chain acetal group (e.g. 25), as a new type of surfactant.[28]

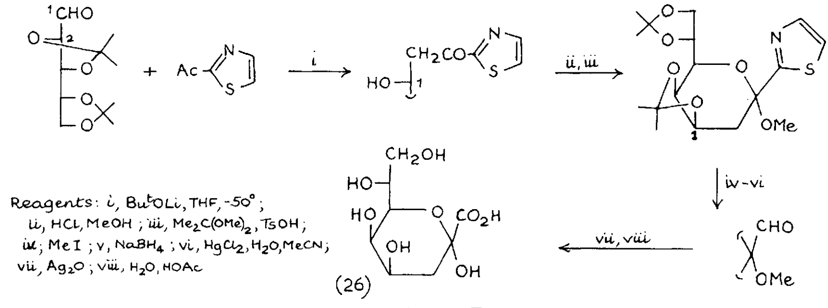


(23) (24) (25)

2 Ulosonic Acids

A study has been made into methods for the production of 3-deoxy-D-*arabino*-2-heptulosonate and its 7-phosphate (DAHP) using plasmid-based biocatalysis,[29] and a full account has been given of Crich's work on the formation of derivatives of 3-deoxy-D-*arabino*-2-heptulosonic acid from D-glucal (see Vol. 22, pp.15-16 and 18).[30]

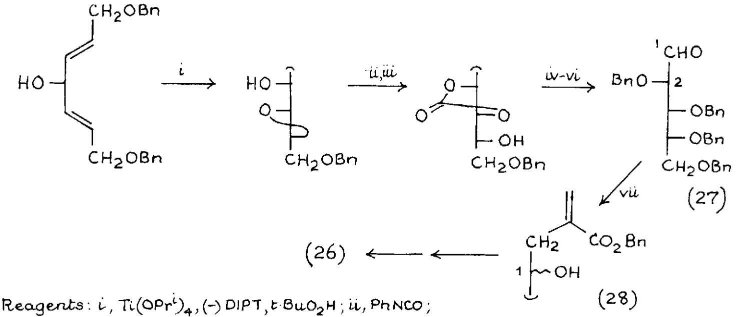
Further syntheses of KDO (26) have appeared. Dondoni and coworkers have used 2-acetyl thiazole as a pyruvate synthon in a stereospecific reaction with an *aldehydo*-D-arabinose derivative (Scheme 7),[31] whilst in another approach (Scheme 8) an alternative pyruvate enolate equivalent reacted non-specifically with a different *aldehydo*-D-arabinose derivative (27). The



Reagents: i, Bu^tOLi, THF, -50°; ii, HCl, MeOH; iii, $Me_2C(OMe)_2$, TsOH; iv, MeI; v, $NaBH_4$; vi, $HgCl_2$, H_2O, MeCN; vii, Ag_2O; viii, H_2O, HOAc

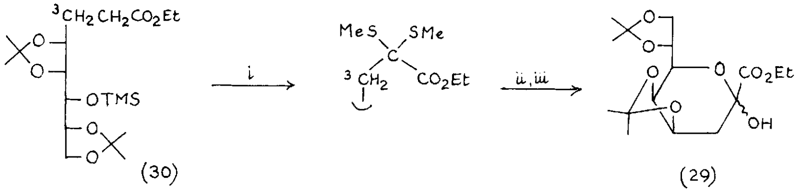
Scheme 7

isomers of (28) were separated and both were converted stereospecifically to KDO (26). The arabinose derivative was produced via asymmetric epoxidation of a divinyl carbinol as shown.[32] D-Arabinose derivative (27) also reacted non-stereospecifically with 2-(trialkylsilyloxy)acrylates to give derivatives of the 1,4-lactone of KDO and its C-4 (D-*gluco*)-epimer.[33] A practical route to the derivative (29) of KDO, a useful synthon for glycosylations, proceeds as indicated in Scheme 9 from the ester (30), itself



Reagents: i, $Ti(OPr^i)_4$, (–) DIPT, t-BuO_2H ; ii, PhNCO ;
iii, $BF_3 \cdot Et_2O$; iv, NaOMe ; v, BnBr, NaH, THF ; vi, O_3, MeOH, then Me_2S ; vii, Br$\frown\Vert\frown$$CO_2Bn$, $CrCl_2$, THF

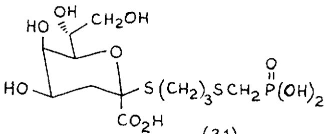
Scheme 8



Reagents: i, LDA, $MeSO_2SMe$; ii, TBAF ; iii, NBS

Scheme 9

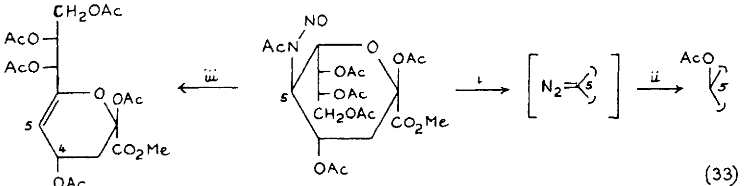
readily available from diisopropylidene D-mannose via a Wittig reaction.[34] A stereocontrolled route to glycosides of KDO, also starting from D-mannose, is discussed in Chapter 3. Improved routes have been described for the conversion of KDO ammonium salt into the pyranose peracetyl methyl ester and the pyranosyl methyl glycoside-methyl ester.[35] The thioglycoside (31) has been made as a potential simplified transition-state analogue inhibitor of CMP-KDO synthetase.[36]



(31)

The 5-*O*-α-L-rhamnopyranosyl derivative of KDO[37] and KDO 7-(2-aminoethylphosphate)[38] have both been isolated from the inner core region of the lipopolysaccharide (LPS) of *E.coli* K12. The syntheses of KDO-7-phosphate and 7-(2-acetamidoethyl phosphate) have been carried out by phosphorylation of an appropriately-protected derivative.[39] It has been shown that in solution KDO 8-phosphate exists as a mixture of α-pyranose (66%), β-pyranose (3%), α-furanose (19%) and β-furanose (12%) forms. By use of the two isomeric 2-deoxy analogues of KDO 8-phosphate it was shown that KDO 8-phosphate phosphatase is specific for the α-pyranose form of the substrate, so that a mutarotation must be involved before the next stage in the formation of LPS, since CMP-KDO synthetase is specific for the β-pyranose form of KDO.[40] Other references to 2-deoxy-KDO and 2-deoxy-Neu*N*Ac can be found in Section 1 of this Chapter.

Full details have been reported on the use of immobilized *N*-acetylneuraminate pyruvate lyase for the preparation of various 2-ulosonic acids, including KDN (see Vol. 21, p.160-161 and Vol. 23, p. 162).[41] The *N*-nitroso derivative (32) of Neu*N*Ac can be used as indicated in Scheme 10 to produce the peracetyl methyl ester (33) of KDN. Thermolysis of (32) gave alkene (34) together with the 4,5-ene and a ring-contracted product. Hydrogenation of (34) led to both the saturated compound and the hydrogenolysis product.[42]



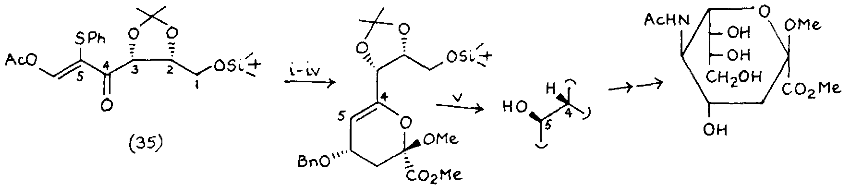
(34) (32) (33)

Reagents: i, CF_3CH_2ONa; ii, Bu_4NOAc; iii, Δ

Scheme 10

A synthesis of *N*-acetylneuraminic acid (Neu*N*Ac) relies upon a hetero-Diels-Alder reaction involving the mannose-derived unit (35) (mannose carbons numbered) as outlined in Scheme 11.[43] Neu*N*Ac has been isolated by an improved procedure from the nests of the Chinese swiftlet, and coupled via aldehydes (36) with bovine serum albumin and tetanus toxoid.[44]

Modification of the structure of Neu*N*Ac continues apace. Routes to the 4-, 7- and 8-oxo- derivatives (as methyl glycosides) have been reported; it was found that, using PCC, selective oxidation at C-4 was possible in the presence of a 7-hydroxyl group, positions 8 and 9 being protected as an isopropylidene group.[45] Oxo compounds were also intermediates in the



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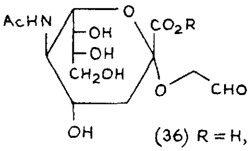
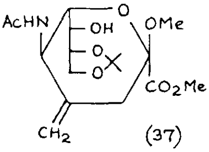
Reagents: i, $=\!\!<^{\text{OMe}}_{\text{CO}_2\text{Me}}$, PhMe, Δ, 7kbar; ii, K_2CO_3, MeOH; iii, BnBr, Ag_2O; iv, Raney Ni; v, BH_3SMe_2, then H_2O_2

Scheme 11

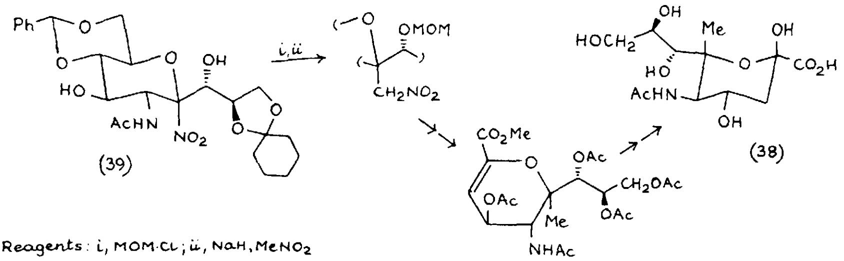


(36) R = H, Me



(37)

synthesis of 4-epi- and 8-epi-Neu*N*Ac.[46] 9-Deoxy-, 7,9-dideoxy-, and 4,7,9-trideoxy derivatives of Neu*N*Ac have been synthesized using free-radical deoxygenations.[47] The 4-methylene compound (37) was prepared from the 4-ketone by use of Cp_2ZrCl_2/CH_2I_2, and acted as a precursor for both the epimeric 4-deoxy-4-*C*-methyl analogues.[48] The 6-*C*-methyl analogue of Neu*N*Ac (38) has been synthesized from the known intermediate (39) (Vol. 21, p.160) as outlined in Scheme 12, and similar 6-*C*-(hydroxymethyl) derivatives were prepared of both Neu*N*Ac and its 2,3-didehydro-2-deoxy analogue.[49] Some pyrrolidine analogues of Neu*N*Ac are mentioned in Chapter 18.



(39)

(38)

Reagents: i, MOM·Cl; ii, NaH, $MeNO_2$

Scheme 12

Various aryl α-thioketosides[50] and the phenyl α-selenoketoside[51] of Neu*N*Ac have been prepared using phase-transfer catalysis.

Treatment of Neu*N*Ac with NaOD-D_2O leads to stereoselective exchange of the α-hydrogen at C-3, with both hydrogens being replaced at longer reaction times; the products were converted into labelled sialyl glycerolipids for dynamic ^2H nmr studies.[52] It is possible to exchange selectively H-8 and

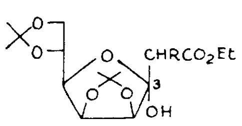
H-9 of Neu*N*Ac -α-methyl glycoside by use of D_2O and Raney nickel with sonication.[53]

Neuraminic acid derivatives variously *N*-acylated have been prepared by reduction-acylation of a 5-azido compound, itself produced from 2-azido-2-deoxy-D-mannose using Neu*N*Ac pyruvate lyase.[54]

Hydrolysis of the polysialic acid colominic acid yields the dimer Neu5Ac-α-(2->8)-Neu5Ac, which can readily be transformed into a peracetylated 1',9-lactone.[55] 9-*O*-Acetyl-KDN and *O*-acetylated *N*-glycolylneuraminic acid units have been identified as constituents of a new polysialoglycoprotein isolated from salmon eggs.[56]

3-Ulosonates of type (40, R=H, Br, F) and 4-ulosonates such as (41) can be prepared from protected aldonolactones, both of the 1,4- and 1,5- types, by Reformatsky-like reactions.[57] Similar products, again with either furanose or pyranose rings, can also be made from aldonolactones using reagents such as $TMSCH_2CO_2Et$ in the presence of Bu_4NF.[58]

D-*xylo*-5-Hexulosonic acid has been shown by n.m.r. to exist predominantly in the β-furanose form in solution; longitudinal relaxation rate data suggest that in the gadolinium(III) complex, the Gd(III) binds preferentially to the keto tautomer in a bidentate fashion involving carboxylate oxygen and O-2.[59]



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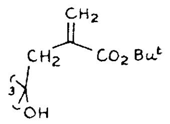

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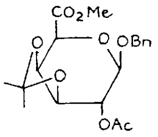

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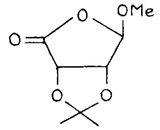

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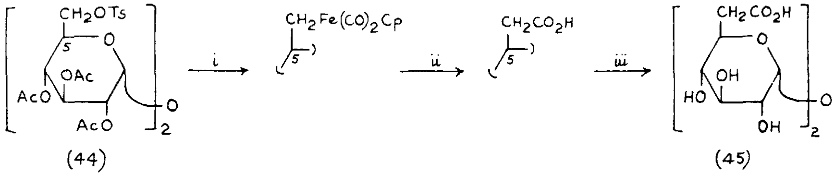
3 Uronic Acids

Various D-galacturonic acid derivatives of potential value for making glycosyl donors have been prepared by oxidation of galactose derivatives;[60,61] the formation of (42)[60] by Jones oxidation followed by methylation is typical. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosiduronic acid can be produced in good yield by oxidation of the galactose derivative with RuO_2-$NaIO_4$ under phase-transfer conditions,[62] and a similar ruthenium-periodate combination was employed in the production of uronic acid derivatives of *N*-acetyl muramic acid.[63] The sugar moiety originally proposed as being present in the nucleoside antibiotic neosidomycin, methyl (methyl 4-deoxy-β-D-*ribo*-hexopyranosid)uronate, has been prepared from 4-deoxy-D-*ribo*-hexose.[64] Oxidation of methyl 2,3-*O*- isopropylidene-β-D-ribofuranoside with PDC gives the 4-oxo-erythroside (43).[65]

A full account has been given of the work by Brimacombe's group (see Vol. 23, p. 9) on the formation of octuronic acid derivatives by catalytic osmylation of α,β-unsaturated esters in the presence of Sharpless' chiral ligands, where double asymmetric induction can be used to enhance the 'Kishi' selectivity.[66] The trehalose derivative (44) could be homologated to the bis-uronic acid (45) using a carbonyl insertion procedure (Scheme 13), as well as by use of the reaction of cyanide ion on the ditriflate analogous to (44).[67]



Reagents : i, NaFe(CO)$_2$Cp ; ii, Br$_2$,H$_2$O ; iii, NaOMe, MeOH

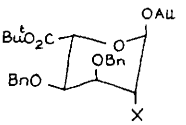
Scheme 13

In studies related to the 2-amino-2-deoxy-α-L-altropyranosiduronic residues found in *Shigella sonnei* phase 1 O-antigen, it was observed that the L-*altro-* derivatives (46, X=NHAc, NH_2, N_3) predominated (*ca* 3:2) over the corresponding D-*galacto*-isomers when the galacturonates were subjected to base-catalysed epimerization.[68]

When D-glucuronic acid was treated with aniline and a water-soluble carbodiimide, the glucuronamide-glycosylamine (47) was formed in high yield. Hydrolysis of the glycosylamine occurred readily to give *N*-phenyl-D-glucuronamide.[69]

Ganem and coworkers have extended their earlier work (Vol. 21, p.176-7) to encompass a synthesis of the aza-analogue of D-galacturonic acid (48), which proved inhibiting to α-galactosidases.[70]

It has been observed that the addition of Cu(II) to mixtures of D-galacturonic acid and Fe(III) salts strongly enhances the amount of reduction to Fe(II). This was rationalized by the formation of stable Cu(II)-galacturonate complexes that lead to opening of the sugar ring to yield aldehyde groups.[71]



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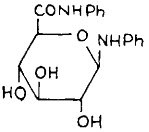

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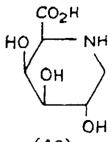

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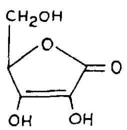

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4 Ascorbic Acids

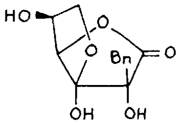
D-Erythroascorbic acid (49) can be synthesized from glucose, with D-arabinono-1,4-lactone as an intermediate.[72]

Enzymic transglycosylation, with maltose as glucosyl donor, can be used to make 2-*O*-α-D-glucopyranosyl-L-ascorbic acid, which may have potential as a storage form of ascorbate in commercial formulations.[73,74] Microorganisms have also been identified which can phosphorylate ascorbic acid specifically at *O*-2.[75]

When 2-*C*-benzyl ascorbic acid (50) was acetylated, the open-chain enone (51) was formed, together with the bicyclic triacetate.[76] A good route to 2-*C*-allyl (and hence by reduction, *C*-alkyl) derivatives of ascorbic acid such as (52) involves the interaction of ascorbate with an allylic acetate or carbonate in the presence of a Pd(0) catalyst.[77]

A reference to 6-amino-6-deoxy derivatives of ascorbic acid is covered in Chapter 9.

When dehydroascorbic acid is treated with hydroxide ion in ethanol, a yellow precipitate is produced. This was characterized as the pyranoid structure (53), formed by ring opening, tautomerization, and ring closure.[78]



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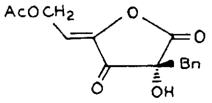

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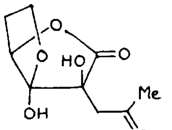
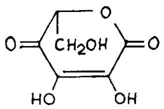


(52)



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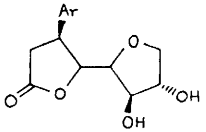
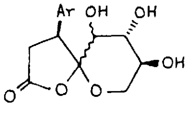


(54)



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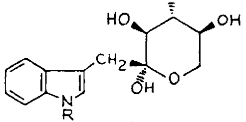

(56)

A series of decarboxylated ascorbigens of types (54) and (55) have been isolated from the heartwood of *Chamaecyperis pisifera*,[79] and the related structures (56) were formed when 2-*C*-(3-indolylmethyl)ascorbic acids were treated with alkali.[80]

A study has been reported of the enolization-dehydration of 2-keto-L-*xylo*-hexonic acid to L-ascorbic acid over heterogeneous catalysts.[81]

Studies of the kinetics and mechanism of oxidation of ascorbic acid by xenon difluoride,[82] by chloropentamminecobalt(III) ions in acidic and basic solution,[83] and by hexacyanoferrate(III) in strongly acidic media,[84] have been reported. The role of trace metal ions on the oxidation of ascorbic acid by peroxodiphosphate in acetate buffers has been investigated; the reaction was found to be strongly catalysed by traces of Cu^{II} or Fe^{III}, and the rate of reaction could be used as a measure of the amount of metallic impurity present.[85] The oxidation of ascorbate in alkaline ethanol has been studied by polarography and by isolation of the oxidation products, one of which was erythroascorbic acid (enantiomer of 49).[86] A reference to the identification of pentos-2-uloses in the degradation of aqueous ascorbic acid is covered in Chapter 15.

The reaction of vitamin C and 6-*O*-stearoyl ascorbic acid with various stable vitamin E radicals has been monitored spectrophotometrically using a stopped-flow technique. The reaction was dramatically slowed by steric hindrance about the aryloxy radical.[87] Sodium nitrite has been shown to accelerate the decomposition of ascorbic acid under aerobic conditions, and an ascorbate-nitrile complex was observed by ^{13}C nmr.[88]

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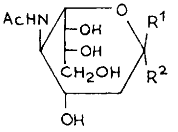
17
Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

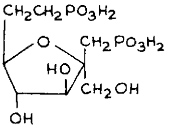
The synthesis of 5-deoxy-5[(R)- and (S)- methylphosphinyl]-α,β-D-manno- and L-gulo-pyranoses,[1] as well as α-1,2,4-tri-*O*-acetyl-5-deoxy-5[(R)- and (S)-ethylphosphinyl]-3-*O*-methyl-D-xylopyranoses[2] have been reported and the 5-deoxy-3-*O*-methyl-5-phenylphosphinyl-L-fucopyranoses have been prepared as the first P-in-the-ring analogues of L-fucose.[3] The 5,6-dideoxy-5-*C*-dimethoxyphosphinyl-D-*xylo*-hex-5-enofuranoses have also been described.[4]

In the phosphonic acid series, the isomeric analogues (1) and (2) of *N*-acetyl-2-deoxyneuraminic acid have been prepared from *N*-acetylneuraminic acid,[5] and the isosteric bisphosphono - analogue (3) of β-D-fructose 2,6-bisphosphate has been synthesized from the *C*-fructoside (4).[6] Chiral 1,6-diphosphine ligands (5) and (6) have been prepared from D-mannitol and utilised unsuccessfully with Rh(I) in attempts to effect asymmetric hydrogenations.[7]

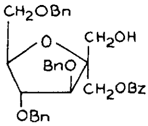


(1) $R^1 = H, R^2 = PO_3H_2$

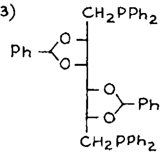
(2) $R^1 = PO_3H_2, R^2 = H$



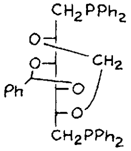
(3)



(4)



(5)



(6)

2 Other Carbon-bonded Derivatives

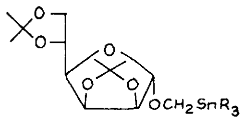
The organotin derivative (7) was prepared from D-mannose, and some reactions involving Sn-Li exchange were studied,[8] while the relative reactivities of some *C*-triphenylstannyl-carbohydrate derivatives in iodine-induced phenyl-tin bond cleavage reactions have been determined.[9] Nucleophilic addition of a carbanionic carborane to a number of sugar aldehydes has provided adducts that were used in attempts to increase the water solubility of carborane - antibody complexes with a view to localising boron on tumors prior to ^{10}B

neutron-capture therapy.[10] The use of organotellurium reagents in radical carbon-carbon bond formation reactions of carbohydrate derivatives is discussed in Chapter 14.

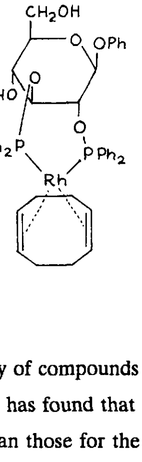
3 Oxygen-bonded Derivatives

Angyal has reviewed the complexes found between metal cations and polyhydroxy carbohydrates in solution,[11] and a review (in Japanese) on the interaction between saccharides, metal ions, and polyamines includes a proposed mechanism for the C-2 epimerisation of aldoses *via* Ni(II) complexes.[12]

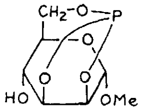
Cationic chelate (8) was prepared and reported to exhibit excellent catalytic properties in asymmetric hydrogenation reactions.[13,14] The phosphitylation of methyl α-D-mannopyranoside with $P(NEt_2)_3$ has afforded the cyclic phosphite (9),[15] and a similar reaction applied to D-xylose gave (10),[16] whereas both the pyranose (11) and furanose (12) derivatives were obtained from 2-*O*-substituted D-glucoses.[17] The synthesis of a carbohydrate derivative of a dibenzo-substituted phosphorus heterocycle is mentioned in Chapter 7, and the conversion of methyl α-D-glucopyranoside into epoxides *via* dioxaphospholanes is covered in Chapter 5.



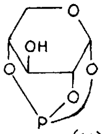
(7) R = Me, Ph



(8)



(9)



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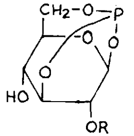
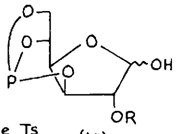


(11)

R = Me, Ts



(12)

A study of the stability of compounds derived from D-glucose and D-fructose with boric acid or phenylboronic acid has found that the stability constants for the fructose compounds are much greater than those for the glucose compounds.[18] The synthesis of crystalline 3-*O*-acetyl-2,4-*O*-phenylboranediyl-β-D-ribopyranosyl bromide in a two pot process from D-ribose has been described along with some of its selective glycosylation reactions.[19] Ethyl (dimethoxy)borane has been used in the synthesis of anomerically pure furanosides from the free sugars. Thus methyl 2,3-*O*-ethylboranediyl-α-D-lyxofuranoside was prepared and then de-esterified under essentially neutral conditions to the glycoside in 80%

yield overall. Similarly, methyl 2,3:5,6-di-*O*-ethylboranediyl-α-D-mannofuranoside and thence the furanoside itself were obtained from D-mannose in high yield.[20] The enthalpies of complex formation of five aldo- and deoxyaldo-pentoses with phenylborate have been determined by calorimetric methods and by potentiometric measurements.[21] The synthesis of β-D-lyxofuranosides from an organoboron-protected derivative is mentioned in Chapter 3, and the preparation of a series of 1-*O*-alkyl-D-glucitols- and -D-mannitols *via* organoboron-protected derivatives is covered in Chapter 18.

The di-n-butylstannylene derivatives of benzyl 4,6-*O*-benzylidene-α- and -β-D-gluco- and -galacto-pyranosides have been studied in solution by ^{1}H-, ^{13}C- and ^{119}Sn-n.m.r. spectroscopic methods. The species present in solution were identified from their spectra and from the products of reactions with electrophiles. It was concluded that it is the orientation of substituents at C-1 and C-4 for a 2,3-*O*-stannylene that determines the structure, *i.e.*, whether there are interconverting (or not) dimers, trimers or tetramers. Only when a single dimer is present is a regiospecific or highly regioselective reaction obtained.[22] The regioselective glycosylation of 1,6-anhydro-β-D-galactopyranose using organotin-mediated reactions is discussed in Chapter 3.

The interactions of cations, especially Ca^{2+}, with various hexoses and pentoses in water have been investigated by determination and interpretation of the enthalpies and entropies of the interactions.[23] The contributions of the isomeric forms of D-fructose to complex formation with Ca^{2+} ions in aqueous solution were determined by ^{13}C-n.m.r. spectroscopy,[24] and a ^{13}C-n.m.r. study of aqueous sucrose solutions in the presence of calcium hydroxide has given some evidence that so-called "calcium sucrates" exist in solution as aggregates of sucrose, Ca^{2+}, and OH^- where the active site of the sucrose is its C-4′ hydroxyl group moiety in the fructose ring.[25] A study of the interaction between alkaline earth metal ions and D-glucono-1,5-lactone in the crystalline form and in aqueous solution has been undertaken using x-ray powder diffraction and spectroscopic methods,[26] and it has been found that di-β-D-fructopyranoside 2′,1:2,1′-dianhydride forms strong complexes with cations, whereas other, isomeric fructose dianhydrides either complex weakly or not at all.[27] Conflicting reports in the literature about whether Cu^{2+} ions form complexes with polyols have been explained. Only at pH values ≥5 will strong complexation occur due to the presence of $[Cu_2(OH)_2]^{2+}$. The pH value of 5% $CuSO_4$ solutions is 3.6, whereas 5% $Cu(OAc)_2$ solutions have a pH of 5.0.[28]

The non-cyclic and cyclic esters formed between vanadate ions and the hydroxyl groups of the ribose moiety in nucleotides has been studied by multinuclear n.m.r. methods,[29] and a chiral titanium complex prepared from $(^iPrO)_2TiX_2$ (X = Cl, Br) and 1,2:5,6-di-*O*-

isopropylidene-D-mannitol has been used in the glyoxylate-ene reaction affording α-hydroxy esters with only low enantiomeric excess.[30]

From a ^{1}H- and ^{13}C- n.m.r. investigation of the complexes formed between 14 selected alditols and ammonium molybdate, it was concluded that four types of binuclear complexes are formed, in which four vicinal hydroxyl groups are involved. In two types, the alditols remain in zig-zag conformations, whereas in the other two the chains are forced into sickle arrangements.[31]

A ^{1}H- and ^{13}C- n.m.r. study of the interactions of molybdate with some hexuronic acids in aqueous solution has provided evidence that complexation involves the carboxylate oxygen and the C-4 hydroxyl group in a $^4C_1$ pyranose.[32] A similar n.m.r. study of the interactions of 2-ketoses with molybdate has concluded that a range of these sugars form cyclic molybdate complexes in aqueous solutions of ammonium molybdate, involving OH groups at C-1, C-2 and C-3. In some cases, the OH groups at C-4 and C-5 can be involved in alternative tridentate complexes. L-Sorbose and D-fructose, in addition to the tridentate complexes with pyranoid structures, also form acyclic tetradentate molybdate complexes involving OH groups at C-3, C-4, C-5 and C-6.[33] The complexes of a number of aldoses, from pentoses to octoses, with molybdate have also been studied using their n.m.r. spectra.[34] The epimerisation of D-[2,3,4,5,6-^{13}C]mannose, catalysed by molybdate ions, has resulted in the formation of D-[1,3,4,5,6-^{13}C]-glucose,[35] and this molybdate-catalysed rearrangement of aldoses has been shown to be completely inhibited by oxalic acid.[35]

4 Nitrogen- and Sulphur-bonded Derivatives

2-Amino-2-deoxy-D-mannose and its methyl α-pyranoside and methyl 2-amino-2-deoxy-α,β-D-galactopyranoside are good chelating agents for Cu(II) ions. The stability constants for complexes with the *manno* compounds are higher than those for 2-amino-2-deoxy-D-galactose and glucose. It was concluded that various hydroxyl groups can be involved in the binding of the metal ions, but the primary binding sites are the amino groups.[36,37]

Various glycosylamines derived by reaction between glucose and α-amino acids and the isomeric Amadori compounds form bis(chelate) complexes of Cu^{2+}, Pd^{2+} and Pt^{2+}. The i.r. spectra indicate that the ligands are co-ordinated through the amino group and a carboxylate oxygen atom.[38] The syntheses, structures, and antitumor activities of a number of platinum complexes of some diamino-sugars have been reported.[39] 1-Thio-β-D-glucose and 1-thio-β-D-galactose have been treated separately with phenyldichloroarsine and adducts containing two arsenic atoms per thiosugar were obtained and studied by n.m.r. methods.[40]

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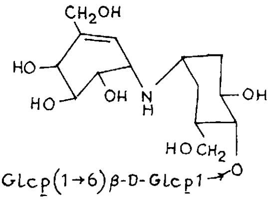
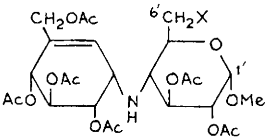
19
Antibiotics

1 Amino-Glycoside Antibiotics

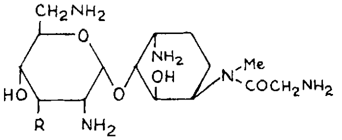
A new fortimicin antibiotic, validamycin H, has been isolated from the validamycin complex produced by an *S. hygroscopicus*. It has been characterized as the *pseudo*-tetrasaccharide (1).[1] The structure of the related *pseudo*-tetrasaccharide acarbose has been confirmed.[2] The *pseudo*-disaccharide (+)-validoxylamine G has been made by coupling appropriate cyclohexane derivatives using an amine/oxiran reaction to link the sub-units together.[3] The *pseudo*-disaccharide antibiotic methyl acarviosin together with its 6'-hydroxy analogue have been prepared as their per-acetates (2) and (3).[4] A 1',6'-anhydro-analogue of acarviosin as well as a 3', 6'-anhydro-analogue has also been synthesized from monomer sub-units using an amine/oxiran condensation reaction; both are good α-glucosidase inhibitors. The β-linked epimer of the 1', 6'-anhydro-compound, which was also prepared, proved to be a poor inhibitor of α-glucosidase, but was an effective α-mannosidase inhibitor.[5] Maltose has been used to synthesize some new fortimicin analogues (4).[6]





(2) $X = H$

(3) $X = OAc$



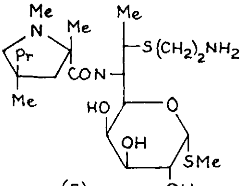
(4) R = H or OH

A *pseudo*-disaccharide related to trehalosamine and β-linked isomers has been prepared by coupling a carbocyclic analogue of the amino-sugar to glucose by conventional methods.[7] Carbohydrate inhibition by *pseudo*-amino-sugars has been studied.[8]

A synthesis of destomycin C is mentioned in Chapter 3, and syntheses of a series of methyl oligobiosaminide derivatives are referred to in Chapter 12.

Syntheses have been reported for 3',4',6'-trideoxy-6'-fluorokanamycin C (DAST treatment of a 6'-hydroxy compound),[9] and 6'''-chloro-6'''-deoxyamikacin and some of its analogues.[10] ^{13}C N.m.r. data on amikacin and kanamycin A in acidic and basic media have been reported.[11]

The lincomycinanalogue (5) has been prepared from a known 6,7-epimine precursor; it was potent against Gram $^{+}$ve organisms, but was only modestly active against Gram $^{-}$ve bacteria.[12] Other papers report attempted syntheses of lincosamine derivatives as precursors to lincomycin and its analogues; a route using dimethylcyanamide and an 6,7-epoxide was successful,[13] whereas an approach using a titanium azide complex on such an epoxide yielded the wrong regioisomer.[14] The lincosamine precursor (6) has been prepared from the corresponding galacto-hexodialdose derivative via acetylene adducts.[15]



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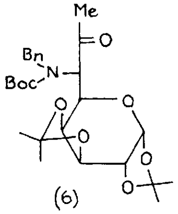


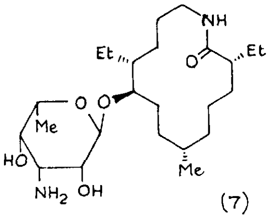
(6)

The conformation of lincomycin has been determined using various 1-D and 2-D n.m.r. techniques in conjunction with theoretical calculations.[16] The proton signals in the ^{1}H n.m.r. spectrum of lividomycin have been fully assigned using 2-D techniques.[17]

2 Macrolide Antibiotics

Structures have been reported for eurocidins D and E, which are present in the culture broth of Streptoverticillium eurocidicum species; they contain mycosamine attached to a novel pentaenic 30-membered lactone.[18] Another mutant strain of this organism yields an antibiotic, YS-822A, which contains mycosamine attached to a tetraene macrolide.[19] A strain of Actinamadura vulgaris has yielded a new macrolactam antibiotic (7) which contains 4-epimycosamine attached to a 14-membered lactam ring.[20] (See also Chapter 9)

4''-O-Methyl derivatives of erythromycin A (methylation on cladinose) have been reported.[21] Another paper describes the selective esterification of the 4''-position in cladinose and the



(7)

2'-position of desosamine in this antibiotic using polyenic fatty acids, with a report on their antibacterial activity.[22] The rearrangement reaction of a 2'-O-methanesulphonyl derivative of erythromycin is referred to in Chapter 9.

The synthesis and biological activity of 34 acyl derivatives of elaiophylin have been reported, the two 2-deoxy-L-lyxo-hexose units being esterified, some of which are biologically active.[23]

The biosynthesis of mycinamicins (16-membered macrolides carrying desosamine and mycinose) by a blocked mutant of Micromonospora griseorubida has been studied.[24]

A synthesis of cytovaricin includes a synthesis of D-cymarose (using a Sharpless asymmetric oxidation procedure on a non-carbohydrate precursor) and its conversion to the requisite glycoside.[24a]

3 Anthracyclines and Related Polycyclic Antibiotics

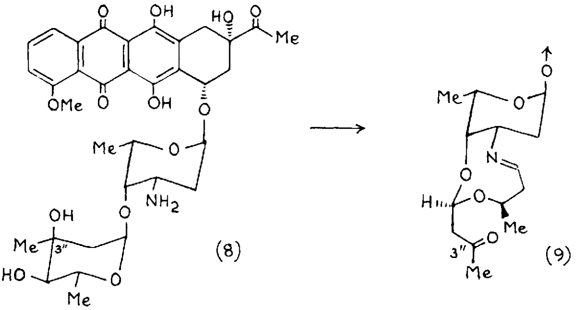
The synthesis and antitumour activity of anthracyclines have been reviewed.[25]

Mutant strains of S. peucetius fed with sodium barbiturates produce biosynthetic anthracyclines having barminomycin structures incorporating barbiturate moieties which show outstanding antileukemic activity.[26]

Ciclamycin 0 has been synthesized by methods involving preparation of the trisaccharide moiety by coupling glycal monomers together and then coupling the product to the anthracycline tetracycle.[27]

Linking anthracycline aglycones to appropriate sugar derivatives by standard glycosidation procedures has also been used to synthesize 3'-hydroxyesorubicin,[28] 4-O-methylrhodomycins[29-31] and a 3',4'-diamino-3',4'-dideoxy analogue,[29] ε-isorhodomycins (3'-amino regioisomers of rhodomycin),[32] (R)-2'-fluorocarminomycin,[33] anthracycline derivatives containing 4-epi-L-vancosamine (L-eremosamine),[34] 4-demethoxyanthracyclines,[35] and the D-ring indole analogue of daunomycin.[36] Syntheses of the D-ring thiophene analogue of daunomycin, the D-ring pyridine analogue of 11-deoxydaunomycin, and syntheses of anthracycline oligosaccharides are mentioned in Chapter 3.

Anthracycline antibiotics have been modified by incorporating the amino-group of the amino-sugar into a triazole ring,[37] or into a Schiff base with substituted benzaldehydes.[38] Rhodosaminyl-anthracyclines can be selectively *N*-monodemethylated by irradiation with visible light.[39] Barminomycins have been converted from mono- to di-saccharide derivatives by glycal glycosidation; the resulting mycarose compound (8) yielded 3"-dehydro-4-*O*-methyl-barminomycin II (9) on treatment with periodate.[40] Other papers report the synthesis of 3'-morpholino-pirarubicin[41] and *N*-nitroso-daunorubicins, which, on alkaline degradation, yielded cyclic 3'-*N*,4'-*O*-carbonyl derivatives, with an inverted sugar ring conformation.[42] *N*-3'-Acylation of dauno- or doxo-rubicin with "liner reagents" produces electrophilic drug analogues for synthesizing bioconjugates; isothiocyanato derivatives gave the best linkages.[43] *N*-Cycloalkyl derivatives of daunorubicin and carminomycin have been synthesized by condensing glutaraldehyde with the amino-group of the sugar residue; m.s. data are given.[44]



(8)

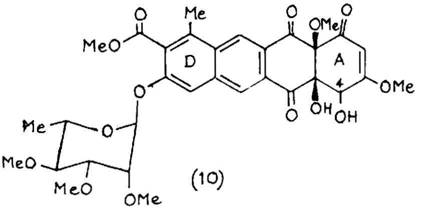
(9)

Confirmation of the L-*ribo* configuration of decilonitrose is referred to in Chapter 10 (see Vol. 23,p.193).

The biogenesis of chromomycin A$_3$ in *S. griseus* has been investigated using ^{13}C labelled precursors, showing that D-glucose is a precursor for all the five sugar units present in the antibiotic.[45]

A compact conformation for mithramycin in aqueous solution is suggested from ^{1}H and ^{13}C n.m.r. data.[46]

Treatment of elloramycin A (10) with anhydrous TFA led to a novel *trans*-glycosylation rearrangement in which the sugar migrates from ring D (O-8) to ring A (O-4); evidence to support an intermolecular mechanism via the glycosyl trifluoroacetate is presented.[47] C-Glycosides of tricyclic aglycones have been synthesized using the Diels-Alder reaction with appropriate quinones and the dienyl carbohydrate (11), *e.g.* naphthazarin gives (12).[48]



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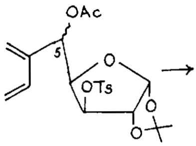

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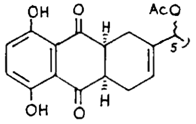
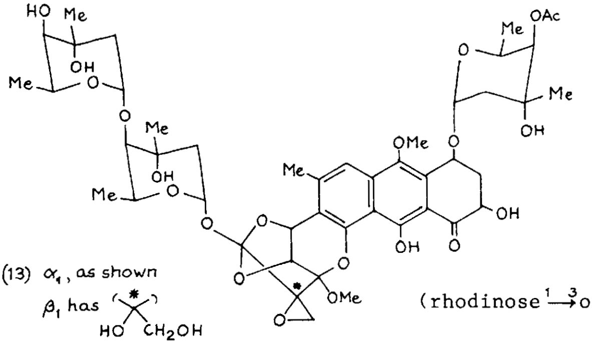


(12)

Pradimicins A-C, new antifungal antibiotics, have been isolated from *Actinomadura hibisca* culture broth; they contain a benzo[a] naphthacenequinone chromophore with attached 4-amino-4,6-dideoxy-D-galactose, and, with A and C, a β-D-xylopyranose glycosidically O-3 linked to the amino-sugar.[49] N,N-Dimethyl-pradimicins have been synthesized by reductive methylation, which improves water solubility and antifungal activity.[50]

Altromycins, which are novel compounds related to pluramycin, and obtained from an actinomyces strain, contain an anthraquinone core to which is attached a 2,6-dideoxy-3-O-methylaltrose$\rightarrow$N-methylvancosamine disaccharide as an O-glycoside, and a 6-deoxy- or 2,6-dideoxy-3-O-methylaltrose monomer linked as a C-glycoside.[51]

Antibiotics obtained from *S. vinaceus-drappus*, LL-D49194 α_1 and β_1, are another new set of antibiotics, with the reported structure (13).[52]



(13) α_1, as shown

β_1 has

$(\text{rhodinose}\xrightarrow{1\quad 3}\text{olivose}\xrightarrow{1\quad 4}\text{olivose})_2\rightarrow$

(14)

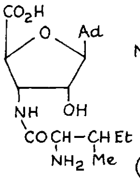
Landomycins are new angucycline antibiotics from a streptomyces strain; landomycins A-D have been investigated by 2D n.m.r.; the major component, landomycin A, consists of a hexasaccharide chain, summarized by the structure (14), linked as a phenolic glycoside to the aglycone, landomycinone A.[53]

A number of 3',4'-O-acetal derivatives of the antitumour antibiotic chartreusin have been prepared, and were further transformed into 6-O-acyl derivatives; some 3',4'-O-*exo*-benzylidene compounds showed high antitumour activity.[54]

Saquayamycins A and B have been modified by the regio- and diastereo-selective addition of alcohols to the L-aculose moiety.[55]

4 Nucleoside Antibiotics

4.1 Ribofuranosyl Analogues. - New nucleoside antibiotics to be reported have included the antifungal compound FR 900403 (15) obtained from the broth of *Kernia* sp. F-19849,[56] the antifungal antibiotic FR 900848 (16) from *Streptoverticillium fervens*, containing a novel pentacyclopropyl acid substituent,[57] and 5-formyloxymethyluridine (17), obtained from *Serratia plymuthica* culture broth.[58]



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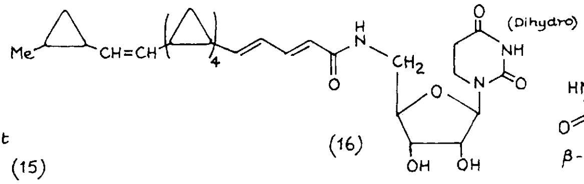

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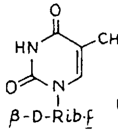
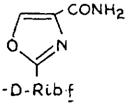
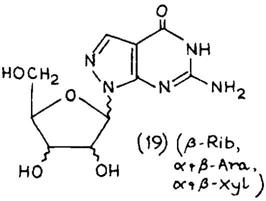


(17)

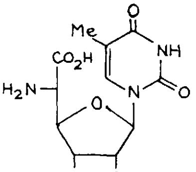
Syntheses have been reported for oxazofurin (18), the oxa analogue of tiazofurin,[59] the pyrazolo[3,4-d]pyrimidine nucleosides (19), which can show significant anti-Leishmanial activity,[60] [5-^{14}C]pentostatin,[61] [5-^{3}H]2',3'-dideoxycytidine, [2,3-^{3}H$_2$]2',3'-dideoxyinosine, [8-^{3}H]2',3'-dideoxyadenosine and -inosine,[62]



(18)



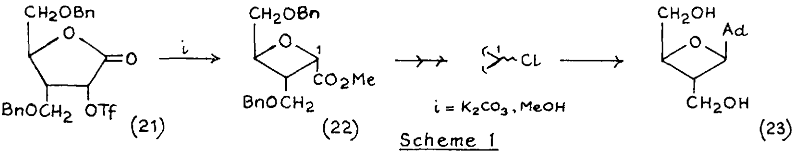
(19) (β-Rib, α+β-Ara., α+β-Xyl)



(20)

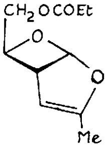
3'fluoro-2',3'-dideoxyadenosine and -guanosine,[63] 2'-deoxypuromycin,[64] [2-^{14}C]3'-deoxythymidin-2'-ene and [5-^{125}I]3'-azido-2',3'-dideoxy-5-iodouridine,[65] thymine polyoxin C (20)[66,67] (both from non-carbohydrate precursors)(see Vol. 23, p.197, ref. 56), and nikkomycin B from polyoxin C.[68] The 5'-O-(N-acetylneuraminic acid) derivative of AZT[69] and 5'-esters of 5-iodo-2'-deoxyuridine[70] have also been synthesized.

4.2 Oxetanocin and its Analogues. - Fleet's group has synthesized oxetanocin (23) in a multistep procedure from D-glucose involving the transformation (21)→(22)(Scheme 1).[71] (±)-Oxetanocin has been



Scheme 1

made from 2-methylfuran which, on irradiation with 2-oxoethyl propanoate, yielded the bicyclic intermediate (24), which was then converted to product by standard procedures.[72] An improved synthesis of D-oxetanose is mentioned in Chapter 14. Fleet's group has also synthesized α- and β-noroxetanocin (25)[73] and epinoroxetanocin (26).[74] Other papers have described routes for the stereoselective synthesis of carbocyclic analogues of oxetanocin[75] and of a cyclobutanone precursor of these,[76] and some cyclopropyl analogues of oxetanocin have been reported.[77]



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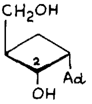
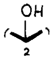
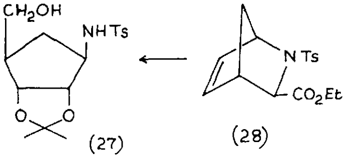


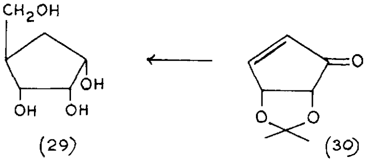
(25)



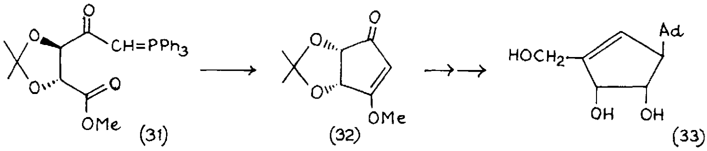
(26)

4.3 Carbocyclic Nucleoside Analogues. - Full details of the synthesis of (-)-aristeromycin from D-glucose have been published[78] (see Vol.23, p.196). The racemic aristeromycin precursor (27) has been prepared from the known Diels-Alder adduct (28).[79] Carba-α-D-ribofuranose (29) has been synthesized from the cyclopentenone (30),



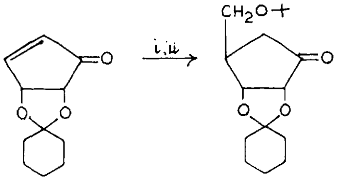


and shown by isotopic dilution experiments to be an intermediate in the biosynthesis of aristeromycin.[80] A synthesis of (-)-neplanocin A (33) from (+)-tartaric acid involves the combined intramolecular Wittig condensation and epimerization (31)→(32) to give the cyclopentene ring (Scheme 2).[81] The cyclohexylidene analogue of (30) has been used to prepare aristeromycin and neplanocin A, the stereo-



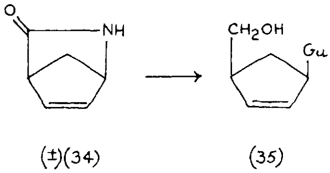
Scheme 2

selective addition shown in Scheme 3 having been employed to introduce the hydroxymethyl unit.[82] A chemo-enzymatic route has been employed to synthesize (-)-carbovir (35), as outlined in Scheme 4; either enantiomer of the azabicycloheptenone (34) could be hydrolysed specifically with different whole cell preparations to the corresponding aminoacid.[83]



Reagents: i, $LiCu(CH_2OBu^t)_2$; ii, H_3O^+

Scheme 3



Scheme 4

The synthesis of a pyrimidine analogue of 2'-deoxyneplanocin A and of 2',3'-dideoxy-6'-fluorocarbocyclic nucleosides, the thymidine derivative showing anti-HIV activity, are mentioned in Chapter 20.

The X-ray crystal structure of sangivamycin has been reported.[84]

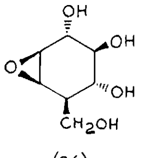
5 Miscellaneous Antibiotics

Two new glycopeptide antibiotics, MM 47761 and MM 49721, have been isolated from a new strain of Amycolatopsis orientalis; they are relatives of vancomycins, containing the disaccharide O-α-L-Rham p-(1→2)-O-β-D-Glc p-(1→ attached to a heptapeptide nucleus, with epi-vancosamine separately attached; they differ from each other in the chlorine content of the nucleus.[85]

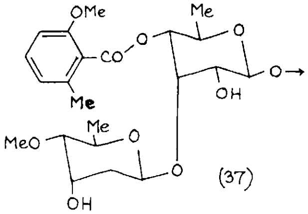
A synthesis of 1-deoxynojirimycin from D-threo-hexodiulose has been described.[86] Other references to nojirimycin and its analogues can be found in Chapters 9, 18, and 20.

The isolation (from a Phellinus mushroom strain) and structure of the β-glucosidase inhibitor cyclophellitol (36) has been described.[87] (See also Chapter 18).

Antibiotics PA-46101A and B, obtained from a Streptomyces strain, contain the deoxy-disaccharide unit (37) attached to a macrocyclic aglycone core, similar to that in kijanimycin and chlorothricin; the B variant also contains 2,4-di-O-methyl-3-C-methyl-α-rhamnopyranose separately attached as a glycoside.[88]



(36)



(37)

Another Streptomyces strain (SP.SN-198) has yielded a new piercidin antibiotic, 3'-rhamnopiercidin A_1; previously a glucose analogue was known.[89]

Detailed spectroscopic and chemical analysis has led to a revision of the structure of moenomycin A; the branched-chain sugar uronic acid is an amide, not the free acid; the latter is a significantly less potent antibiotic.[90]

Polysaccharide-protein complexes isolated from the edible mushroom Himematsutake show marked antitumour activity, notably a (1-6)-β-D-glucan compound; xyloglucans and glucoxylans were also active.[91,92]

A synthesis of the octose moiety of ezomycin A from D-galactal has been described.[93]

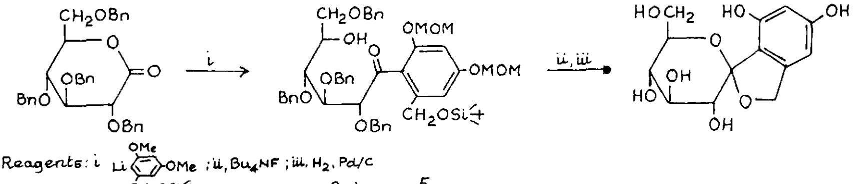
Sinay's group has reported a synthesis of the BCDE tetrasaccharide unit of orthosomycins, using selenium derivatives to form the characteristic ortho-lactone linkage between rings C and D.[94]

The first total synthesis of hikizimycin has been reported, a 3-azido-3-deoxy-D-glucose derivative being coupled to the amino-undecose nucleoside moiety which was prepared from non-carbohydrate precursors.[95]

Ogawa's group has announced a total synthesis of methoxyhygromycin and its 5-epimer; the required O-methylinosamines were synthesized from myo-inositol and then coupled to the sugar-cinnamate unit.[96]

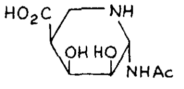
Tetrabenzyl-D-glucono-δ-lactone has been coupled to an aryl lithium derivative giving a ketose and hence a spiro-ketal which could be selectively esterified at O-3 to give papulacandin D. (Scheme 5).[97] The glycosidation is also referred to in Chapter 3, as is the synthesis of the β-C-arylglycoside nucleus of chaetiacandin.

Siastatin B (38) has been prepared from L-ribose in a multistep

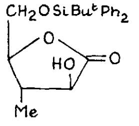


Reagents: i Li–C₆H₂(OMe)₂–CH₂OSi; ii, Bu_4NF; iii, H_2, Pd/C

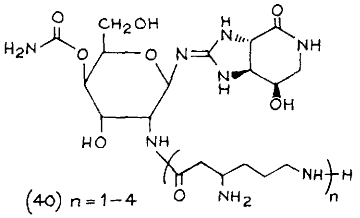
Scheme 5



(38)



(39)



(40) n = 1–4

procedure in 17% overall yield, giving the absolute configuration of this neuraminidase inhibitor.[98] The conversion of the lactone (39) into the enantiomer of a degradation product of ansamycin likewise served to define the absolute stereochemistry of this family of antibiotics.[99]

Further details of the biological activity of racemomycins (40) have been published.[100]

Studies on the construction of kijanimycin oligosaccharides, and a structural proof of ristotriose and ristotetraose by synthesis, are referred to in Chapter 4, and a synthesis of the α-glucosidase inhibitor 8-epi-kifunensine is mentioned in Chapter 9.

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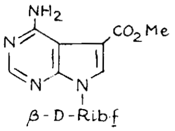
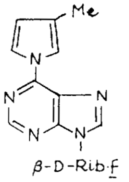
20
Nucleosides

5-(Methoxycarbonyl)tubercidin (1) has been isolated, together with toyocamycin, from a Fijian sponge,[1] and an investigation of cytokinin biosynthesis has led to the isolation of the new metabolite (2).[2]

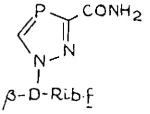

(1)


(2)

1 Synthesis

Standard condensation procedures have been used to synthesize β-D-ribofuranosyl derivatives of 4-nitro/amino-5-substituted imidazoles,[3,4] 1,2,4-triazoles (and 2'-deoxyanalogues),[5] 1,2,4-diazaphospholes including the interesting ribavirin analogue (3),[6] 5-trifluoroethoxypyrimidine (and also the β-D-arabinofuranosyl analogue),[7] some 5-(2-substituted-propyl)uracils,[8] pyridazinones,[9] and 2-pyridones (3-deaza-cytidines and -uridines).[10]

Some N^1, N^3-dialkyl xanthines have been converted to their 7-β-D-ribofuranosyl derivatives by silylation-condensation,[11] and the 8-thiono-derivative (4) of guanosine has been similarly prepared.[12] As regards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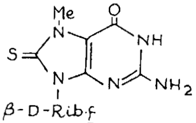
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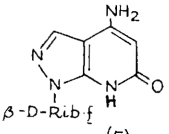
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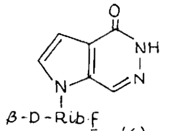
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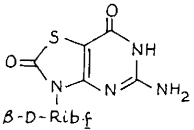
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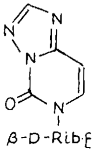
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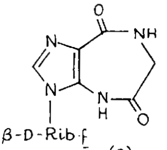
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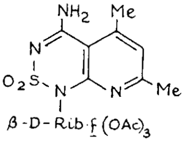
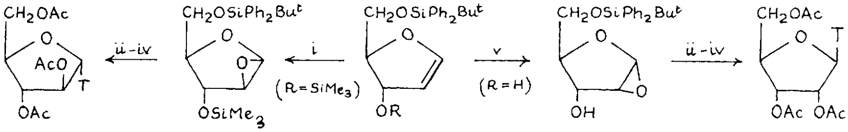

(10)

aza- and deaza- analogues of the purine nucleosides, conventional routes have been employed to prepare β-D-ribofuranosyl derivatives of pyrazolo[3,4-*d*]pyrimidin-4(5H)-ones[13,14] (and some arabino- and xylofuranosyl isomers),[14] pyrazolo[3,4-*d*]pyrimidin-3(2H)-ones,[15] pyrrolo[2,3-*d*] pyrimidines,[16,17] pyrrolo[3,2-*d*]pyrimidines,[18] pyrazolo[3,4-*b*]pyridines [e.g. (5)] by annulation onto a pyrazole nucleoside,[19] pyrrolo[2,3-*d*]pyridazinones of type (6) via pyrrole nucleoside intermediates,[20] some 2-substituted benzimidazoles,[21] and thiazolo[4,5-*d*]pyrimidines such as the guanosine analogue (7).[22]

The triazolo[2,3-*c*]pyrimidinone (8) and its *xylo*-analogue have been prepared by conventional sugar-base condensation,[23] as has the ring-expanded xanthosine analogue (9), together with its *N*3-regioisomer.[24] These latter compounds could also be made by initial condensation of ribofuranosyl derivatives with a 4-nitroimidazole derivative followed by cyclization of the 7-membered ring, in which case, under certain conditions, only the *N*3-isomer of (9) was obtained.[25] The pyrido[2,3-*c*]-1,2,6-thiadiazine (10) has been prepared by silylation-condensation, along with related β-D-glucopyranosides.[26]

Danishefsky's group has shown that 1,2-anhydro sugars can act as precursors of nucleosides. In hexopyranosyl systems, modest yields but high 1',2'-*trans*-stereoselectivities are obtained, whilst with furanosyl glycals, the chemistry can be directed towards either β-D-*ribo*- or α-D-*arabino*- products depending on the presence or otherwise of a 3-hydroxy group to direct epoxidation of the glycal (Scheme 1).[27]



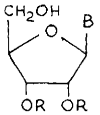
Reagents: i, $\mathrm{{}^{Me}_{Me}{>}{<}{}^{O}_{O}}$, Me_2CO; ii, bis($SiMe_3$)-thymine; iii, TBAF; iv, Ac_2O, DMAP; v, $\mathrm{{}^{Me}_{Me}{>}{<}{}^{O}_{O}}$, CH_2Cl_2, Me_2CO (6:1)

Scheme 1

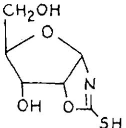
It has been shown that nucleoside derivatives of type (11) can be obtained directly by silylation-condensation procedures using 5-*O*-monomethoxytrityl ribofuranose derivatives, the protecting group being lost from the primary position during the condensation.[28]

The four nucleosides of RNA have been prepared with ^{13}C labels at either C-1 or C-2, for use in nmr studies,by condensation with an appropriately-labelled D-ribose derivative. Label at C-1 was introduced by a Kiliani reaction, and at C-2 by molybdate-catalysed rearrangement of 1-^{13}C-D-arabinose.[29]

Samples of 5-amino-1-(β-D-ribofuranosyl)imidazole and its 5'-phosphate (AIR), labelled separately with ^{15}N in each of the three nitrogen atoms, have been prepared from 2,3-*O*-isopropylidene-β-D-ribofuranosylamine by Shaw's methodology,[30] and similar methods were used to make the α-isomer of AICA riboside and hence α-guanosine from the isoxazole (12),[31] and also in the preparation of the imidazole phosphonate (13).[3] The novel mesoionic nucleoside (14) and its 2'-deoxyanalogue have been prepared from ribofuranosylhydrazine derivatives.[32]



(11) R = Ac, Bz



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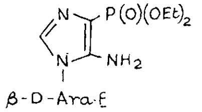

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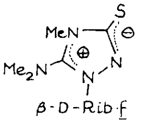

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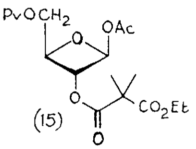

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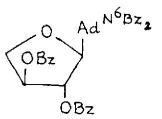

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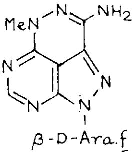
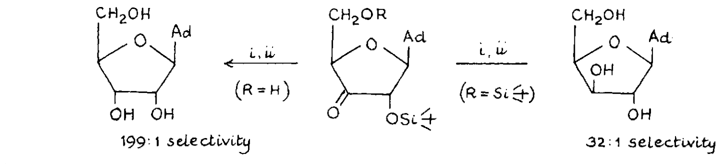


(17)

Condensation of the oxetan derivative (15) with silylated heterocycles did not lead to oxetanocin-like compounds, but instead L-threofuranosyl derivatives, mostly of α-configuration (16), could be isolated.[33]

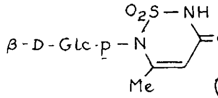
The arabinofuranosyl nucleoside (17) has been prepared by oxidation-reduction from the analogous D-*ribo*-compound, and the 2'-deoxy nucleoside was also reported.[34]

Anomerically-pure 9-(β-D-xylofuranosyl)adenine has been prepared by standard glycosylation,[35] whilst the same compound is also available by a highly stereoselective reduction of a 3'-ketone, as indicated in Scheme 2. If the 5'-position is not protected, hydroxyl-directed reduction leads almost exclusively to a *ribo*-product, and this chemistry can be used for deuterium-labelling at C-3.[36]



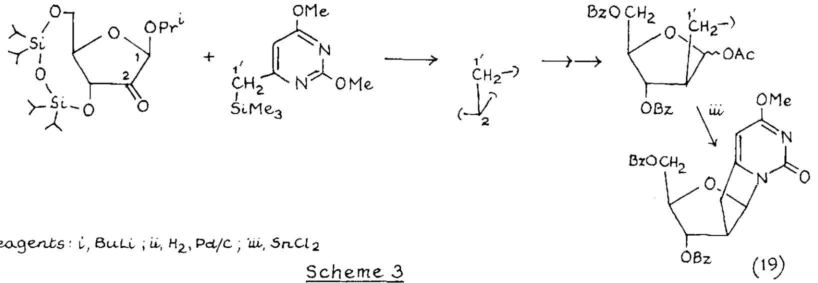
Scheme 2

The glucoside (18) has been prepared by conventional coupling, along with the N^2,N^6-bis-glucoside.[37]


(18)

2 Anhydro- and Cyclonucleosides

2'-Deoxy-6,2'-methano-pyrimidine nucleosides are accessible by a sequence including Peterson olefination and intramolecular glycosidation, as outlined in Scheme 3 (for an earlier route, see Vol. 19, p.198-9). Intermediate (19) can be transformed into the uridine, cytidine and 4-thiouridine systems.[38]

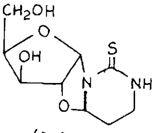


Reagents: i, BuLi ; ii, H_2, Pd/C ; iii, $SnCl_2$

Scheme 3

The 4,2'-anhydronucleoside (20) is produced by the reaction of 3,5-*O*-isopropylidene-D-xylofuranosylamine and β-isothiocyanatopropionaldehyde, followed by hydrolysis.[39]

Novel types of cyclonucleosides have been obtained from the 3',5'-*O*-TIPDS derivative of 2'-ketouridine. Reaction with hydroxylamine gave a mixture of *E* and *Z*-oximes together with a cyclonucleoside from which (21) could be prepared by acidic methanolysis. Reduction of the deprotected oxime to the *arabino*-hydroxylamine also led to cyclization to the cyclonucleoside (22).[40] A full account has been given of the synthesis of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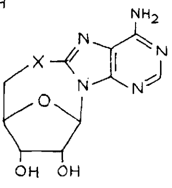
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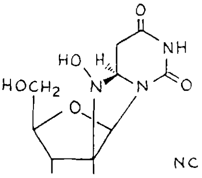
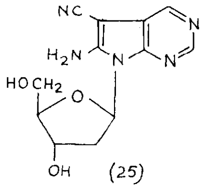

(21) R = OMe

(22) R = H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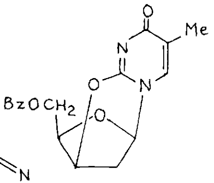

(23)

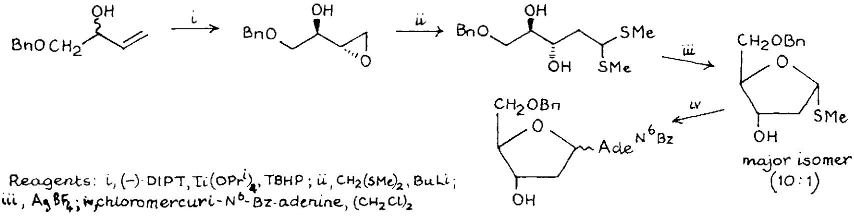
piperidine nucleoside analogues with 2,3'-imino-bridges (see Vol. 23, p.209).[41]

Thymidine can be converted into its 2,3'-anhydride 5'-ester (23) in a one-pot sequence in high yield by the use of Mitsunobu conditions; the displacement at the 5'-position was shown to be the first step.[42] 5',8-Cycloadenosines (24, X=NH, S) have been obtained by thermal cyclization of 8-substituted 5'-chloro-5'-deoxyadenosines.[43]

3 Deoxynucleosides

2'-Deoxy-5-trifluoromethyluridine has been prepared from the silylated base and 2-deoxy-3,5-di-*O*-toluoyl-α-D-*erythro*-pentofuranosyl chloride, with conditions being optimized for high (93:7) β-selectivity.[44] Sodium salt or phase-transfer glycosylations involving the same deoxyribose synthon have been used to prepare 2'-deoxyribosides, with the β-anomers predominating, of some 2,6-disubstituted purines,[45] 2-azapurines,[46] the pyrrolo[2,3-*d*]pyrimidine (25),[47] some 1,3-bisalkyl-7-deazaxanthines which give conformationally-locked deoxynucleosides,[48] 3-deazaadenine (and also the 2',3'-dideoxynucleoside), [49,50] and benzotriazoles, where regioisomers were obtained with unsymmetrically-substituted heterocycles.[51]

High yields of separable anomeric mixtures of regiospecifically N-9 purine and N-1 pyrimidine 2'-deoxyribonucleosides can be obtained by interaction of 1-*O*-acetyl-3,5-di-*O*-benzoyl-D-ribofuranose with a silylated nucleobase under phase-transfer conditions using dibenzo-18-crown-6 and potassium iodide in acetonitrile-toluene.[52] An asymmetric route to nucleosides from non-carbohydrate precursors is outlined in Scheme 4.[53]



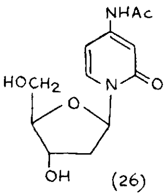
Reagents: i, (–)-DIPT, Ti(OPr^i)$_4$, TBHP ; ii, CH$_2$(SMe)$_2$, BuLi ; iii, AgBF$_4$; iv, chloromercuri-N^6-Bz-adenine, (CH$_2$Cl)$_2$

Scheme 4

An improved procedure for the conversion of uridine to 2'-deoxyuridine has been reported,[54] and free-radical deoxygenation has been used to prepare 2'-deoxyribonucleosides of pyridones, such as (26).[55]

There have been further reports of the use of enzymic methods in this area. [7-^{15}N]-Labelled 2'-deoxyadenosine and 2'-deoxyguanosine have been prepared by transfer of deoxyribose units from thymidine to an isotopically labelled purine by the combined use of thymidine phosphorylase and purine nucleoside phosphorylase,[56] whilst the N-deoxyribosyl transferase from *Lactobacillus leichmanii* has been used to transfer 2-deoxyribose from thymidine to 1-deazapurine,[57] and to benzimidazole and 4-amino-5-carboxamidoimidazole.[58] Purine 2'-deoxyriboside has been prepared from purine and ribose-1-phosphate by application of a commercial nucleoside phosphorylase,[59] and [5,6-^{3}H]-2'-deoxyuridine has been synthesized enzymically from the labelled base.[60] There has been a brief report on the synthesis of 2'-deoxy-5-amino- and -5-hydroxyaminoimidazole nucleosides by chemical methods and by biotransformations.[61]

The 3'-deoxy-pyrazolo[3,4-*d*]pyrimidine nucleoside (27) has been prepared by conventional coupling,[62] and various 3'-deoxyinosine analogues modified in the base unit were synthesized from guanosine by free radical deoxygenation of a 2',5'-di-*O*-TBDMS derivative.[63]



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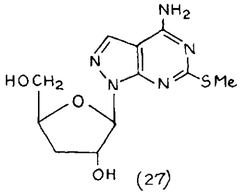

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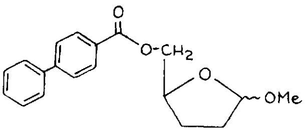
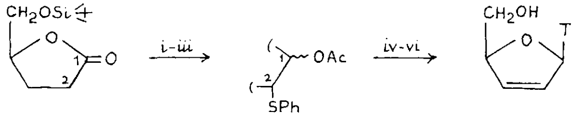


(28)

2',3'-Dideoxynucleosides and their related 2'-enes continue to attract attention. The compounds (28) (either anomer) have been used in a new but non-stereoselective synthesis of 2',3'-dideoxycytidine (ddC),[64] and stereoselectivities in the coupling between silylated pyrimidines and 5-*O*-acyl-1-halo-2,3-dideoxyriboses have been investigated; moderate β-selectivities could be attained.[65] Various 6-substituted purine 2',3'-dideoxynucleosides have been synthesized non-stereospecifically from 1-*O*-acetyl-5-*O*-TBDMS- 2,3-dideoxy-D-ribofuranose.[66]

Two groups have independently developed a highly β-selective route to 2',3'-didehydrodideoxy nucleosides, which involves the introduction of an α-phenylthio group at C-2 of the sugar unit to direct the orientation of the coupling in the desired sense;[67,68] Scheme 5[67] illustrates the principle, and other workers have reported closely similar work in which selenium replaces sulphur.[69]

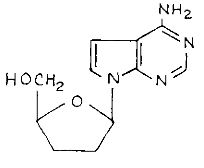


Reagents: i, LDA, PhSSPh; ii, DIBAL; iii, Ac_2O,Py; iv, bis(TMS)thymine, $SnCl_4$; v, Δ, Py; vi, TBAF

Scheme 5

There have been further reports on the formation of 2',3'-didehydrodideoxy nucleosides, and hence their saturated hydrogenation products, from 2',3'-bisxanthates or cyclic thionocarbonates (see Vol. 23, p.212). 2',3'-Dideoxyadenosine has been made by this approach,[70,71] as have 2',3'-dideoxynucleosides of various 8-substituted purines[72] and of 6-methyluridine.[73] 2',3'-Dideoxytubercidin (29) has been synthesized by free-radical deoxygenation of the 3'-deoxyanalogue.[74]

The chemistry in Scheme 6 has been used to prepare 2',3'-didehydro-dideoxy nucleosides,[75] and a similar reductive elimination using Zn-Cu has been employed in a large-scale preparation of the cytosine analogue d4C.[76]



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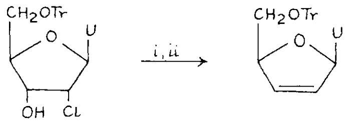


Reagents: i, PhOC(S)Cl; ii, Bu_3SnH, AIBN

Scheme 6

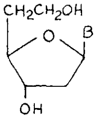
Elimination reactions of 2'-deoxynucleosides have been used to prepare 2',3'-didehydrodideoxy derivatives of cytosine (d4C), and hence ddC,[77] some 6-azapyrimidine nucleosides,[78] and some indole nucleosides.[79] A thermal elimination on a 3'-phenylselenoxide was a key step in a streamlined procedure for making d4T from thymidine in a three-pot sequence.[80] Various deoxygenated derivatives of ribavirin have been reported,[81] and d4T has been prepared radiolabelled at C-2.[82]

The 'homothymidine' (30,B=T) has been prepared from a 5-deoxy-D-*ribo*-hexofuranose derivative by condensation followed by deoxygenation at C-2',[83] whilst the deoxyuridine and deoxycytidine analogues (30, B=U or Cyt) are available following cyanide displacement applied to 2',5'-dideoxy-5'-iodouridine.[84] Displacements of the sulphonyloxy groups of nucleoside 5'-tosylates with Me_2CuLi were used to prepare the 5'-*C*-methyl analogues (31, B=U, T, 5-FU, R=H or OH).[85]

4 Halogenonucleosides

2'-Deoxy-2'-fluorouridine (32) has been prepared by the action of DAST on precursors of both D-*arabino*[86,87] and D-*ribo*-configuration;[86] further substitution at C-3' with overall retention of configuration gave 3'-azido-2',3'-deoxy-2'-fluoropyrimidines (33), and the 2',3'-difluoro analogues (34).[87,88] Difluoropyrimidine nucleosides of D-*arabino*-configuration (35) have been reported, the 3'-fluoro-group being incorporated with overall retention of configuration via cyclonucleoside intermediates,[89] as have 2'-fluoro-2'-enes

(36) in the pyrimidine series.[89,90] Two groups have prepared the AZT analogue (37) by similar methods, [90,91] and the 'up'-fluorinated analogue of ddC (38) has also been synthesized,[91] as have similar analogues of adenosine and hypoxanthine,[92] and of *N*6-methyladenosine,[66] which show some anti-HIV activity and are much more acid-stable than the non-fluorinated dideoxy-nucleosides.



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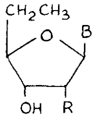

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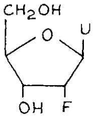

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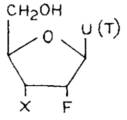
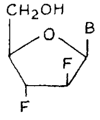


(33) X = N_3

(34) X = F



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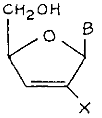
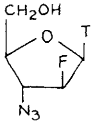


(36) X = F

(40) X = Cl



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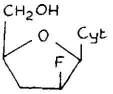

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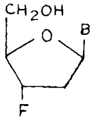

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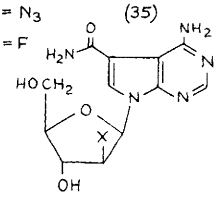


(41)

The Leiden group have reported further details of their syntheses of a series of five 3'-deoxy-3'-fluoro-ribonucleosides (see Vol. 23, p.213),[93] and others have synthesized 3'-deoxy-3'-fluoroadenosine by similar methods from adenosine itself via D-*xylo*-intermediates.[94] The same adenosine analogue has also been made by transglycosidation from the corresponding uridine derivative.[95] A short route to 3'-deoxy-3'-fluorothymidine (39, B=T) involves the β-selective condensation of silylated thymine with a 2,3-dideoxy-3-fluororibofuranose derivative which was made from deoxyribose,[96] and the adenosine and guanosine analogues (39, B=Ad or Gua) can be prepared by chemical transglycosylation using the 5'-*O*-acetyl derivatives of the thymidine/uridine compounds (39, B=T or U).[97]

5'-Deoxy-5'-fluorouridine has been prepared by the use of DAST.[86]

Unsaturated 2'-chloronucleosides (40) have been prepared in the pyrimidine series by regioselective elimination from a 2'-chloro-3'-*O*-triflyl derivative,[98] and the halogenated analogues (41, X=Cl, Br, I) of sangivamycin have been prepared from toyocamycin.[99]

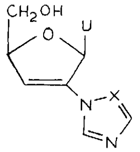
5 Nucleosides with Nitrogen-substituted Sugars

Some 2'-azido-2',3'-dideoxypyrimidine nucleosides, including the isomer of AZT, have been prepared via 2,2'-anhydronucleosides, and using free-radical deoxygenation at C-3.[100]

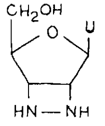
Some additional synthetic applications have been described for the uridine-derived 2',3'-ene-3'-phenylselenone reported in Vol. 23,(p. 217). These include addition-elimination reactions with heterocycles to give products (42), and addition-substitution reactions with diamines to yield for example (43) and (44).[101]

3'-Amino-2',3'-dideoxyuridine has been prepared by similar methods to those reported last year (Vol. 23, p.216) for the thymidine analogue.[102] There have been further reports on the use of 3'-amino-3'-deoxythymidine as a precursor of the 3'-isocyano-,[103,104] 3'-isothiocyano-, and 3'-isoselenocyano-derivatives (45) related to AZT (see Vol. 23, p.215-6),[103] and 2',3'-dideoxy-3'-isocyanouridine has been prepared in similar fashion.[104] 3'-Amino-3'-deoxythymidine was also used to prepare some heterocyclic analogues such as (46), and similar compounds were also made by opening a 2',3'-*lyxo*-epoxide with an intact heterocycle followed by deoxygenation at C-2'.[105]

The formation of 5'-*O*-trityl-AZT by reaction of the 2,3'-anhydronucleoside-5'-ether with lithium azide in DMF is accompanied by the formation of the regioisomer (47).[106] Anhydronucleosides were used as intermediates in the synthesis of the AZT isomer derived from 6-methyluridine,[73] analogues involving 5-(substituted) benzyluracil as base,[107] and the homologue (48), the sugar component of which originated as diisopropylidene glucose.[108]



(42) X = N,CH



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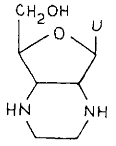

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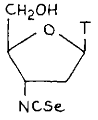

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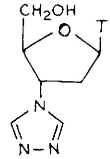

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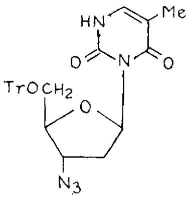

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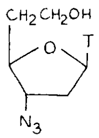

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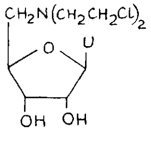

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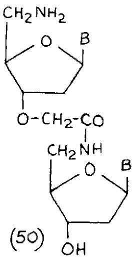

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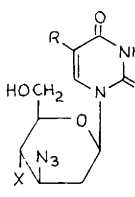


(51) X = OH, R = Me, Hal
(52) X = H, R = Me

The uridine mustard compound (49) has been synthesized for anti-tumour evaluation.[109] Oligodeoxynucleosides of type (50), and related trimers, have been prepared by coupling 3'-*O*-carboxymethyl derivatives with 5'-aminodeoxy-compounds.[110]

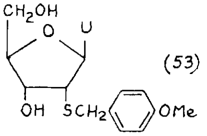
A Michael addition of azide ion was a key step in syntheses of hexopyranosyl nucleosides of type (51); in contrast to findings in similar work reported last year which led to furanosyl systems (Vol. 23, p.216), the addition of azide was not accompanied by acyl migration.[111] The same group has also employed somewhat similar methods to produce the deoxy system (52) and its C-3' epimer.[112]

Some azidonucleosides also containing fluorine were mentioned in the previous section.

6 Thionucleosides

The thioether (53) is available from the 2,2'-anhydronucleoside; on treatment with phenol in TFA it is converted efficiently into 2'-thiouridine, from which the cytidine analogue can be prepared.[113]

The bis-thioether (54) can be obtained in good yield by interaction of the 2',3'-ene-3'-phenylselenone (Vol. 23, p.217) and ethane dithiol in the presence of DBU.[101]



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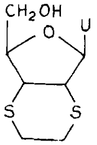


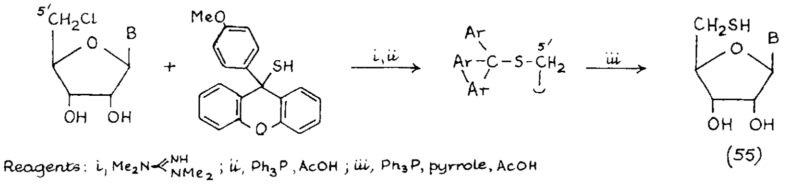
(54)

The chemistry outlined in Scheme 7 gives access to 5'-deoxy-5'-mercaptonucleosides (55),[114] and 5'-deoxynucleoside 5'-thiosulphates can be prepared in the purine series from 5'-chloro-5'-deoxynucleosides and sodium thiosulphate in refluxing aqueous conditions.[115]

Branched-chain sulphur nucleosides of type (56), the cyclic derivative (57), and its sulphone, have been prepared from 1,2-*O*-isopropylidene-α-D-xylofuranose.[116] Another reference to a branched-chain thionucleoside is discussed below.

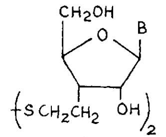
7 Nucleosides with Branched-chain Sugars

The mechanism of addition of MeMgBr to 2'-ketonucleosides in the pyrimidine series (see Vol. 22, p.213 and Vol. 21, p.209-210) has been investigated. By use of a range of compounds with different substituents at C-5, Grignard reagents were shown to coordinate with the pyrimidinone oxygen, thereby delivering the incoming nucleophile to the β-face; other organometallics and hydrides approach exclusively from the less hindered α-face.[117]



Reagents: i, $Me_2N{-}C(=NH)NMe_2$; ii, Ph_3P, AcOH; iii, Ph_3P, pyrrole, AcOH

Scheme 7



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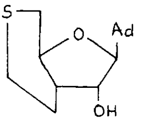

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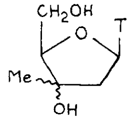

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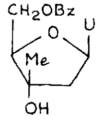
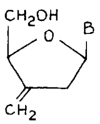


(59)

A stereorandom addition of MeMgI to a 3-ketosugar was used in a synthesis of the 3'-*C*-methyl derivatives (58),[118] and the same group have synthesized the uridine analogue (59) in a stereospecific manner by Grignard addition to a 1,2-*O*-isopropylidene-3-ulose, and later deoxygenation at C-2' (see Vol. 22, p.213-214 for related earlier work).[119]

Oxidation of 5'-*O*-tritylthymidine or -2'-deoxyuridine with $CrO_3.2Py$ gives unstable 3'-ketocompounds which react with CH_2Br_2-Zn-$TiCl_4$ to give a route to dideoxy-3'-methylene pyrimidine nucleosides (60).[120] In a synthesis of the isomeric thymidine analogue (61) with the double bond endocyclic, the later stages summarized in Scheme 8 were used. Precursor (62) was made by base-sugar condensation.[121]



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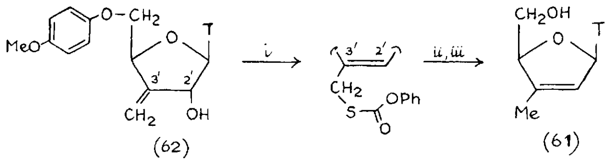
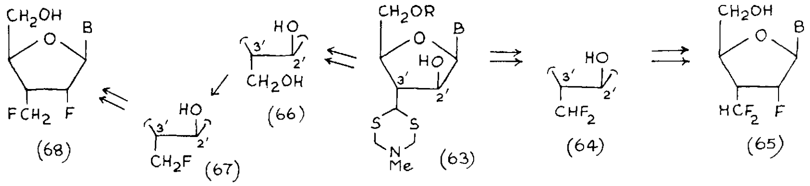


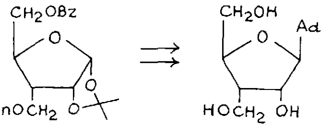
Reagents: i, PhOC(S)Cl, DMAP; ii, Bu_3SnH; iii, $(NH_4)_2Ce(NO_3)_6$

Scheme 8

Regioselective opening of 2',3'-*lyxo*-epoxides with a lithiated dithian gave rise to branched structures of type (63, B=U or T) which could be converted (Scheme 9) into 3'-*C*-difluoromethyl compounds (64) and thence into analogues (65) with an additional fluorine atom at C-2'.[122] Alternatively, intermediates (63) could be used as precursors for 3'-*C*-hydroxymethyl systems (66),[123] and, by successive fluorination, fluoromethyl analogues of types (67) and (68) were obtained.[122] In a synthesis of 3'-deoxy-3'-hydroxymethyl adenosine (69), the branched-chain sugar derivative (70), produced by a Wittig reaction involving benzyloxymethyltriphenylphosphorane and subsequent hydrogenation, was a key intermediate.[124]

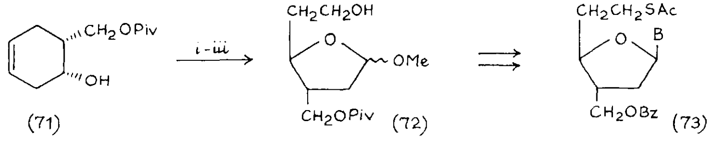


Scheme 9



(70) (69)

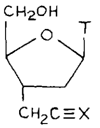
The cyclohexene (71) (Scheme 10), resolved enzymically, has been converted as indicated into the synthon (72). This was used to produce nucleoside analogues (73) involving all the RNA bases, which are proposed as precursors for oligonucleotide analogues with -CH$_2$S-CH$_2$-, or an oxidized form, replacing the phosphate link.[125]



Reagents: i, O$_3$, Me$_2$S ; ii, MeOH ; iii, NaBH$_4$

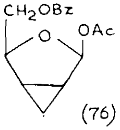
Scheme 10

There has been a further report on the preparation of 3'-deoxy-3'-*C*-allyl thymidine by free radical coupling (see also Vol. 23, p.218), and this has been converted into the AZT analogues (74) and (75).[126] The adenosine and 2'-deoxyadenosine derivatives corresponding to (75) have also been reported via a Wittig-reduction approach operating on a 3'-ketonucleoside.[127]



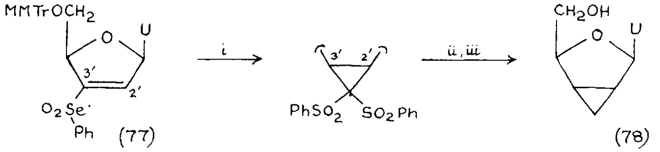
(74) X = CH

(75) X = N



(76)

An alternative approach to cyclopropacytosine (see Vol. 23, p.218) involves condensation of silylated cytidine with (76),[128] whilst the versatile ene-selenone (77) (Vol. 23, p.217) can act as a precursor for cyclopropa-uridine (78) as indicated in Scheme 11.[129]



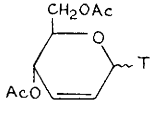
Reagents: i, $CH_2(SO_2Ph)_2$, KOBu^t ; ii, Mg,MeOH; iii, H_3O^+

Scheme 11

8 Nucleosides of Unsaturated Sugars, Keto-sugars and Uronic Acids

Some papers dealing with 2',3'-didehydro-2',3'-dideoxypentofuranosyl nucleosides (d4 systems) were discussed in Section 3 along with the saturated analogues. The unsaturated pyranosyl compound (79, both anomers) can be obtained by thermal reaction of triacetyl-D-glucal and thymine. The products (79) were converted routinely to the enones (80) and aminouronates (81). The analogous nucleoside derived from diacetyl-D-xylal was formed with α-stereoselectivity.[130]

A review on recent applications of activated DMSO for the oxidation of alcohols includes cases where ketonucleosides and nucleoside 5'-aldehydes are the products.[131] A potentially useful reagent for making 2'- and 3'-ketofuranosyl nucleosides is the Dess-Martin periodinane; oxidation of 2',5'- and 3',5'-di-*O*-silylribonucleosides gives the 3'- and 2'-ketones respectively in good yield, and this reagent permitted the first synthesis of a 3'-ketone (82) from a purine 2'-deoxynucleoside.[132] The synthesis of the 2'-ketone (83) by 1,2-hydride shift is described in a report from a symposium.[133]



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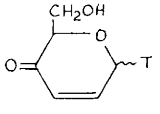

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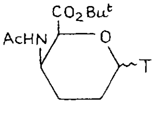

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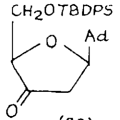

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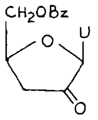

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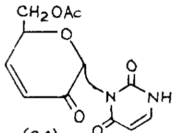

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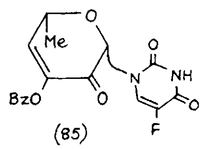

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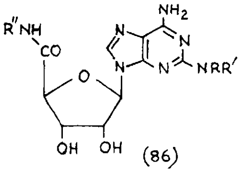
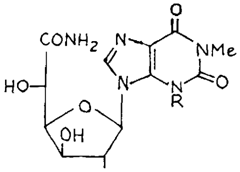


(86)

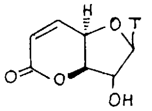
Reaction of peracetylated 2-acetoxyglycals with silylated uracil in the presence of $SnCl_4$ affords the α-anomers of nucleoside enones such as (84) from the galactal derivative, with linkage being to N-3 of the uracil.[134] The similar enone (85) has been prepared from tetra-*O*-acetyl-α-L-fucopyranose.[135]

A series of adenosine uronamides of type (86) have been identified as a new class of selective adenosine A_2 receptor ligands. They were prepared from 2-chloroadenosine using permanganate oxidation to generate the uronate.[136] The nucleosides (87) were made by conventional condensations involving tri-*O*-acetyl-glucurono-6,3-lactone,[137] and the analogue (88), related to the anticancer compound goniothalenol, was synthesized using an intramolecular Wittig reaction to make the double bond of the enone.[138]

A study has been made of the diastereotopy of the methylene and methyl protons in ethyl and isopropyl esters of purine nucleoside uronates. Anisochromism of the diastereotopic protons was conditional upon both close spatial proximity and fixed orientation of the heterocycle *vis-a-vis* the alkoxycarbonyl group.[139] Unsaturated nucleoside uronates such as (89) have been prepared by β-elimination and their chirooptical properties investigated.[140]



(87) R = Me,Bu^t



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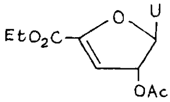

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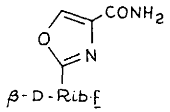
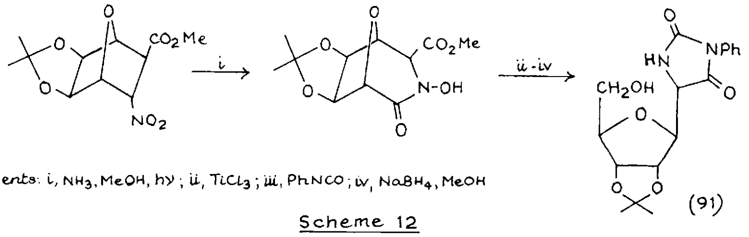


(90)

9 *C*-Nucleosides

The oxazole analogue (90) of the antitumour agent tiazofurin has been prepared from 2,5-anhydro-D-allonic acid by a fairly conventional annulation.[141] An interesting photochemical ring expansion was used (Scheme 12) in a synthesis of the racemic hydantoin *C*-riboside (91), the starting material illustrated being made by a Diels-Alder-hydroxylation sequence.[142] Further extensions of the application of Wittig reactions for the



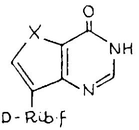
Reagents: i, NH_3, MeOH, hν ; ii, $TiCl_3$; iii, PhNCO ; iv, $NaBH_4$, MeOH

Scheme 12

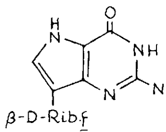
synthesis of glutarimide *C*-nucleosides have been reported (see Vol. 22, p.215), leading to analogues of 1-deazathymidine.[143]

A new natural product, pyrrolosine, isolated from a *Streptomyces* species, has been assigned the structure (92), on the basis of X-ray data. Structure (92) is that of the known synthetic 9-deazainosine, but the natural product has different chemical and biological properties![144] A full report has appeared on the synthesis of furo[3,2-*d*]pyrimidine *C*-nucleosides (see Vol. 20, p.212), this full paper also reporting the inosine analogue (93).[145] Direct *C*-glycosylation under Friedel-Crafts conditions gave rise to 9-deazaguanosine (94), and the same conditions applied to a pyrrolo[2,3-*d*]pyrimidine led to the 8-*C*-ribosyl-7-deazaguanine (95); the presence of an 8-methyl group in the aglycone gave 8-methyl-7-deazaguanosine.[146] A full account has been given of the synthesis of the thieno[3,4-*d*]pyrimidine analogue of inosine (see Vol. 22, p.215); attempts to extend this chemistry to furopyrimidine systems failed when 2-(β-D-ribofuranosyl)furans could not be elaborated into bicyclic systems.[147]

The AZT isosteres (96) and (97) have been prepared from 2'-deoxy-1-methylpseudouridine and from the corresponding fluoroanalogue (Vol. 21, p.211) respectively, by standard manipulations; neither showed significant anti-HIV activity.[148]



(92) X = NH
(93) X = O



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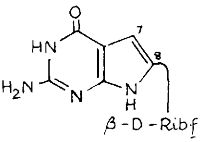

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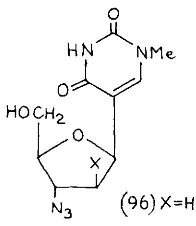
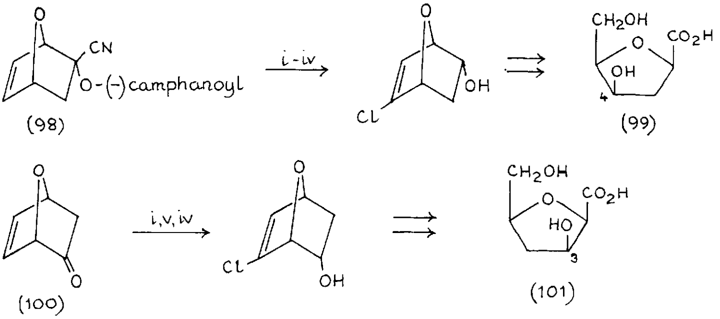


(96) X=H
(97) X=F

In extensions of Vogel's 'naked sugar' approach to nucleosides, the camphanoate (98) could be converted (Scheme 13) into the anhydrohexonic acid (99), and the C-4 epimer was also made by incorporating an inversion of configuration. The ketone (100) could be converted into the 4-deoxy system (101), relying upon the different regiochemistry of electrophilic attack on such ketones as opposed to their cyanohydrin esters. Again, the epimer (at C-3) could also be prepared. These four acids were converted into deoxyadenosine analogues with the sugar linked to C-8 of the purine, including 'cordycepin C' which the same workers reported last year using somewhat similar chemistry (Vol. 23, p.219).[149]

Arabinofuranosyl pyrazole-*C*-nucleosides (102) have been prepared by cyclodehydration of polyol chains of D-*manno*-configuration; β-isomers



Reagents: i, PhSeCl ; ii, H_2O_2 ; iii, OH^- ; iv, $NaBH_4$; v, MCPBA

Scheme 13

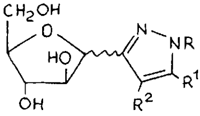
predominate, corresponding with preferential cyclization with inversion of configuration.[150]

There have been reports on the synthesis of 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxyderivatives of formycin[74] and tiazofurin[81] starting from the parent *C*-nucleosides.

Further examples have been provided of the formation of hexopyranosyl derivatives of barbituric acid from unprotected hexoses and barbituric acid (see Vol. 20, p.35).[151]

10 Carbocyclic Nucleoside Analogues

A review on natural product synthesis using asymmetric Diels-Alder reactions includes references relevant to the synthesis of carbocyclic nucleosides in an enantiomerically pure state.[152] The phosphonate (103), made via Diels-Alder reaction, gives rise to (104), claimed as a potential precursor for carbocyclic *C*-nucleosides, on treatment with K_2CO_3-$NaBH_4$.[153]



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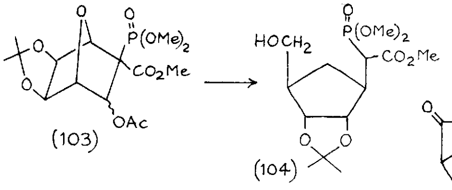
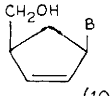


(103) (104)



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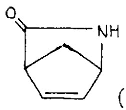
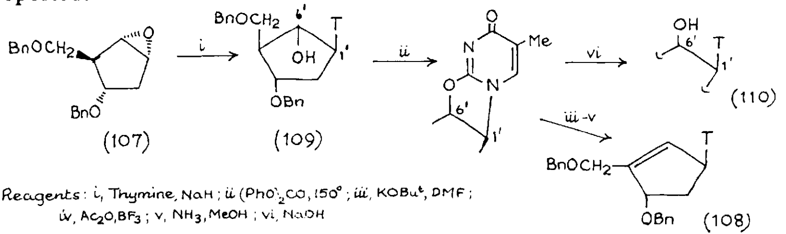


(106)

Work on the synthesis of 2',3'-didehydro-2',3'-dideoxy carbocyclic nucleosides has led to the emergence of the guanosine analogue carbovir (105, B=Gua) as a potent and selective anti-HIV agent.[154] The precursor (106) of the bioactive (-)-isomer of carbovir can be resolved by the enantioselective hydrolysis of the unwanted isomer by a *Pseudomonas* species.[155] The same (racemic) precursor has been used to make carbocyclic d4T (105, B=T),[156] and also carbocyclic analogues of lyxofuranosides of 2-amino-6-substituted purines and 8-azapurines using methods employed earlier for the adenosine analogue (see Vol. 14, p.191).[157]

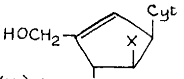
The chiral epoxide (107) (Scheme 14) can be used as a precursor for the thymidine analogue of neplanocin A (108), and also for the 6'-α- and 6'-β-hydroxy-derivatives (109) and (110) of thymidine.[158] The alkenes (111) and (112), related to the cytosine analogue of neplanocin, have also been reported.[159]



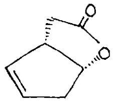
Reagents: i, Thymine, NaH ; ii, (PhO)$_2$CO, 150° ; iii, KOBu^t, DMF ; iv, Ac$_2$O,BF$_3$; v, NH$_3$,MeOH ; vi, NaOH

Scheme 14

Several alternative routes have been developed to convert the bicyclic lactone (113) into carbocyclic nucleosides, including (+)-carbathymidine and its 3'-epimer, the carba analogue of AZT, and the 6'-α-methyl compound (114).[160] Carbathymidine has also been made from carbocyclic thymidine riboside by free-radical deoxygenation.[161] The racemic azides (115) and their corresponding amines are accessible by inversion at C-3', and heterocycle functionalization, from a previous intermediate (Vol. 20, p.213),[162] and two pyrrolo[2,3-*d*]pyrimidine carbocyclic nucleosides (116) and (117) have been described.[163]



(111) X = H
(112) X = OH



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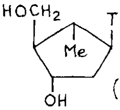

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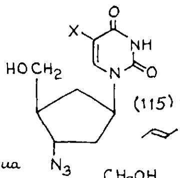
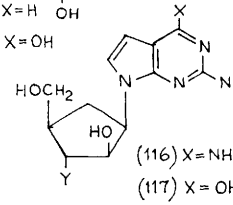
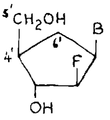


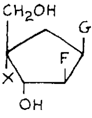
(115) X = I, Br



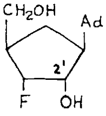
(116) X = NH₂, Y = OH
(117) X = OH, Y = N₃



(118) B = Ad
(119) B = Gua

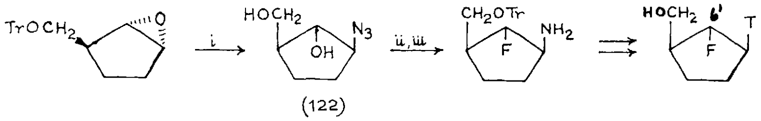


(120) X = OH, F



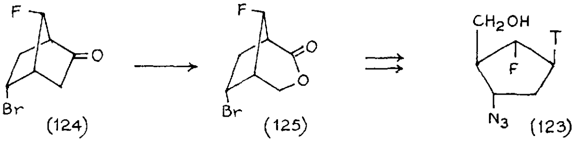
(121)

Fluorinated carbocyclic nucleosides have again attracted attention. The Glaxo group have reported further (see Vol. 22, p.217) on their conversion of aristeromycin (carbaadenosine) into the 2'-fluoro-derivative (118), and hence, by heterocycle modification, into the anti-herpetic guanosine analogue (119). This route to the latter is preferable to the previously-reported procedure from a cyclopentane derivative (Vol. 22, p.217). The key step in the route to (118) is the selective debenzoylation of *N,O,O,O*-tetrabenzoylaristeromycin at O-2' using KO-^{t}Bu.[164] The same group have also carried out modifications of (119) at C-4' to give, via a 4',5'-ene, compounds (120) and also the 4',6'-ene (neplanocin-type).[165] Various similar pyrimidine nucleoside analogues have been reported, with fluorine at C-2' or C-6'.[166] 3'-Deoxy-3'-fluoroaristeromycin (121), and its 2'-deoxyanalogue have been prepared; they show antileukaemic activity.[167] The preparation of a CHF analogue of ddT is outlined in Scheme 15, the retentive fluorination by DAST being noteworthy. The epimer at C-6' was also made by a displacement on (122) using Bu$_4$NF.[168] Similar CHF replacements in AZT were described last year (Vol. 23, p.222); an alternative chiral route to the α-fluorocompound (123) involves microbiological oxidation of a racemic ketone to convert the unwanted isomer into its Baeyer-Villiger oxidation product. The residual chiral ketone (124) (Scheme 16) was then chemically oxidized (with opposite regioselectivity to the enzyme) to lactone (125), an intermediate in the previous route.[169]



Reagents: i, NaN$_3$, NH$_4$Cl; ii, DAST; iii, H$_2$, Lindlar cat.

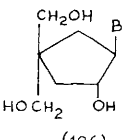
Scheme 15



Scheme 16

Racemic aminocyclopentane intermediates were used to prepare the hydroxymethyl derivatives (126, B=Ad, Gua).[170] the nor-nucleoside (127),[171] and the carbocyclic analogue (128) of the insecticidal agent clitocine.[172]

Some references to phosphates of carbocyclic nucleosides are mentioned in the next section.



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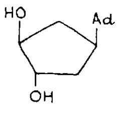

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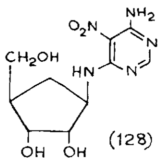
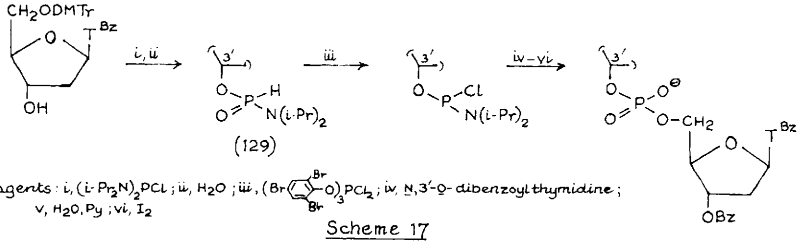


(128)

11 Nucleoside Phosphates and Phosphonates

Diastereomers of deoxynucleoside 3'-(*O*-β-cyanoethyl, *N*-diisopropyl)-phosphoramidites can be separated by chromatography. The proton n.m.r. spectra show characteristic differences which can be used to assign absolute configurations at phosphorus.[173] A study has been reported on the use of such intermediates for oligoribonucleotide synthesis.[174]

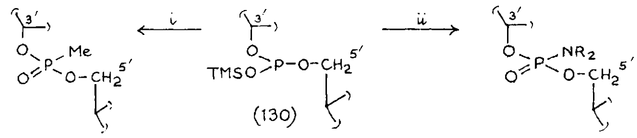
O-Alkyl-2'-deoxynucleoside 3'-phosphonates[175] and the corresponding *N*,*N*-dialkylphosphonamidates (129) (Scheme 17)[176] can be activated to the corresponding phosphorochloridites by the use of tris(2,4,6-tribromophenoxy) dichlorophosphane, and these intermediates can be used for oligodeoxynucleotide synthesis (see also Vol. 22, p.219).



Reagents: i, $(i\text{-}Pr_2N)_2PCl$; ii, H_2O; iii, $(Br_3C_6H_2O)_3PCl_2$; iv, N,3'-O-dibenzoylthymidine; v, H_2O, Py; vi, I_2

Scheme 17

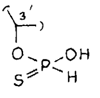
Di(deoxynucleoside)-trimethylsilylphosphites (130) have been used (Scheme 18) to prepare methylphosphonates and phosphoramidates (see also Vol. 22, p.218-9).[177]

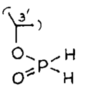


Reagents: i, MeI; ii, $R_2NCOCONR_2$

Scheme 18

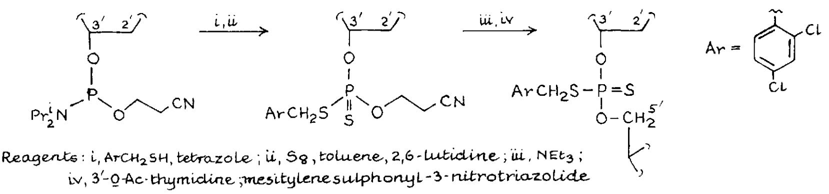
A convenient preparation of deoxynucleoside 3'-H-phosphonates involves the reaction of a suitably-protected nucleoside with phosphonic acid in the presence of pivaloyl chloride.[178] Ribo- and deoxyribo-nucleoside 3'-phosphonothioates (131) can be obtained by reaction of the corresponding protected nucleoside with triethylammonium phosphinate and pivaloyl chloride to give the nucleoside phosphinate (132), followed by oxidation with sulphur.[179]

(131)




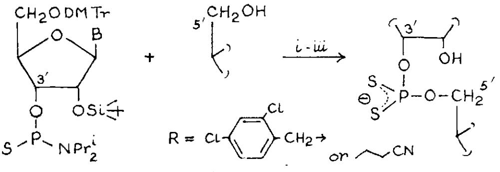
(132)

There have been further reports on the synthesis of nucleoside phosphorodithioates. Reese has extended his approach via hydrogen phosphonothioates (Vol. 23, p.223) to the synthesis of a thymidine trimer with two phosphorodithioate links,[180] and Caruthers' group have described a phosphotriester approach as outlined in Scheme 19.[181] A route which is applicable to di(ribonucleoside) phosphorodithioates proceeds via phosphorothioamidites as indicated in Scheme 20.[182]



Reagents: i, ArCH$_2$SH, tetrazole; ii, S$_8$, toluene, 2,6-lutidine; iii, NEt$_3$; iv, 3′-O-Ac-thymidine; mesitylenesulphonyl-3-nitrotriazolide

Scheme 19



Reagents: i, tetrazole; ii, S$_8$; iii, deprotection

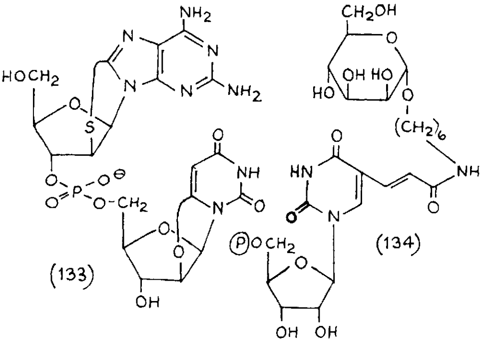
Scheme 20

Carbocyclic thymidine has been incorporated into short oligonucleotides,[183] and the dinucleoside phosphate (133) containing two anhydronucleosides, and the isomer with the two bases reversed, have both been prepared by the phosphodiester procedure.[184]

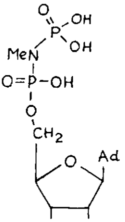
A review has appeared dealing with the synthesis of ^{14}C and ^{3}H-labelled nucleoside 5'-phosphates by enzymic methods.[185] An improved method has been developed for the synthesis of highly substituted alkyl phosphates including nucleoside 5'-phosphates. This procedure, involving sequential treatment with (t-BuO)$_2$PNEt$_2$, MCPBA, and 1M HCl, was applied to the preparation of AZT 5'-phosphate and the 5'-phosphate of carbocycle (123).[186] The 5'-phosphate of ribosyl zeatin has been synthesized,[187] and pyrimidine nucleosides can be directly converted to the 5'-diphosphates, albeit in low yield, by the action of partially dehydrated phosphoric acid and *m*-cresol.[188]

Uridine and deoxyuridine 5'-mono- and -triphosphates with long chain sugar-terminated substituents at C-5, such as (134), have been synthesized; these are designed as RNA/DNA monomers with tethered lectin target groups.[189]

The structure of deoxyadenosine 5'-α-thiotriphosphate has been determined by ^{31}P n.m.r.[190] A paper on mass-spectrometric differentiation between regiomeric nucleoside phosphates is covered in Chapter 22.



(133) (134)



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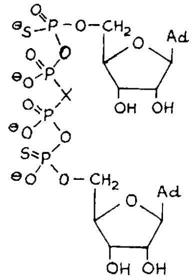


(136) X = O

(137) X = CH_2, CHF, CF_2

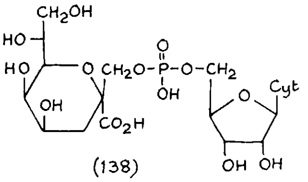
The N-methylimido analogue (135) of ADP has been synthesized, and it could be converted enzymically to the triphosphate analogue. The β,γ-methylimido-triphosphate was also made.[191] Blackburn's group have described the synthesis of the P^1,P^4-dithioderivative (136) of diadenosyl tetraphosphate (Ap4A), and some phosphonate analogues (137),[192] and also phosphonate and thiophosphate analogues of Ap3A.[193]

Whitesides and coworkers have carried out a comparison of enzymic and chemical routes to CTP, GTP and UTP on a 10-gram scale. They concluded that CTP and GTP were best made enzymically, and UTP by reaction of CTP with nitrous acid. The triphosphates were then employed for the enzymic synthesis of UDP-Glucose, UDP-Glucuronic acid, and GDP-Mannose.[194] Cytidine diphosphate sugars have been prepared from the 3,6-dideoxyhexoses paratose and abequose,[195] and all four nucleoside diphosphate sugars of 6-sulpho-α-D-quinovose have been synthesized for studies of sulpholipid biosynthesis in chloroplasts.[196] The stable analogue (138) of CMP-KDO has been prepared by a triester approach, but was only a weak inhibitor of KDO incorporation into lipopolysaccharides.[197] A reference to acetylated forms of UDPGlc is mentioned in Chapter 7.

Two groups have reported the synthesis of compounds of type (139) as potential models for ring-opening reactions of cyclic AMP. These studies included cases where the dioxaphosphorinane ring was both apical-equatorial and diequatorial, and conformations were studied by n.m.r.[198,199] The predominant formation of 3'-monophosphates in the base-catalysed hydrolysis of nucleoside 3',5'-cyclic phosphates has been interpreted in terms of the lone pair orientation effect, which may decrease the energy of the transition state for P-O5' bond-breaking.[200] Conformational studies have been carried out on the diastereomers of adenosine cyclic 3',5'-phosphorothioate, where chair conformations predominate, and for the *R*p-isomer of deoxyadenosine cyclic phosphoranilidate, where a chair-twist equilibrium was observed.[201] Butyl 2'-*O*-tosyladenosine 3',5'-cyclophosphite has been prepared using BuOP(NEt$_2$)$_2$,[202] various N^2-dimethylaminomethylene derivatives of cGMP have been made from guanosine,[203] and a range of N^4, $O^{2'}$-alkylated derivatives of cAMP have been prepared for evaluation of antitumour and cardiac activities.[204]

The hydrolysis of adenosine 2',3'-cyclic phosphate is catalysed by alkane 1,2-diamines. This has been explained in terms of intramolecular cooperation between the neutral and protonated forms of the diamine.[205]

There have been reports on the synthesis of 5'-*O*-phosphonomethyl derivatives of 2'-deoxynucleosides (140, R=OH)[206] and 3'-modified structures (140, R=H, F, N$_3$, OMe).[207]



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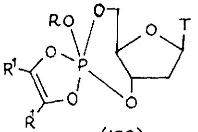

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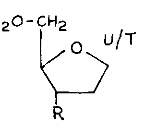

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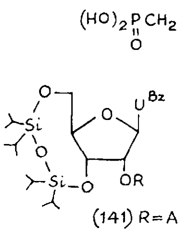


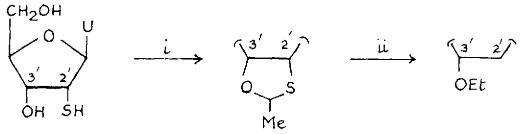
(141) R = All

(142) R = $-CO_2$All

12 Ethers, Esters and Acetals of Nucleosides

A synthesis of 2'-*O*-methyluridine has been carried out by a procedure in which the 3',5'-*O*-TIPDS derivative of uridine was protected at N-3 by the *p*-methoxybenzyl group,[208] and the "wobble position" nucleoside 2'-*O*-methyl-5-(methoxycarboxylmethyl)uridine has also been prepared by similar means.[209] The 2'-*O*-allyl derivative (141) of uridine is accessible by a palladium-catalysed decarboxylation of (142), and a similar reaction is possible on an adenosine derivative.[210] 2'-*O*-Propargyl uridine can be prepared via the 2',3'-*O*-dibutylstannylene derivative; the triple bond of this derivative could then be converted into an unusual carboranyl group, the resultant structure being of potential use in the neutron capture therapy of cancer.[211] A conference report has discussed the use of 2-(methylthio)-phenylthiomethyl (MPTM) ethers for protection of the 2'-hydroxyl group in oligoribonucleotide synthesis.[212]

3'-*O*-Ethyl-2'-deoxyuridine can be prepared from 2'-thiouridine (see Sect. 6) as outlined in Scheme 21, and other ethers can be made in a similar way.[213] A ^{13}C-n.m.r. study of 2'- and 3'-*O*-methyl/ethyl ethers of AMP has been carried out.[214] 2'-Deoxynucleosides have been converted into 5'-*O*-dimethoxytrityl ethers protected on nitrogen with allyloxycarbonyl groups; to make these intermediates, for use in solid phase oligonucleotide synthesis, protection of the 3'-hydroxyl group as a silyl ether was needed.[215]

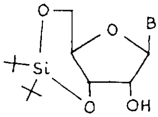


Reagents: i, $MeCH(OMe)_2$; ii, Bu_3SnH, AIBN

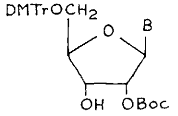
Scheme 21

Procedures for efficient direct regiospecific introduction of the TBDMS group at O-5' of nucleosides have been documented,[216] whilst other workers have reported that silylation of nucleosides with TBDMSCl in DMF-dioxane in the presence of dibutyltin oxide gives, surprisingly, the 5'-*O*-silyl derivatives highly specifically, even in the presence of excess reagents.[217] A further study (see Vol. 23, p.225) on the suitability of TBDMS groups for protection of O-2' during oligoribonucleotide formation has shown that phosphodiester linkages are formed cleanly in a 3'-5' sense using phosphoramidite methodology. Similarly, 3'-*O*-TBDMS intermediates give exclusively 2'-5' linked oligomers.[218] Protection of O-2' and O-3' by TBDMS groups was also employed in the synthesis of 3'-5' and 2'-5' linked oligomers of α-uridine.[219] Ribonucleosides can be converted in high yields into their 3',5'-*O*-(di-*t*-butylsilanediyl)-derivatives (143) using $(tBu)_2Si(OTf)_2$ and similar reagents,[220] and the breakdown of these compounds using Bu_4NF in THF via intermediate monosilylated intermediates has been studied.[221]

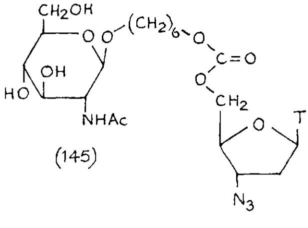
Ribonucleosides protected at O-5' can be converted regioselectively into their 2'-*O*-t-butoxycarbonyl derivatives (144), but the selectivity is not always very high.[222] 5-Fluoro- and 5-trifluoromethyl-2'-deoxyuridines can be acylated regioselectively on O-3' using a lipase from a *Pseudomonas*, and a vinyl ester as acyl donor.[223] A series of 5'-*O*-(unsaturated acyl)-5-fluorouridines have been prepared from reaction of the 2',3'-acetonide with the alkenic acid and DCC-DMAP,[224] although in the case of the 5'-*O*-acryloyl derivative it was necessary to protect N-3 as its *p*-methoxybenzyl derivative before condensation.[225] 5'-*O*-Acyl derivatives of 5-iodo-2'-deoxyuridine have



(143)



(144)



(145)

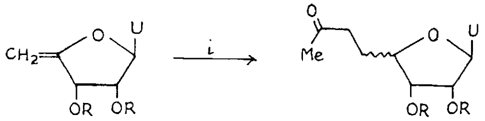
been synthesized as potential prodrugs,[226] and AZT has been converted into a series of 5'-esters,[227] and into the alkyl glycoside carbonate (145) and its α-D-mannopyranosyl analogue as potential drug carriers.[228]

Treatment of adenosine with sodium toluene-*p*-sulphinate and sodium hypochlorite gives a 50% yield of 2'-*O*-tosyladenosine. *N*-Chloro intermediates are thought to be involved, which then give tosyl chloride by reaction with the sulphinate, but it is unclear why this procedure gives a higher yield than direct tosylation.[229] Amino acids linked to (deoxy)-nucleosides via a sulphamoyl group have been reported; they are structurally similar to the antibiotic ascamycin (see also Vol. 23, p.226).[230] 3'- and 5'-*O*-dansyl derivatives of thymidine have been prepared, and shown to act as inhibitors of thymidine kinase from herpes simplex virus.[231]

AZT has been linked via a glycosidic link to *N*-acetyl neuraminic acid, both α- and β- isomers being obtained.[232]

13 Miscellaneous Nucleoside Analogues

A number of papers have described nucleoside analogues chain-extended at C-5'. The free-radical method indicated in Scheme 22 gives good L-*lyxo*-selectivity if R=TBDMS, but is D-*ribo*-specific if R=H.[233] Aldol[234] and Wittig reactions[235,236] appied to ribonucleoside 5'-aldehydes have been used for similar chain extensions, and such methods were employed to make adenine nucleosides such as (146) related to sinefungin.[237,238] Reactions of dianions of β-ketoesters and β-diketones with 5'-deoxy-5'-iodothymidine gave products (147), and similar reactions occurred with dianions from β-ketophosphonates and β-keto sulphones.[239] Acetylenic structures such as (148) have been prepared as analogues of *S*-adenosyl homocysteine and potential inhibitors of methyltransferases.[240] A full paper has appeared concerning a chain-extended thymidine epoxide reported recently (Vol. 23, p.227).[241]

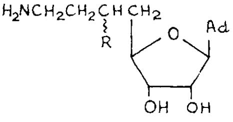


Reagents: i, PhSeCH$_2$COMe, Bu$_3$SnH

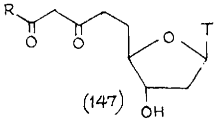
Scheme 22

Porphyrinyl nucleosides have been reported, in which uridine and adenosine are linked via their 5'- positions to phenyl rings of a tetraarylporphin.[242]

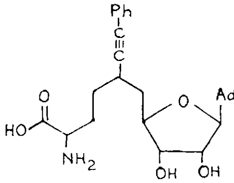
The cyclobutyl nucleosides (149) have been prepared; they are related structurally to carbocyclic oxetanocin analogues of known antiviral activity (Vol. 23, p.197-8), but were inactive.[243] Other references to oxetanocin analogues are given in Chapter 19.



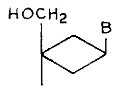
(146) R = NH_2, CH_2NH_2, $CONH_2$



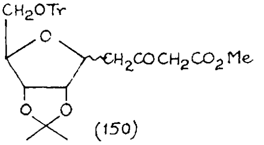
(147)



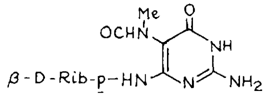
(148)



(149) B = Ad, Gua



(150)



(151)

There has been a report on the preparation of triazole and pyrimidine homo-*C*-nucleosides, which were made from *C*-glycosides such as (150),[244] and further nucleocyclitols similar to those reported earlier (Vol. 18, p.202) have been described.[245]

14 Reactions

The hydrolysis of 2-methyladenosine occurs by a process of depurination over a wide acidity range of pH <4.7, whereas 2-amino- and 2-methyl-9-(β-D-ribofuranosyl)purines are depurinated only at high hydronium ion concentration, and undergo opening of the imidazole ring under mildly acidic conditions.[246] The hydrolysis, by depurination, of some 7-alkyladenosines has been studied; it was found that for *N*-methyl derivatives of adenosine, the hydrolysis of the 3-methyl derivative was faster than that of the 7-methyl isomer, with both hydrolyses occurring much faster than for the N^6- or 1-methyl compounds.[247] The depurination of 7-alkylguanosines, and their 5'-monophosphates, is independent of pH over the range pH 2-6; the process is acid-catalysed below pH 2, whereas imidazole ring opening occurs above pH 6.[248] For 7-methylguanosine this ring opening in base has been studied by n.m.r., and glycosylamine (151), together with the α-pyranose and the furanoses, have been identified as products. Similar studies were also carried out on GpppG, as a model of mRNA cap structures.[249] It has been shown that the hydrolysis of the glycosidic bond in 3-methylisoguanosine in 0.1N HCl occurs 650 times faster than for the unmethylated compound.[250]

For 2-pyrimidinone-2'-deoxynucleosides, sugar-base cleavage occurs readily at pH 3 and ambient temperature. Thus the incorporation of 2-pyrimidinones into chemically-synthesized DNA fragments provides a way to generate base-less sites at specific positions in an oligonucleotide sequence.[251]

A study has been made of the rates of hydrolysis for 2',3'-dideoxy purine nucleosides with various substituents in the purine ring. The most significant rate effects were observed with changes in substitution at the 8-position.[252]

In bleomycin-mediated degradation of DNA, the predominant pathway for base release has been shown to involve formation of radicals at C-4' of the nucleotides, the sugar produced being 2-deoxypentos-4-ulose.[253] By examination of three adducts formed with the trapping agent 2-methyl-2-nitrosopropane, abstraction of hydrogen atoms from C-1', C-4' and C-5' in thymidine 5'-monophosphate was detected in its reaction with hydroxyl radicals.[254]

15 Spectroscopic Properties and Conformational Studies

The *syn-anti* conformational equilibria of a series of fifty nucleoside derivatives have been studied using ^{1}H n.O.e. difference spectra.[255]

Nucleosides stereospecifically deuteriated at C-5' have been prepared in order to assign the signals for the prochiral protons at this position. In all cases, the more deshielded proton occupied the *pro-R* position. The data was used to determine the rotamer population about the C(4') - C(5') bond based on ^3J values.[256]

On the basis of CD and NMR studies and force-field calculations, it has been concluded that 5'-*C*-methyl nucleosides (i.e. 6-deoxyhexofuranosyl systems) with either D-*allo*- or L-*talo*- configurations have essentially the same conformation as the corresponding natural nucleosides.[257] Conformational analysis of some biologically-active arabinofuranosyl nucleosides has revealed that the range of pucker conformations available to the sugar ring is much greater than for the β-D-ribofuranosyl moiety, which prefers C(2')-*endo* puckering.[258]

A comparative study in both the solid state and in solution of AMP, GMP and dGMP, and their sodium salts, using FT i.r., ^{1}H-n.m.r., and X-ray powder diffraction has established the conformational preferences of these mononucleotides, and the influence of Cd(II), Ni(II) and Co(II) on them.[259]

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21

N.M.R. Spectroscopy and Conformational Features

1 General Aspects

A symposium report has been published on the conformational properties of deoxygenated sugars, with emphasis on furanose derivatives.[1] A review with 18 references is concerned with certain stereochemical problems associated with small carbohydrate molecules and aims to show how the combination of experimental n.m.r. studies and theoretical computer simulation can be brought to bear on their resolution.[2] In connection with the total synthesis of palytoxin, a review has been written covering the conformational analysis of *O*- and *C*-disaccharides and presents a useful mode (diamond lattice diagrams) for predicting the solution conformations of these compounds.[3] A further review deals with ^{13}C-n.m.r. studies, especially by use of relaxation probes, of the interaction between metal ions and carbohydrates.[4]

A new molecular mechanics procedure has been developed based on energy minimisation with respect to internal geometrical parameters and designed for investigation of the molecular structures of flexible saccharides and for prediction of their minimum energy conformations. The potential of this technique is illustrated by application to the disaccharide glycoside (1).[5]

The ^{13}C solid state cross-polarised magic-angle spinning (CPMAS) n.m.r. spectra of partially deuterated methyl β-D-glucopyranoside and sucrose have been assigned by use of the spectral editing technique of interrupted proton decoupling (IPD). Assignments were possible without recourse to ^{13}C-labelling by exploitation of the direct relationship between the level of deuteration and observed ^{13}C-n.m.r. resonance intensity. The procedure is especially suitable for the location of methine carbons with exchangeable protons and shows promise as a convenient method for the identification of isotropic ^{13}C chemical shifts in the solid state spectra of oligosaccharides.[6]

Spin-lattice relaxation and transient nuclear Overhauser enhancement (tnOe) experiments with ^{13}C- and ^{2}H-labelled substrates have been used for the conformational analysis of several mono- and di-saccharides.[7] An investigation of the molecular dynamics of polycrystalline mono- and di-saccharides involved measurements of the temperature dependencies of proton spin-lattice relaxation times and second moments of n.m.r. lines.[8]

Results from measurements of the spin-lattice relaxation times of fructose in aqueous solutions containing alkali metal halides have been interpreted in terms of structure-making and -breaking properties of the alkali metal ions.[9]

Attempts have been made to correlate the n.m.r. chemical shifts of carbonyl carbons, anomeric protons, ring protons and the methyl protons of acetyl groups of different monosaccharide units contained in peracetylated mono- and oligo-saccharides. By use of the SIMCA soft modelling algorithm for pattern recognition, these were classified according to their structures and glycosidic linkages to neighbouring "units".[10]

The equilibrium compositions (anomers, tautomers, conformers) of D-glucose, D-ribose, methyl β-D-glucopyranoside, and methyl β-D-ribopyranoside severally in D_2O and in DMSO-d_6 have been determined by ^{1}H-n.m.r. spectroscopy at temperatures ranging from 0 to 90°C. The experimental results are discussed in terms of the contributions of solvation to the relative free energies of the different species.[11] Similar studies have been undertaken with D-fructose and related compounds, including disaccharides with D-fructose units at the reducing end and the homomorphic ketose L-*galacto*-2-heptulose.[12] Solid state and solution ^{1}H- and ^{13}-C n.m.r. methods have been used to elucidate the tautomeric composition of sodium α-L-guluronate dihydrate in the crystal, in D_2O, and in DMSO-d_6. The authors consider solid state ^{13}C-n.m.r. spectroscopy to be superior to x-ray diffraction for obtaining information on the anomeric composition in the crystal.[13] The ^{1}H-n.m.r. signals for the anomeric protons of nineteen per(trifluoro)acetylated mono-, di-, and tri-saccharides in CD_2Cl_2 were located significantly downfield of all other resonances, and in general at least 0.4 p.p.m. downfield of equivalent signals from the same carbohydrates derivatised with other groups. This greatly facilitated the determination of the tautomeric compositions. [See however Chapter 7, Part 1, regarding mutarotation during per(trifluoro)acetylation].[14]

"Dynamic hydration numbers" as a new approach to the study of physico-chemical properties of sugars are referred to in Part 7 of this Chapter.

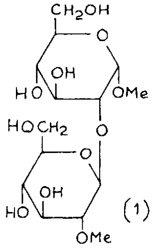
2 Acyclic Systems

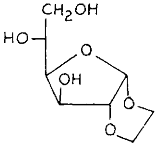
The cross-polarisation magic-angle spinning solid state ^{13}C-n.m.r. spectra of D,L-mannitol and of three polymorphs of D-mannitol have been recorded and assigned.[15] Extensive n.m.r. experiments have been carried out with [1-^{13}C]glycerol, D-[1-^{13}C]-arabinitol, -ribitol, -xylitol, -glucitol, -mannitol, and -talitol, prepared by $NaBH_4$ reduction of the corresponding [1-^{13}C]aldoses. A comparison of the ^{13}C- and ^{1}H-n.m.r. spectra of natural and ^{13}C-enriched disymmetric alditols (*e.g.*, D-[1-^{13}C]arabinitol) permitted the unequivocal assignment of their hydroxymethyl proton- and carbon- resonances and the measurement of several ^{13}C-^{1}H and ^{13}C-^{13}C spin-coupling constants. Similar data for symmetric alditols (*e.g.*, D-[1-^{13}C]ribitol) were more difficult to extract, since their spectra contained overlapping ^{13}C-coupled- and -noncoupled subspectra.[16]

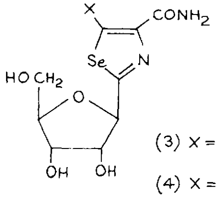
The ^{1}H-n.m.r. solid state and D_2O solution spectra of D-glucitol and maltitol, assigned with the help of extensive spin simulation of 1D spectra supplemented by 2D experiments, formed the basis of a comparative conformational analysis. Computed low-energy conformations were in good agreement with observed conformations in the crystals, but less so with those found in solutions.[17] Results from new computer simulations of ^{1}H-n.m.r. spectra of alditols containing at least one deoxy group supported previous findings on polyols.[18]

Complexes of homotopic 18-crown-6-ethers derived from D-mannitol and D-glucitol with chiral ammonium salts have been subjected to ^{1}H- and ^{13}C-n.m.r. analysis. In some cases, enantiodifferentiation was displayed with respect to the racemates of these salts.[19]

^{1}H- And ^{13}C-chemical shift assignments have been made for both the E- and Z-forms of the oximes of all aldopentoses in D_2O. The arabinose- and lyxose-derivatives appeared to adopt an extended zig-zig, and the ribose- and xylose-oximes bent sickle conformations.[20]


(1)


(2)


(3) $X = NH_2$

(4) $X = H$

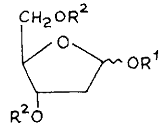
Satisfactory agreement was found between calculated and experimentally determined $^{3}J_{H,H}$ values for the peracetylated aldononitriles of threose, of all the pentoses and hexoses, and of one heptose. The possibility of identifying the configuration of any aldose by examination of the ^{1}H-n.m.r. spectrum of the derived aldononitrile is discussed.[21,22]

3 Furanose Systems

The ^{13}C-n.m.r. spectrum of 1,2-*O*-ethylene-α-D-glucofuranose (2) has been recorded and assigned,[23] and detailed 1- and 2-D n.m.r. experiments supplemented by molecular mechanics calculations allowed the unequivocal assignment of all ^{1}H-, ^{13}C-, and ^{31}P-n.m.r. resonances of D-fructose 2,6-diphosphate. The study showed, in addition, that the activator of fructose 6-phosphate 1-kinase is the β-anomer in the $^{4}T_3$ conformation.[24]

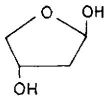
Heteronuclear n.m.r. studies have been carried out on 5-amino-selenazofurin (3) and its parent compound (4) to determine their conformations in solution.[25] The conformational preferences of 4-thiohexofuranose derivatives with α- and β- D-*galacto*-, α- and β-D-*manno*-, and α-D-*talo*-configurations have been assigned from $^{3}J_{H,H}$ values on the basis of a Karplus equation, the parameters for which were obtained by molecular mechanics calculations for tetrahydrofuran and tetrahydrothiophene.[26] An analysis of their 620 MHz ^{1}H-n.m.r. spectra indicated that, contrary to reports in the literature, the methyl 2-deoxy-D-*eythro*-pentofuranosides (5) are unsuitable as conformational models of the diphosphate (6) incorporated in abasic DNA.[27]

Ab initio Molecular Orbital calculations by use of the 6-31-G* basis set have been performed on 2-deoxy-β-D-*glycero*-tetrofuranose (7) to evaluate the effect of ring conformation on the molecular parameters (bond lengths, angles, torsion). The observed concerted behaviour of C-O bond lengths in the vicinity of the anomeric centre was taken as an indication that the orientation of the C-1 - O-1 bond of aldofuranoses affects the mechanism of glycosidic bond hydrolysis.[28] The dipole moments and potential energy curves of 2-deoxy-α- and β-D-*erythro*-pentofuranose and of eighteen D-pentofuranose halides and azides have been calculated and compared, and the application of these data to the prediction of the behaviour of nucleotide analogues in enzymic systems related to DNA- and RNA-synthesis has been discussed.[29]

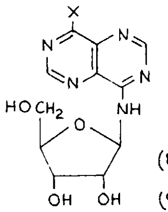


(5) R^1 = Me, R^2 = H

(6) R^1 = H, R^2 = PO_3H_2



(7)



(8) X = NH_2

(9) X = OMe

The use of 2D ^{1}H- and ^{13}C- shift correlated n.m.r. techniques permitted the unambiguous assignment of all proton and carbon chemical shifts of the C-nucleosides of [1,2,4]-triazolo[1,5-c]- and [4,3-c]-pyrimidines.[30]

The *syn-anti*-conformational equilibria of fifty nucleoside derivatives have been determined by inspection of their 1D proton NOE difference spectra.[31]

The conformational flexibility of adenosine in the gas phase has been examined. Based on molecular mechanics modelling, a set of "active conformations" of this nucleoside at the active site of adenosine deaminase have been proposed which are consistent with the experimental substrate specificity reported in the literature.[32] In solution, adenosine showed preference for S-type conformation of the ribofuranose ring, and a *gauche-gauche* arrangement about the C-4′ - C-5′ bond, as evidenced by ^{1}H-n.m.r. spectroscopy. Substitution of the 5′-hydroxyl group by chlorine led to an increase in the population of the N-type ring conformer and to a simultaneous decrease in that of C-4′ - C-5′ *gg*-rotamer. Substitution at the 8-position had no significant effect on the conformation but shifted the *syn-anti* equilibrium about the glycosidic bond in favour of the *syn* form.[33] Based on experimental n.m.r. data obtained with adenosine, cytidine, guanosine, and uridine ^{13}C-enriched at C-1′ and C-2′, a crude Karplus curve has been constructed for the ^{13}C-C-N-^{13}C coupling across the *N*-glycosidic bond, for use in the evaluation of current models describing the conformational dynamics of these nucleosides in aqueous solution.[34]

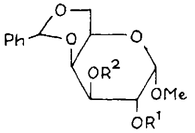
The structural properties of the antitumor agents 4-amino- and 4-methoxy-8-(β-D-ribofuranosylamino)pyrimido[5,4-d]pyrimidine (8) and (9), respectively, and of their α-anomers have been investigated by molecular mechanics, n.m.r. spectroscopy, and x-ray diffraction.[35] The conformational analysis of certain, medically important arabinonucleosides revealed that the range of puckered conformations available to their furanosyl moieties is much greater than that available to the β-ribofuranosyl moiety which has a strong preference for C-2′-*endo* puckering.[36]

The diastereotopy of the methyl and methylene protons of ester groups in purine nucleosides of uronic esters is referred to in Chapter 20.

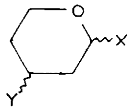
4 Pyranose Systems

The ^{1}H-n.m.r. spectrum for D-*myo*-inositol 1,4-bisphospate has been reported for the first time,[36a] and the ^{1}H- and ^{13}C-n.m.r. spectra of the following compounds have been assigned: 2-, 3-, and 6-*O*-(2-hydroxyethyl)-D-glucopyranose and 1,2-*O*-ethylene-α-D-glucopyranose,[23] 1,2,3-tri-*O*-acetyl-β-L- and 1,2,4-tri-*O*-acetyl-α-L-rhamnopyranose,[37] ten methyl 4,6-*O*-

benzylidene-D-hexopyranoside derivatives such as compounds (10),[38] and twenty three quinic acid derivatives.[39] The assignment of the resonances of methyl α-D-glucopyranoside tetranitrate is referred to in Part 7 of this Chapter.



(10) $R^1 = Me, R^2 = H$;
$R^1 = H, R^2 = Me$;
$R^1 = Me, R^2 = Ts$
$R^1 = Ts, R^2 = Me$

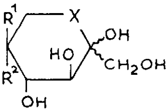


(11) $X = OMe, Y = H$
(12) $X = OEt, OCH_2CH_2F, OCH_2CHF_2, OCH_2CF_3$
$Y = H$ or Me
(13) $X = NHMe, Y = H$

A theoretical study has been presented on the conformation dependence of $^1J_{C,H}$ and $^3J_{C,H}$ values in model compounds [dimethoxymethane, 2-methoxytetrahydropyran (11)] related to glycosides. Agreement between calculated and experimental findings was satisfactory, especially for three bond couplings.[40] The conformational equilibria of the 2-(substituted ethoxy)-tetrahydropyrans (12) were studied by ^{13}C-n.m.r. spectroscopy as a contribution to the understanding of the anomeric effect. In general, the conformers with axial orientation of the substituent at O-2 were found to predominate, due to their higher entropy.[41] 2-Methylamino-tetrahydropyran (13) served as model in a theoretical investigation of the conformational properties of the *N*-glycosidic linkage of glycosylamino moieties in glycoproteins. In twenty different solvents an equatorially disposed methylamino group was consistently favoured.[42] N.m.r.-spectroscopic data on the rotameric states of the tetrahydrofuran derivatives (11) and (13) suggested a strong *exo*-anomeric effect resulting in pronounced preference for the rotamer with an exocyclic hetero-atom lone pair antiperiplanar to the endocyclic C-2 – O bond.[43]

By use of the semi-empirical molecular orbital method AM1, the optimised geometries and energies of the pyranoid forms of D-fructose (14), L-sorbose (15), 5-deoxy-D-*threo*-hexulose (16), and *carba*-D-fructose (17) have been determined. The findings that a low-energy conformation exists for each of the three sweet compounds (14), (16), and (17) [but not for the non-sweet analogue (15)] in which HO-2 is hydrogen-bonded to O-3, is thought to provide an explanation for the relative sweetness of these compounds.[44]

Several *C*-glycosides related to palytoxin, for example the glucose derivatives (18), were the subjects of extensive conformational studies by molecular mechanics.[45]

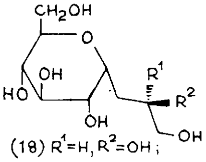


(14) X=O, R^1=H, R^2=OH

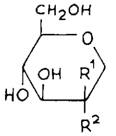
(15) X=O, R^1=OH, R^2=H

(16) X=O, R^1=R^2=H

(17) X=CH_2, R^1=H, R^2=OH

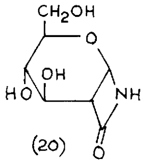


(18) R^1=H, R^2=OH; R^1=OH, R^2=H

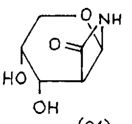


(19) R^1=H, R^2=OH; R^1=OH, R^2=H; R^1=R^2=H

The rotamer distribution about the C-5 - C-6 bond of D-mannose and its methyl glycosides has been studied by ^{1}H-n.m.r experiments with stereospecifically 6-deuterated substrates. As was found with glucose (see Vol. 22, Chapter 21, ref. 35), the *gg* and *gt* rotamers were predominant.[46] The conformations of the 1,5-anhydro-D-alditols (19) and six further close analogues in aqueous solution were found, by ^{1}H-n.m.r. spectroscopy, to be mainly $^4C_1$. Results from experiments involving chiral deuteration at C-6 indicated rotamer distributions about the C-5 - C-6 bond very similar to those found in the corresponding free sugars and methyl glycosides (preference for the *gg* and *gt* conformations in compounds with equatorial hydroxyl groups at C-4, and prevalence of the *gt* conformation in analogues with axial HO-4), *i.e.*, the anomeric HO- and MeO- groups do not seem to play a significant role in determining the conformation of the hydroxymethyl group.[47] The rotamer distribution about the exocyclic C-6 - O-6 bond of tetra-*O*-acetyl-β-D-glucopyranosyl chloride has been examined in detail. In the crystal, the *gg* and *gt* rotamers prevailed, the former displaying unusually short C - Cl and C-1 - O-5-bonds (1.70Å and 1.37Å, respectively), the latter an exceptionally long C-5 - O-5 bond (1.536 ± 0.025Å). In $CDCl_3$ solution only the $^4C_1$, *gg* conformation was observed.[48] Molecular mechanics studies on the effect of solvent on the conformation of the hydroxymethyl group of methyl β-D-glucopyranoside indicated that the *tg* rotamer, although lowest in energy in isolated molecules, was unstable in aqueous solution. The absence of this rotamer in polar solvents must, therefore, be attributed to a solvent effect.[49]



(20)



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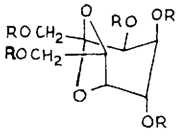
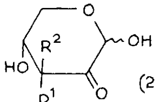


(22)

The eight configurationally isomeric 6-amino-6-deoxyhexonolactams and their tetraacetates have been studied by CD and by n.m.r. spectroscopy. Most ^{1}H- and ^{13}C-chemical shifts and vicinal coupling constants were obtained, and the preferred conformations assigned as either $^{1,N}C_4(D)$ or $^4C_{1,N}(D)$, the decisive configuration-determining requirement apparently being the equatorial disposition of the substituent α- to the carbonyl group. The CD results, interpreted according to currently used rules, agreed only partly with the n.m.r. results and the reasons for the discrepancies are discussed.[50] The ^{1}H-n.m.r. spectra of the β-lactams (20) and (21), available from the cycloaddition of trichloroisocyanate to glycals, and of a variety of partially protected analogues, have been recorded and interpreted in terms of an equilibrium of two rapidly interconverting half-chair forms ($^4H_5 \rightleftharpoons {}^5H_4$). Strong additional support was provided by diffractiometric data (see Chapter 22).[51]

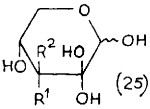
2,7-Anhydro-L-*glycero*-β-D-*manno*-octulopyranose and its per-*O*-acetyl derivative both exist in the chair-like conformation (22), as evidenced by ^{1}H- and ^{13}C-n.m.r. studies.[52]

On the basis of 2D ^{1}H-n.m.r. spectral data, $^4C_1$ conformations have been proposed for both the unhydrated and hydrated pyranose forms (23) and (25), respectively, of D-*threo*-pentos-2-ulose, whereas the unhydrated *erythro*-isomer (24) appears to prefer the $^1C_4$ conformation and its hydrated form (26) exists as an equilibrium mixture of both conformers.[53] Barriers of 46 and 32 kJ/mol, respectively, have been calculated for chair → boat inversion in 1,6-anhydro-β-D-gluco-pyranose and its triacetate; the role of intramolecular H-bonding in determining the conformational energy of the former compound is discussed.[54]



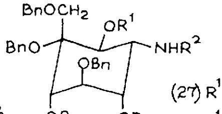
(23) $R^1 = H, R^2 = OH$

(24) $R^1 = OH, R^2 = H$



(25) $R^1 = H, R^2 = OH$;

(26) $R^1 = OH, R^2 = H$.



(27) $R^1 = Tf, R^2 = \overset{O}{\overset{\|}{C}}CF_3$

(28) $R^1 = Ms, R^2 = Boc$

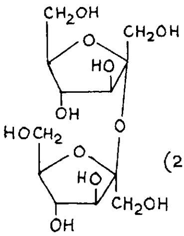
The cyclitol derivatives (27) and (28) (see Chapter 18) were found to adopt in solution the "inverted" conformations shown, with the benzyloxymethyl groups axially disposed.[55]

The anomeric effect of the cyano group has been estimated by a study of the $BuNF_4$-catalised equilibrium between 2,3,4,6-tetra-*O*-acetyl-l-cyano-α- and β-D-glycopyranosyl bromides. Values of 3.42 and 1.95 kcal mol^{-1} were arrived at for peracetylated gluco- and galacto-pyranosyl cyanide, respectively.[55a]

5 Disaccharides

An adiabatic potential energy map for sucrose[55b] and molecular dynamics simulations applied to the minimum energy conformations indicated by this map[55c] have been reported. An analysis of sucrose, maltose, and lactose by n.m.r. spectroscopy, differential scanning calorimetry (DSC), and x-ray diffraction was aimed at an understanding of molecular behaviour in the crystals.[55d]

The proton spin-spin relaxation times T_2 and spin echo amplitude decay curves of concentrated solutions of maltose, sucrose, and glucose have been measured,[56] and detailed n.m.r. data have been reported for trehalulose (1-*O*-α-D-glucopyranosyl-D-fructose, see Chapter 2). In D_2O, the tautomers with β-pyranose-, β-furanose-, and α-furanose-configurated fructose moieties were present in 20:4:1 ratios.[57]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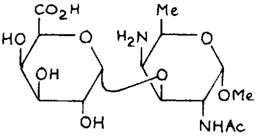

(30)

The assignment of the n.m.r. spectra of β-cellobiose octanitrate is referred to in Part 7 of this Chapter.

Conformational studies by combined n.m.r. spectrometric and computational methods have been carried out on a variety of disaccharides. They include amygdalin,[58] methyl xylobioside,[59] inulobiose (29) (a model compound for inulin),[60] the disaccharide (30),[61] the disaccharide repeating unit (31) of an immunoadjuvant peptidoglycan,[62] the methyl α-glycoside of carrabiose (32) (the repeating unit of carrageenans), its 4′-sulphate, its 4′,6′-disulphate,[63] and its isomer neocarrabiose (33),[64] the α-(1→2)- and α-(1→3)-linked

β-D-Glc*p*NAc-(1→4)-MurNAc

(31)

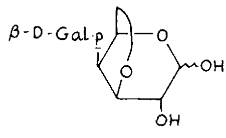
α-D-Man*p*(1→x)-β-D-Glc*p*OMe
x = 2 or 3

(34)

disaccharides of 4-amino-4,6-dideoxy-D-mannose their methyl glycosides,[65] eight 2-*O*-glycosylated methyl manno- and rhamno-pyranosides,[66] six methyl glycosides of (1→4)-linked disaccharides containing rhamnose or fucose at the reducing end,[67] and eight (1→2)- and

(1→3)-linked disaccharide derivatives, such as compounds (34), where particular attention was given to the effects of mannosylation and glucosylation on the chemical shifts of nuclei in the neighbourhood of the glycosidic bond.[68]

The temperature dependent conformation of gentiobiose octaacetate in solution has been determined by ^{1}H- and ^{13}C-n.m.r. spectroscopic methods including relaxation and NOESY experiments.[69] A comparison of the ^{1}H- and ^{13}C-n.m.r. data of the tri-*O*-isopropylidene lactose dimethyl acetal derivatives (35) - (37) with those of their sulphated analogues (38) - (40) indicated that the conformation of the galactopyranose ring changes from a slightly distorted $^4C_1$ chair to a $^{3,O}B$ boat on sulphation at O-2′. According to theoretical calculations with the GESA program this change cannot, however, be explained by unfavourable steric interactions.[70]



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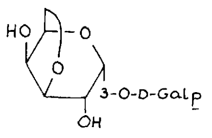

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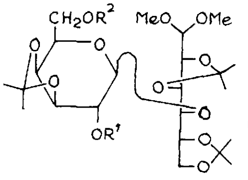


(35) $R^1 = H, R^2 = Tr$
(36) $R^1 = H, R^2 = Si\not{+}$
(37) $R^1 = R^2 = H$

(38) $R^1 = SO_3^- Et_3NH^+$
(39) $R^1 = SO_3^- Et_3NH^+, R^2 = Si\not{+}$
(40) $R^1 = R^2 = SO_3^- Et_3NH^+$

Molecular mechanics calculations on crystalline diheterolevulosan II [α-D-fructofuranose β-D-fructofuranose 1,2′:2,1′-dianhydride; see Vol.22, p. 62, structure (27)] and diheterolevulosan IV di-β-D-fructofuranose 1,2′:2,1′-dianhydride) showed that their central dioxane rings adopt a chair and a boat conformation, respectively.[71]

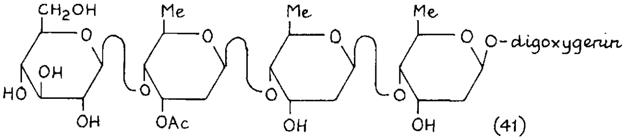
The potential of a recently developed model for saccharide optical rotation calculations has been tested by application to lactose. The new method readily accounted for the large difference between the optical rotations of lactose and cellobiose which have the same structures in the linkage region.[72]

6 Oligosaccharides and Related Compounds

Reviews have been published on progress over the last 20 years in computional methods for studying oligo- and poly-saccharide conformations in the solid state and in solution,[73] and on the newer techniques of ^{1}H-n.m.r. spectroscopy which have proved useful in the elucidation of oligosaccharide structures.[74] A review and a symposium report have appeared on the conformational analysis of oligosaccharides in solution by n.m.r. methods combined with theoretical calculations,[75,76] and a further symposium report is concerned with the reconciliation of theory and experiment in the conformational analysis of oligosaccharides.[77]

An updated version of an earlier computer program that can be implemented on IBM compatible microcomputers has been used to interpret the ^{1}H-n.m.r. spectra of a series of mucin-derived oligosaccharide alditols. The program allows comparison between the chemical shifts of resonances in the spectra of unknown oligosaccharides with those in a standard library constructed from literature data (see Vol. 19, p. 223, ref. 43).[78]

A method has been presented for obtaining 1D versions of 2D n.m.r. experiments, which is useful for the sequence analysis of oligosaccharides. It involves application of Gaussian-shaped pulses for selective COSY experiments, combined with one- or two-step-relayed coherence transfer. As an illustration, the method has been applied to the structural analysis of lantacoside C (41).[79] A heptasaccharide and a decasaccharide from natural sources were chosen as examples to explain the advantage of an integrated approach of homonuclear (COSY, HOHANA) and ^{1}H-detected heteronuclear (HMQC, HMBC) shift-correlated n.m.r. spectroscopy for the sequencing of complex carbohydrates; the particular use of this technique for locating sites of *O*-acylation was demonstrated with a highly esterified trisaccharide.[80]



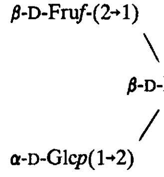
(41)

Both 1D and 2D versions of DOUBLE TOCSY were used to extract the subspectra of individual monosaccharides from overlapping regions in the spectra of oligosaccharides,[81] and structural studies on complex carbohydrates by means of ^{1}H/^{13}C 2D and 3D HMQC-NOE techniques at natural abundance have been reported.[82]

New molecular mechanical force field-[83] and integrated ^{1}H-n.m.r.[84] approaches have been described for the structural and conformational analysis of oligosaccharides. Trisaccharide (42) and a heparin type oligosaccharide, respectively, served as models. The problem of uncertainty in the determination of oligosaccharide conformations [*e.g.*, the conformation of a branched Man$_9$(GlcNAc)$_2$ undecasaccharide] by n.m.r. spectroscopy has been addressed. A possible solution is seen in the use of NOE measurements across the glycosidic linkages.[85]

α-D-Man*p*(1→3)-β-D-Man*p*(1→4)-GlcNAc

(42)



$$\begin{array}{l} \beta\text{-D-Fru}f\text{-}(2\rightarrow 1) \\ \quad\quad\quad\quad\quad \backslash \\ \quad\quad\quad\quad\quad \beta\text{-D-Fru}f \\ \quad\quad\quad\quad\quad / \\ \alpha\text{-D-Glc}p(1\rightarrow 2) \end{array}$$

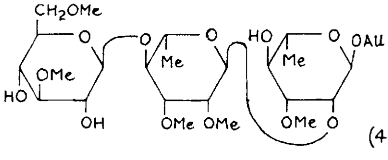
(43)

α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→3)-α-L-Rha*p*OMe

(44)

Various combinations of n.m.r. techniques allowed the determination of the structures and/or conformations of 1-kestose (43),[86] stachyose,[87] the rhamnotrioside (44) and five similar rhamnose-containing tri- and tetra-saccharides,[88] several inulo-oligosaccharides (triose, tetraose, pentaose, obtained from the partial acid hydrolysis of inulin),[89] the aminoglycoside antibiotics paromomycin[90] and lividomycin (see Vol.16, p.189),[91] the oligosaccharide moiety of calicheamycin,[92] the inclusion complexes of azo dyes with some cyclomalto-oligosaccharides,[93] and the complexes of cyclomaltohexaose (α-cyclodextrin) with some alkyl glycosides.[94]

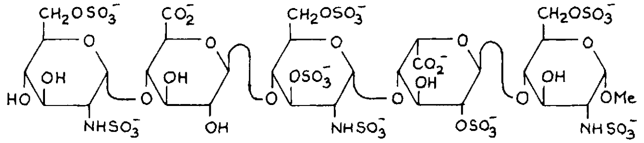
The torsion angles about the glycosidic bonds of oligosaccharides containing six to twenty sugar units have been estimated from the $^3J_{C,H}$ values across the glycosidic linkages obtained by use of 2D n.m.r. techniques,[95] and the ^{1}H- and ^{13}C-spectra of the terminal trisaccharide from the phenolic glycolipid I of *mycobacterium leprae*, as its allyl glycoside



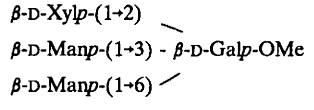
(45)

(45), have been recorded and fully assigned in D_2O, CD_3OD, and $CDCl_3$. The preferred conformation was found to be different in each of the three solvents.[96] A 2D ^{1}H- and ^{13}C-n.m.r. investigation of natural polyphenols was focused on the positions of ester linkage of the phenolic acids to glucose.[97]

A combination of n.m.r. spectroscopy and theoretical calculations was employed in conformational studies on the pentasaccharide (46) which represents the binding site of antithrombin III,[98] on xylose-containing oligosaccharides, such as the tetrasaccharide (47), related to N-glycoproteins,[99] and on the branched trisaccharides (48) for each of which a highly predominant (≥90%) conformer was detected.[100,101]

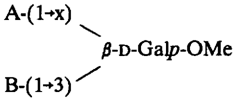


(46)



β-D-Xylp-(1→2)
β-D-Manp-(1→3) - β-D-Galp-OMe
β-D-Manp-(1→6)

(47)



A-(1→x)
β-D-Galp-OMe
B-(1→3)

A = α-D-Glcp or β-D-Glcp
B = β-D-Manp or α-L-Rhap or β-L-Rhap
x = 2 or 4

(48)

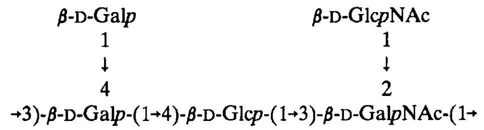
D_2O solutions of natural and synthetic oligosaccharides representing the biologically important sequences of dermatan sulphate, heparan sulphate, and heparin have been analysed by ^{1}H-n.m.r. spectroscopy. Particular attention was given to the $^3J_{H,H}$ values of the L-iduronic acid residues which were rationalised by force-field calculations, to allow the determination of the relative proportions of conformers ($^1C_4$, $^2S_0$, $^4C_1$) present. These proportions were found to vary widely as a function of sequence and pattern of sulphation.[102]

Molecular mechanics simulations of the α-Manp-(1→2)-α-Manp glycosidic bond found in N-linked glycoproteins were performed *in vacuo* and in the presence of water. The results were in agreement with experimental, n.m.r. derived parameters and provide further evidence that, in solution, oligosaccharides can maintain fixed geometries with relatively long life spans.[103] The three-dimensional structure of the oligosaccharide moiety (49) of the GMl ganglioside has been studied by application of a distance-mapping procedure, based on NOE contacts between amido-, OH-, and CH-protons, to the intact ganglioside in DMSO-d_6. The experimental work was supported by molecular mechanics calculations, which were thought to give more accurate predictions for the 3D structure than the alternative HSEA model.[104,105] The preferred conformations of the hexose and heptose regions of the core oligosaccharides from several *Enterobacteriaceae* lipopolysaccharides

β-D-GalpNAc-(1→3)-α-D-Galp-(1→4)-β-D-Galp-(1→4)-β-D-Glcp(1→1)Cer

(49)

have been determined by semi-empirical calculations *via* the HSEA approach,[106] and the conformational properties of 6^2-α-D-glucosylmaltotriose, a model for the branching point of amylopectin, were examined by theoretical calculations.[107] The structure determination of the repeating unit (50) of the *Hafnia alvei* 039 antigen by methylation analysis was supplemented by ^{13}C-n.m.r. spectroscopy, in particular by computer assisted ^{13}C-n.m.r. analysis of Smith degradation products.[108]

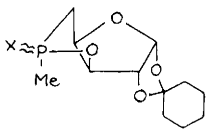


$$\begin{array}{lcl}
\beta\text{-D-Gal}p & & \beta\text{-D-Glc}p\text{NAc}\\
\quad 1 & & \quad 1\\
\quad \downarrow & & \quad \downarrow\\
\quad 4 & & \quad 2\\
\multicolumn{3}{l}{\rightarrow 3)\text{-}\beta\text{-D-Gal}p\text{-}(1\rightarrow 4)\text{-}\beta\text{-D-Glc}p\text{-}(1\rightarrow 3)\text{-}\beta\text{-D-Gal}p\text{NAc-}(1\rightarrow}
\end{array}$$

(50)

7 Nuclei other than ^{1}H and ^{13}C

All ^{1}H-, ^{13}C-, and ^{15}N-n.m.r. resonance signals of methyl β-D-glucopyranoside tetranitrate and β-cellobiose octanitrate have been unambiguously assigned by use of ^{13}C-^{1}H- and ^{15}N-O-C^{1}H-shift correlation spectroscopy. Based on these data and on selective decoupling experiments, the ^{15}N resonance signals of cellulose trinitrate were tentatively assigned.[109]



(51) X = Se, S, O

The separated diastereomers of the xylose derivatives (51) have been subjected to ^{1}H- ^{13}C-, ^{31}P- and ^{77}Se-n.m.r. spectroscopy in an effort to determine the configurations about the phosphorus atoms.[110]

From the T_1 values of $H_2{}^{17}O$, measured for aqueous solutions of melibiose, trehalose, maltotriose, melezitose and α- and γ-cyclodextrins as a function of concentration, "dynamic hydration numbers" (^{n}DHN), a quantity which expresses the hydration properties of solutes, were calculated. The ^{n}DHN values for these compounds and for several monosaccharides correlated linearly with the mean number of equatorial hydroxyl groups.[111]

The application of ^{31}P-n.m.r. spectroscopy to fructose diphosphate is referred to in Part 4 above.

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22
Other Physical Methods

1 I.r. Spectroscopy

The absorption band frequencies and intensities in the i.r. spectrum of crystalline α-D-glucose have been calculated, taking into account intermolecular hydrogen bonds.[1] Intra- and inter-molecular hydrogen bonds in methyl 4,6-*O*-benzylidene-2- and 3-*O*-methyl-α-D-altropyranoside have been assessed from an examination of their i.r. spectra and those of their deuterated analogues in the temperature range 18 to 300 K.[2] In an i.r. spectral investigation of six isomeric methyl xylobiosides, absorptions were observed in the 700-950 cm^{-1} range that were characteristic for the interglycosidic anomeric configuration and possibly the position of the link.[3] The application of F.t.i.r. reflection-absorption spectroscopy to the study of glucose oxidation on a platinum electrode is discussed in Chapter 2.

2 Mass Spectrometry

Applications of m.s. to the determination of complex carbohydrate structues (60 refs.)[4] and in the analysis of nucleosides, nucleotides and oligonucleotides (6 refs.)[5] have been reviewed.

In the fast atom bombardment (FAB)-m.s. of the anti-ulcer therapeutic agent sucralfate (sucrose octasulphate - aluminium hydroxide complex), stable molecular cations were produced when the volatile tetramethylammonium hydroxide was included in the thioglycerol sample matrix.[6] FAB-m.s. of the 2-acetamido-2-deoxy-β-D-glucose-containing disaccharide antigenic determinant of *Staphyloccus aureus* and its synthetic precursors have been reported.[7] FAB-m.s. with a Cs^+ ion source, which is also known as liquid secondary ion m.s., together with g.c.-m.s. and 500 MHz ^{1}H-n.m.r. spectroscopy, have been used for structural studies on eleven major penta- and hexa-saccharides released from human fetal gastrointestinal mucins (i, mild H_3O^+, ii, mild HO^-/BH_4^-) and purified by chromatography. Several sugar sequences were identified that have previously been uncommon in mucins.[8] A variety of high-mannose oligosaccharides released from glycoproteins by enzymic cleavage have been separated chromatographically, derivatised either by reduction and permethylation or by reductive amination with ethyl *p*-aminobenzoate, and analysed by FAB-m.s.[9] Naturally occurring sphingolipids have been separated chromatographically as their per-*O*-benzoates, and their oligosaccharide compositions have been determined by conventional g.c.-m.s. techniques for sugar composition and glycosyl linkage analysis, and by negative-ion FAB-m.s.[10]

Reduction of azido-sugar and -nucleoside derivatives to the corresponding amines appears to occur under the conditions of desorption c.i. (NH_3 or CH_4) and FAB-m.s.[11]

Peracetylated oligosaccharide derivatives formed from polysaccharides by sequential periodate oxidation, reduction ($NaBD_4$), acetylation, partial degradation, reacetylation and isolation by h.p.l.c., could be sequenced by positive ion FAB-m.s. using 3-nitrobenzyl alcohol as matrix. Fragmentation occurred to both sides of the glycosidic oxygen in intact residues, and to both sides of the acetal atoms in the periodate degraded residues. The fission products observed with these acetylated derivatives were of more use for sequence determination than those reported early for analogous permethylated derivatives (Angel *et al*, *Carbohydr. Res.*, 1987, *168*, 15).[12]

One of the problems in FAB-m.s. of carbohydrates is the general absence of fragment ions, the presence of which can give useful structural information. Laser-desorption m.s. has been shown to give abundant fragment ions from two-bond ring cleavages, as compared to plasma desorption and FAB-m.s. in which glycosidic bond cleavage is observed but often only weakly.[13] This disadvantage of the FAB ionization technique can be overcome by analysis of metastable ions and through the use of collision activated dissociation (CAD, also known as collision induced dissociation or CID) to enhance the population of metastable ions though collision of the parent ions with helium atoms. Aldohexose isomers can be differentiated from their metastable ions and CAD spectra of selective positive and negative ions generated by FAB-m.s.; spectra of several 2- and 6-deoxyhexoses were also recorded.[14] The linkage position and sugar sequence in a series of di- and linear oligo-saccharides have been determined by negative-ion FAB-m.s. with linked scans analysis of the negative metastable ions. Ionization is initiated selectively by deprotonation of the relatively acidic anomeric hydroxy-group in a basic matrix, and fragmentation occurs in a stepwise fashion from the reducing end to the non-reducing end.[15]

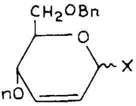
Ions generated by FAB ionization of carbohydrates have been extensively analysed on tandem m.s. and m.s.-m.s.-m.s. instruments. Differences observed in the CAD spectra of glucose and galactose have been attributed to differences in the tertiary structure of the ion at *m/z* 271.[16] The fragmentation pathways in the unimolecular and CAD reactions of the ions generated from peracetylated methyl α-D-glucopyranoside by FAB ionization have been elucidated by sequential m.s. techniques and the use of deuterium-labelled acetate groups.[17] The identification of amino-sugars by sequential m.s. and the analysis by triple m.s. of several ions generated from peracetylated galactosamine and mannosamine has been reported.[18] In the FAB-m.s. of *N*-acetylated oligosaccharides, collisions between the oligosaccharide ions and ammonia can be used to induce fragmentation initiated either at the protonated acetamido-function by an endothermic reaction at very low beam energy, or at a remote site at higher beam energy. The former result mimics that attained by CAD but uses a less expensive triple quadrupole instrument.[19] Tandem m.s. of the $[M + 2Li - H]^+$ ions generated from isomeric disaccharides has been used to determine the linkage position. The method can be applied to the linkage analysis of higher oligosaccharides.[20] Preliminary experiments in tandem m.s. of oligosaccharides have been described which are necessary to establish a limited database for specific classes of saccharides; examples were given in the area of lactosamine oligosaccharides.[21]

The FAB-m.s. and tandem m.s. analysis of nearly thirty chemically modified cyclodextrins has been reported.[22] Tandem FAB-m.s. studies on a series of isomeric methyl glycopyranosides have demonstrated that the intensities of the $[M + K]^+$ ions relative to those of the $[DEA + K]^+$ ions (where DEA = diethanolamine) produced by CAD (as alternative fragments of the selected $[M + K + DEA]^+$ precursor cluster ions) are sensitive to sugar configuration. Methyl α-D-talopyranoside yielded the most intense $[M + K]^+$ ion because it complexes the potassium ion strongest.[23]

Anomers of the *C*-glycosides (1) have been differentiated by FAB-mass analysed ion kinetic energy (MIKE) and FAB-CAD-MIKE spectral analysis of the protonated molecular ions;[24,25] e.i. spectra of related *O*-glycosidic and 1-deoxy analogues, *e.g.* (2), have also been reported.[26] Desorption c.i. (NH_3)- and FAB-m.s. along with tandem m.s. and CAD have been used in the characterisation of the adducts formed by reaction of phenyl glycidyl ether with nucleosides, the methodology being developed for the study of the adducts of industrially used epoxides with DNA.[27] FAB-MIKE spectroscopy has been used to distinguish between the 2′-, 3′- and 5′-monophosphates of adenosine, guanosine and cytidine,[28] and between the 2′, 3′- and 3′,5′- cyclic nucleotides.[29]

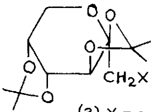
The e.i. fragmentation of topiramate (3, $X=OSO_2NH_2$) has been examined in detail using tandem m.s. E.i.-m.s. and g.c.-m.s. data were also reported for a variety of related 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose derivatives (3) and for sugar sulphamate derivatives isomeric with topiramate.[30] A simple, rapid microtransfer technique for indirect coupling of t.l.c. and e.i., c.i. or FAB-m.s. for the analysis of carbohydrates has been demonstrated for topiramate and related derivatives.[31]

The formation of methylene acetal derivatives has been observed in the c.i.-m.s. of cyclic glycols and monosaccharides with a combination of formaldehyde dimethyl acetal and methane as reagent gas. Stereoisomers could be distinguished from the relative abundances of characteristic ions associated with these methylene acetal derivatives.[32] The c.i.-m.s. of various iridoid glycosides obtained using amines (*i.e.*, Et_3N, Et_2NH, $H_2NCH_2CH_2NH_2$ or NH_3) as reagent gases can be used to identify the molecular mass and some structural features of the sugar and aglycone components.[33] E.i.- and c.i. (NH_3)-m.s. studies on carbohydrate 1,2-orthocarbonate derivatives such as (4) have been reported.[34]

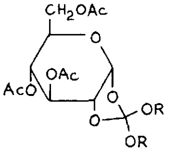


(1) $X = -\overset{R^1}{\underset{R^2}{C}}-CO_2Et$,
where R^1 = H or NO_2,
R^2 = H or CO_2Et.

(2) X = H or OPh.



(3) X = e.g., OH, Cl, NH_2, $OCONH_2$, OSO_2NH_2, OSO_2NHMe, etc.,



(4) R = Me, Et, Pr^i

Negative ion spectra of flavonoid *O*- and *C*- glycosides have been recorded using desorption c.i.-m.s. at a low reagent gas pressure.[35] In laser desorption m.s., cationization of saccharides is best achieved by introduction of cations in the +1 oxidation state rather than other oxidation states, and it was shown that sample preparation and the concentration of salt and saccharide (above a threshold level) had little effect.[36]

A variety of 1-deoxy-1-[4-(*p*-nitrophenyl)butoxyamino]alditol derivatives have been prepared by reduction ($NaBH_3CN$) of the corresponding aldose and oligosaccharide *O*-substitued-oxime derivatives. They were separated by h.p.l.c., permethylated, and analysed by e.i.-m.s., g.c.-m.s., and FAB-m.s. to determine the feasibility of using this approach in the analysis of polysaccharides. These derivatives gave particularly intense molecular ions on FAB-m.s.[37] To enable 2-amino-2-deoxy-D-glucose phosphates to be analysed by g.c. - e.i. and c.i. (NH_3)-m.s. techniques, samples were first *N*-acetylated, reduced, and permethylated, firstly with diazomethane to give dimethylphosphate derivatives and then by the Hakomori procedure.[38] The observation of appropriate high mass and fragmentation ions in the g.c.-e.i.-m.s. of pertrifluoroacetylated aldose, ketose and deoxyaldose *O*-methyloximes makes these derivatives suitable for structural identification of sugars.[39] Hexoses released from glycoproteins by hydrolysis have been detected by g.c.-m.s. analysis using selective ion monitoring of the derived alditol acetates.[40]

An h.p.l.c. - thermospray m.s. interface has been described that permits the use of an anion exchange column with an alkaline eluant through incorporation of a post-column membrane suppressor to remove non-volatile alkali salts. Its use was exemplified by analysis of a mixture of mono- and di-saccharides with a detection limit in the μg range.[41] A packed capillary and a microbore h.p.l.c.-FAB-m.s. system,which incorporates gradient elution, on-line u.v.-detection, and post-column matrix addition, has been demonstrated for the glycopeptide antibiotic teicoplanin.[42]

3 X-ray and Neutron Diffraction Crystallography

A detailed review (93 refs.) of the crystal and molecular structures of sugars, particularly mono- to oligo-saccharides, sugar acids, alditols and cyclitols, has appeared.[43]

Specific X-ray crystal structures have been reported as follows:

Free Sugars and Simple Derivatives thereof.- α-D-Glucopyranose. $(NaCl)_{0.5}$ hydrate,[44] 1,2,3-tri-*O*-acetyl-β-L-rhamnopyranose,[45] D-galactose 1-phosphate dipotassium salt,[46] D-glucose 6-phosphate bis(cyclohexylammonium) salt,[47] amiprilose [3-*O*-(3-dimethylaminopropyl)-1,2-*O*-isopropylidene-α-D-glucofuranose]hydrochloride,[48] 2,3:4,5-di-*O*-isopropylidene-1-*O*-methyl-β-D-fructopyranose,[49] and the 3,5,6-bicyclothiono- and seleno-phosphates of 1,2-*O*-isopropylidene-α-D-glucofuranose.[50]

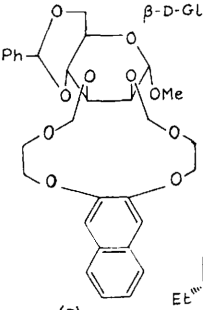
Glycosides, Disaccharides and Derivatives thereof.- Rutin.$5H_2O$ (a flavonoid 6-*O*-α-L-rhamnopyranosyl β-D-glucopyranoside),[51] methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-tosyl-α-D-glucopyranoside and methyl 4,6-*O*-benzylidene-2-*O*-methyl-3-*O*-tosyl-β-D-glucopyranoside,[52] the 18-crown-6 derivative (5),[53] methyl 2-*O*-(β-D-xylopyranosyl)-β-D-mannopyranoside hexaacetate,[54] the carbon-linked gentobioside analogue (6),[55] the 2,3,4-tri-*O*-acetyl-α-D-xylosylated Diels-Alder adduct (7),[56] diheterolevulosan II (α-D-fructofuranose-β-D-fructopyranose 1,2′:2,1′-dianhydride,[57] and the strontium(II) complex with di-β-D-fructopyranoside 2′,1:2,1′-dianhydride.[58]

Oligosaccharides.- Raffinose.$5H_2O$ at 119K,[59] *p*-nitrophenyl α-maltohexaoside (A) crystallised as its $(A)_2.Ba(I_3)_2.27H_2O$ complex,[60] and cycloinulohexaose (which is composed of six (2→1)-linked α-D-fructofuranosyl residues).[61]

Anhydro-sugars. - Methyl 3,4-anhydro-α-DL-allopyranoside[62] and neocarrabiose [3-*O*-(3,6-anhydro-α-D-galactopyranosyl)-β-D-galactopyranose].[63]

Halogeno-sugars. - The 2-*C*-chloro-xylosyl chloride derivative (8).[64]

Nitrogen- and Sulphur-containing Compounds. - The new marcolactam antibiotic (9) with a 4-epimycosamine residue,[65] the cyclic carbamate derivative (10),[66] the β-lactam (11) with an α-D-gluco-configuration and congenors with the β-D-*arabino*- and 3-*O*-acetyl-4,6-*O*-benzylidene-β-D-*altro*-configurations,[67] the 2-deoxy-2-hydroxylamino-derivative (12),[68] 1-deoxy-1-nitro-derivatives of D-arabinitol, D-galactitol, L-mannitol, L-glucitol, and D-iditol,[69] hexa-*O*-acetyl-1,2-dideoxy-2-*C*-nitro-D-*threo*-L-*talo*-octitol, [70] *C*-glycosidic α-D-glucopyranosyl, tetra-*O*-acetyl-α-D-mannopyranosyl and tri-*O*-acetyl-α-D-xylopyranosyl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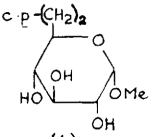

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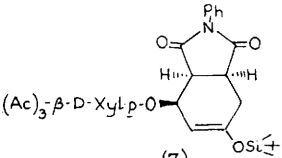

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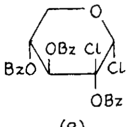

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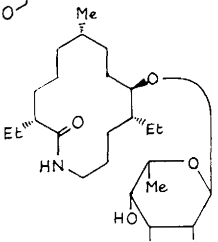

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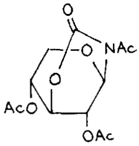

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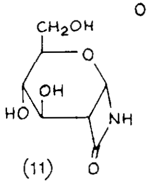

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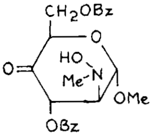
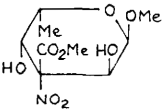


(12)

nitromethanes,[71] the branched-chain nitro-sugar derivative (13),[72] 6-epicastanospermine hydrochloride (14),[73] the hydrochloride salt (15) of 1,7-*O*-isopropylidene-1,7a-diepialexine, [74] α-hydroxyminopentyl 1-thio-β-D-glucopyranoside,[75] and the 4-thio-sugar derivative (16).[76]



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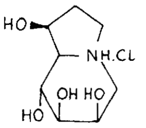

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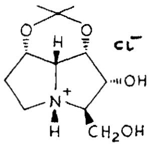

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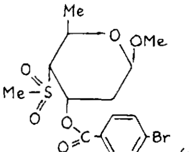

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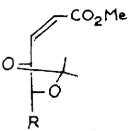
Unsaturated Sugars. - The enopyranuronates (17) and (18),[77] 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl benzene,[78] a 4:1 mixture of 6-amino-6-*N*-*tert*-butoxycarbonyl-2,3,6,7-tetradeoxy-α-DL-*erythro* - and β-DL-*threo*-hept-2-enopyranos-4-uloses,[79] and the chain extended sugar alkene (19). [80]

Branched-chain Sugars. - 5-*C*-Methyl-α-L-idopyranose,[81] 6-deoxy-7-*C*-(2-furyl)-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose,[82] *tert*-butyl 4-*C*-aminomethyl-3-*C*-carboxymethyl-2,3,4-trideoxy-α-D-*lyxo*-hexopyranoside-δ-lactam,[83] the 3-*C*-substituted 3-deoxy-α-D-altroside (20),[84] methyl 4,6-*O*-benzylidene-2-*O*-(4-bromobenzoyl)-3-*C*-(3-methyl-



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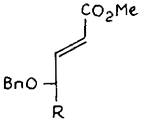

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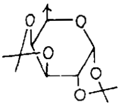
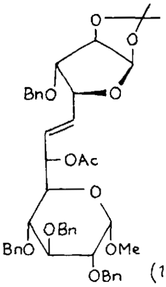
R =





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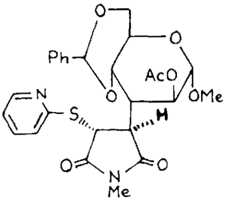

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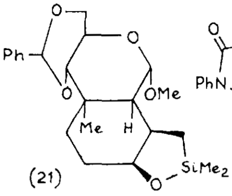
phenyl)-β-D-galactopyranoside,[85] and the fused tricyclic derivatives (21)[86] and (22)[87].

Diuloses, Sugar Acids, and their Derivatives. - The aldodiulose derivative (23),[88] *N*-n-undecyl-D-gluconamide,[89] 3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,5-lactone and 2-azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,5-lactone,[90] methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate,[91] and the methyl α-glycoside of methyl *N*-acetyl-D-neuraminate.[92]

Inorganic Derivatives. - The copper(II) - 2-carboxypentonic acid complex ($[Cu_9Br_2(cpa)_6]^{2-}_n.xH_2O$) formed from copper(II) bromide and L-ascorbic acid.[93]



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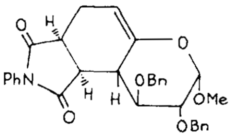

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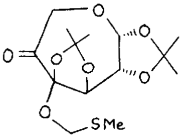

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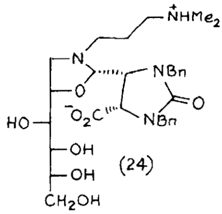

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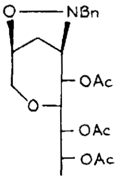

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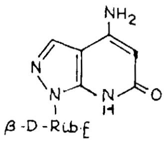

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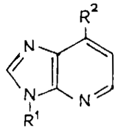
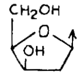
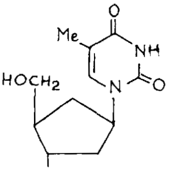


(27) $R^1=\beta$-D-Rib*f*, R^2 = H

(28) $R^1=\beta$-D-Ara*f*, R^2 = OH

(29) R^1 = , R^2 = OH or OMe



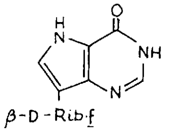


(30)

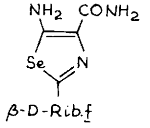
Alditols, Cyclitols, and Derivatives thereof. - D-Perseitol (D-*glycero*-D-*galacto*-heptitol),[94] galactitol hexa(4-chlorobenzozoate),[95] maltitol (4-*O*-α-D-glucopyranosyl-D-glucitol),[96] lactitol (4-*O*-β-D-galactopyranosyl-D-glucitol),[97] the 1-amino-1-deoxy-D-glucitol *O,N*-acetal (24),[98] 1-deoxy-1-nitro-heptitols with the D-*glycero*-L-*manno*-, D-*glycero*-L-*gluco*-, D-*glycero*-D-*ido*- and

D-*glycero*-D-*gluco*-configurations,[99] 4-(penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1-phenylpyrazole,[100] 1,1-bis(3-methyl-5-oxopyrazol-4-yl)-1-deoxy-D-galactose,[101] 1,2:3,4:5,6-trianhydro-galactitol.[102] The cycloadduct (25) derived from 3-*O*-allyl-D-glucose,[103,104] hexa-*O*-acetyl-*myo*-inositol,[105] and 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-*cis*-inositol.[106]

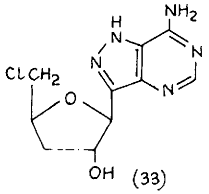
Nucleosides and their Analogues and Derivatives. - 7-Methyl-8-thioxo-7,8-dihydroguanosine,[107] the 1:1 complex of 7-methylguanosine monophosphate with a dipeptide,[108] the pyrazolo[3,4-*b*]pyrimidine nucleosides (26)[109] and (27)-(29),[110] 5-[(1S,2S)-2-chlorocyclopropyl]-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)uracil,[111] 1-(2,6-dideoxy-α-L-*lyxo*-hexofuranosyl)thymidine,[112] ethyl 5-amino-1-(2,3-*O*-isopropylidene-β-ribofuranosyl)-imidazole-4-carboxylate,[113] 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)adenosine,[114] 5-methoxymethyl-N^4-methyl-2′-deoxycytidine,[115] 1-(5-*O*-sulphamoyl-β-D-riboruranosyl)-1-*H*-1,2,4-triazole-3-carboxamide[116] and its 3-thiocarboxamide[117] and 3-carbonitrile[118] analogues, 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3-acetoxy-2-pyridone,[119] 3′-deoxy-3′-fluorouridine,[120] 1-(2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl)thymidine,[121] 2′,3′-dideoxy-3′-fluoro-5-iodouridine,[122] 2′,3′-dideoxy-3′-fluoro-5-cyanouridine,[123] 1-(3-deoxy-3-fluoro-β-D-xylofuranosyl) uracil,[124] 3-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)cytosine hydrochloride,[125] 4-methoxy-8-(α- and β-D-ribofuranosylamino)pyrimido[5,4-*d*]pyrimidines,[126] 9-[2,4-*O*-(R)-benzylidene-β-D-*threo*-oxetanosyl)adenine,[127] the carbocyclic nucleoside analogue (+)-carbathymidine (30),[128] and *C*-nucleosides (31),[129] (32)[130] and 5′-chloro-3′,5′-dideoxy-formycin (33).[131]



(31)



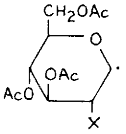
(32)



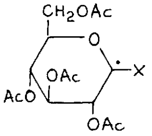
(33)

4 E.s.r. Spectroscopy

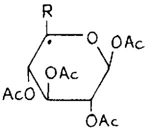
The degradation of glucose in DMSO in the presence of tetrabutylammonium hydroxide has been studied by e.s.r. techniques, and several radical intermediates have been discussed. The first step, however, appears to be a retro-aldol C-3/C-4 bond cleavage.[132] The conformations adopted by a variety of glycopyranos-1-yl and glycopyranos-5-yl radicals, *e.g.* (34) - (36), have been deduced from their e.s.r. hyperfine splittings.[133,134] While the 2-fluoro-radical (34, R = F) exists in a boat-like conformation, the other C-1 unsubstituted radicals retain the $^4C_1$-conformation. The presence of a captodative substituent at the radical centre does not influence the conformation. It was concluded that the conformations reflect the combined action of quasi-anomeric and quasi-homo-anomeric stabilisation effects. The radicals were produced by reaction of precursor bromide or phenylselenide derivatives with trimethyltin radicals.



(34) X = H, F, NHTs, Pr



(35) X = CN, Cl



(36) R = CH_2OAc, CO_2Me

To aid in the identification of radicals formed on δ-irradiation of monosaccharides by spin trapping and e.s.r. spectroscopy, two routes have been developed for generating specific spin adducts. Monosaccharide radicals were thus generated from iodo-sugar precursors by reaction with carbon dioxide radical anion in aqueous solution, and were trapped *in situ* with 2-methyl-2-nitroso-propane. Alternatively, these same adducts could be obtained by reaction of sugar nitrones with hydroxy-radicals.[135] Electrons trapped in X-irradiated rhamnose crystals have been studied by ENDOR, which gives hyperfine couplings of the electrons with neighbouring protons.[136]

5 Polarimetry, Circular Dichroism and Related Studies

A newly developed calculation model for optical rotation has been applied to the determination of the conformation in solution of β-lactose[137] and trehalose.[138]

O.r.d., c.d. and u.v. spectra of the four D-aldopentoses in neutral and alkaline solution have been studied to investigate the conformations of these sugars.[139] C.d. spectra of *p*-nitrophenyl glycosides with axial aglycons show positive bands at 219 and 304 nm, while those with equatorial aglycons show negative bands at 220 and 314 nm. These spectral results were interpreted in terms of the Kirkwood-Tinoco equation and were in good agreement with those predicted by MNDO and molecular mechanics calculations.[140] The Drude equation has been used to investigate the origin of the Cotton effects in the c.d. spectra of a series of aldono-1,4-lactones below 200 nm. Bands at 130, 170 and 220 nm could be correlated with certain stereochemical and/or conformational features. The applicability of Hudson's lactone rule for the optical rotation of sugar lactones could be explained by considering the sum of the rotational contributions of these bands at 589 nm.[141] In a similar way, by use of a graphic method of applying Drude equations, the Cotton effects below 180 nm were calculated for a series of 1,5-anhydro-D-alditols and their deoxy-derivatives.[142] In a c.d. study of vanadate(V) complexes with optically active polyols and sugars, up to four separate Cotton effects were observed in the 200-350 nm wavelength range. From these it was possible to determine the configurations and orientations of the hydroxy-groups attached to pyranose rings.[143]

The application of Nakanishi's circular dichroic exciton chirality method to oligosaccharide structure elucidation has been described. The method exploits the highly characteristic c.d. spectra of sugars selectively derivatized with exciton chromophores to differentiate free hydroxy-groups from those involved in glycosidic linkages, and does not require authentic standards.[144] The c.d. spectra of 126 reference methyl glycosides with chromophoric 4-bromobenzoate and 4-methoxycinnamate ester substituents have been reported. The compounds were prepared from per(4-bromobenzoylated) oligosaccharides by glycosidic cleavage (two alternative procedures), followed by 4-methoxycinnamoylation of the liberated hydroxy-groups and h.p.l.c. separation.[145] The 24 possible derivatives of methyl α-D-mannopyranoside bearing the above two chromophoric ester groups and two acetate groups have been prepared and their c.d. spectra recorded. Each spectrum was unique and distinctive and could be used to identify the sugar.[146] A modification involving 4-phenylbenzyl ether and 4-phenylbenzoate ester substituents was shown to be applicable to the analysis of oligosaccharides containing amino-sugar residues, through the determination of the additivity relationships in a series of di- and tri-*O*-substituted *N*,*N*-disubstituted 2-amino-2-deoxy-D-glucoses, -D-galactoses and -D-mannoses.[147] Pairs of chromophores have been evaluated for the linkage analysis of oligosaccharides, and for determining the stereochemistry in acyclic polyhydroxy-compounds. In the latter case, introduction of the 9-anthroate chromophore at primary hydroxy-groups and the 4-methoxycinnamate at the secondary hydroxy-groups gave derivatives with highly characteristic c.d. spectra. All possible D-tetrose and D-pentose diethyl dithioacetals were examined by this method.[148]

The nett Cotton effects for the 230-250 nm transition in the c.d. spectra of polyol per(4-chlorobenzoates) with various configurations and conformations have been calculated by summing the component exciton Cotton effects for all participating pairs of *p*-chlorobenzoate ester chromophores, the components having been determined in earlier work by Nakanishi *et al.* Reasonably good agreement was attained between the preferred conformations as determined from n.m.r. studies of the polyols and those indicated by the c.d. data recorded for their per(4-chlorobenzoate) derivatives.[149]

6 Miscellaneous

The glass transition temperatures and heat capacity increments for the transitions have been determined for a number of mono- and oligo-saccharides using differential scanning calorimetry.[150] Aqueous gels and micellar fibres prepared from *N*-alkylaldonamide mixtures have been studied by electron microscopy.[151]

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23
Separatory and Analytical Methods

1 Chromatographic Methods

General:- A comprehensive, critical review (228 refs.) has covered developments over the last ten years in the chromatographic analysis of carbohydrates by g.c., h.p.l.c., t.l.c., and supercritical fluid chromatographic methods.[1] T.l.c., h.p.l.c., and g.c.-m.s. methods for analysis of cardiac glycosides,[2] and h.p.l.c. and g.c. methods for the analysis of nucleoside antiviral drugs,[3] have also been reviewed.

Gas-Liquid Chromatography:- Unless otherwise stated, all analyses were performed on capillary g.c. columns.

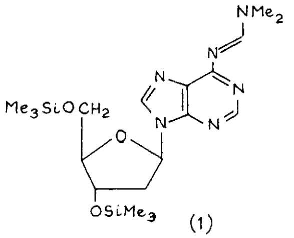
A new procedure for the analysis of mono- and oligo-saccharides has been investigated. 1-Deoxy-1-[4-(4-nitrophenyl)butoxyamino]-alditols were prepared by reduction ($NaBH_3CN$) of the corresponding *O*-substituted oxime derivatives. They could be separated by h.p.l.c. with u.v.-detection, per-*O*-methylated and analysed by g.c.-m.s. and other m.s. techniques. The corresponding 1-benzyloxyamino- and 1-(4-nitrobenzyloxyamino)-1-deoxy-alditols were also prepared but were not stable under methylation conditions, yielding the 1-deoxy-1-trimethylammonium derivatives which, as salts, were unsuitable for g.c. analysis.[4]

A method for the simultaneous analysis of nine neutral and three amino-sugars (including muramic acid) as their alditol acetate derivatives combines and modifies a number of existing methods to permit improved quantitative determinations of the carbohydrate components of the complex mixture of polysaccharides in the lumen of the gastrointestinal tract.[5] A modified procedure (*cf.*, Vol. 23, p. 248) has been reported for the g.c. analysis on both packed and capillary columns of the peracetylated *O*-hydroxyethyl-glucitols and 1,2-*O*-ethylene-α-D-glucosides derived from carboxymethyl-cellulose and -starch. It involves carbodiimide-borohydride reduction and conversion of the constituents of the resulting hydroxyethylglucans into their alditol acetate derivatives.[6] 1-Methylimidazole has been recommended as catalyst to ensure complete acetylation in the preparation of alditol acetate derivatives for g.c. analysis from sugar mixtures containing apiose.[7] Naturally occurring sphingolipids have been preparatively separated as their perbenzoyl derivatives by h.p.l.c., and their oligosaccharide compositions determined by conventional constituent sugar and glycosyl linkage analyses.[8]

Improved procedures for the preparation and g.c. analysis of peracetylated aldoses have been developed. Acetylation (Ac_2O-1-methylimidazole) can be performed directly on acid hydrolysates, and factors influencing the ratios of isomers produced have been studied. This method was compared with the alditol acetate procedure for the quantitative analysis of four plant materials.[9] G.l.c.-m.s. data have been reported for partially methylated and acetylated derivatives of L-*glycero*-D-*manno*- and D-*glycero*-D-*manno*-heptoses and -heptitols.[10]

Enantiomeric mixtures of free sugars, *e.g.*, DL-ribose or DL-arabinose, have been separated as their pertrifluoroacetylated derivatives by g.c. on di-*O*-pentyl- and (S)-hydroxypropyl-per-*O*-methyl-cyclodextrin stationary phases.[11] Arabinitol enantiomers were similarly resolved as their pertrifluoroacetylated derivatives on pentylated cyclodextrin stationary phases.[12,13] D-Arabinitol-^{2}H could then be used as the internal standard in the g.c.-m.s. analysis with selected ion monitoring of the D-isomer as an indicator of fungal infection by *Candida* species.[13]

Trimethylsilylation -g.c.-m.s. has been used for the determination of isosorbide-5-mononitrate (in which both the hydroxy- and nitro-functions are silylated) in human serum,[14] modified nucleosides in human urine[15] and zeatin and its riboside in plant tissues[16] after separation by solid-phase extraction and h.p.l.c. fractionation. The g.c. analyses of sucrose pertrimethylsilylated monostearate isomers and homologues with different acyl chains have been investigated on packed columns.[17] For the g.c.-m.s. of amino-containing nucleosides, the use of *N*-dimethylaminomethylene-*O*-trimethylsilyl derivatives [as in compound (1)] has been advocated. The derivatives are formed by reaction with DMF dimethyl acetal follwed by silylation.[18]



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Glycosyl linkage analysis by g.c.-m.s. of partially methylated and trimethylsilylated aldose diethyl dithioacetals (*cf.*, Vol. 15, p.244) has been reviewed (in Japanese with 7 refs).[19] Sugars present in electrolytically reduced glucose solutions,[20] and sugars (mainly Glc, Fru and sucrose) and organic acids in apples,[21] were determined by packed column g.c. analysis after oximation-petrimethylsilylation. Commercial D-glucitol-containing products were often found to be contaminated with 2-deoxy-D-glucitol.[20]

Thin-Layer Chromatography:- A simple, rapid microtransfer technique for indirect t.l.c.-m.s. analysis of carbohydrates has been demonstrated using 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose and its 1-sulphamate and 1-carbamate derivatives.[22] The complete separation of up to 6 isomers of sucrose monostereate was achieved by a combination of t.l.c. on silica modified with potassium sulphate and reversed-phase h.p.l.c. Enzymic cleavage with invertase was used to determine if the ester moieties were linked to the glucose or fructose units. Homologues with different acyl chains were also examined.[17] A class-separation of glucosyl- and galactosyl-ceramides in various tissues has been achieved on borate-impregnated silica.[23] The steric properties of a series of 5-alkyl-, 5-alkenyl- and 5-alkynyl-substituted deoxyuridines were measured by estimating their cyclodextrin inclusion complex stability constants from reversed-phase t.l.c. methods.[24] The mobility of a series of xanthine and adenosine derivatives on silicone and C_{18} reversed-phase t.l.c. has been correlated with their lipophilicity as measured by their partition coefficients (log P).[25] Reversed-phase h.p.l.c. and centrifugal t.l.c. have been used to used to separate adducts formed by reaction of 2'-deoxyadenosine or thymidine with phenyl glycidyl ether.[26] Glycosides of volatile components present in grapes and apricots have been isolated by medium pressure column chrmatography on a reversed-phase resin (Fractogel TSK-HW-40S) and purified by preparative overpressure layer chromatography, following a study of 13 synthetic monoterpene and aryl β-D-glucosides and β-D-rutinosides.[27]

High-Pressure Liquid Chromatography:- A review of anion-exchange h.p.l.c. with pulsed amperometric detection (64 refs) included an assessment of the advantages and disadvantages of the method for carbohydrates.[28] The performance of pulsed amperometric detection can be severely affected by a shifting baseline during elution with aqueous sodium hydroxide gradients, but this problem can be greatly alleviated by use of a pH-sensitive reference electrode in place of the more traditional pH-independent SCE reference electrode.[29]

Photooxygenation chemiluminescence has been adapted for the detection of "hydrogen atom-donating" analytes (C-H bond strengths $<95\text{kcal.mol}^{-1}$) including glucose, fructose and ascorbic acid, in eluants from reversed-phase or primary amino-bonded silica h.p.l.c. columns. Such analytes produce H_2O_2 in a photochemical reactor which employs anthraquinone photooxygenation sensitisers, and this is detected by chemiluminescence on reaction with peroxyoxalate in the presence of an immobilised fluorophore.[30] A new constant-potential amperometric detection system has been applied to the detection of aldoses, alditols and di- and tri-saccharides in micro-flow injection analysis and micro-h.p.l.c.

using 0.35 mm i.d. size-exclusion or ion-exchange columns with aqueous sodium hydroxide being added post-column. The method employs an active nickel(III) oxide electrode formed *in situ* on a nickel wire, and this acts as a strong oxidant causing hydrogen abstraction from the analyte. Applications to the analyses of honey, cola and orange juice were described.[31] A new detector that uses a polarized laser beam to measure optical activity in h.p.l.c. eluants has been assessed for its use in determining the purity of synthetic oligosaccharides, such as heparin oligomers. In combination with ^{1}H-n.m.r. this new technique gives a more reliable indication of purity than traditional u.v. monitoring of the eluant.[32]

Supercritical fluid chromatography on polar columns (diol- and cyano-bonded silica) with CO_2-MeOH mobile phases and light scattering detection has been investigated for the separation of aldoses, glycosides, desulphoglucosinolates, di- and tri-saccharides, cyclitols and ketoses.[33,34]

Separations of aldoses, sugar acids and alditols on pellicular anion-exchange resins at high pH, suitable for use with electrochemical detection, particularly with a copper-based chemically modified electrode, have been reported. Because alditols were only weakly retained under alkaline conditions, an alternative cation exchange resin column eluted with aqueous NaOH-$NaNO_3$ was investigated. Acceptable separation of alditols was achieved but an elution time of *ca.* 2 hours was required.[35] In a study of the behaviour of various analytes during ion-exclusion chromatography on a polystyrene-based cation exchange resin in the H^+-form with strongly acidic eluant, the retention of carbohydrates (aldoses, ketoses, sucrose) proved to be independent of the concentration of acid or acetonitrile in the eluant or of temperature, in the ranges investigated.[36] Neutral sugars and uronic acids (GlcA and GalA) could be concurrently analysed on primary amine-bonded silica columns using a buffered aqueous eluant.[37] The determination of enhanced levels of D-mannose in sera of humans infected with *Candida albicans* as a diagnostic aid was effected on a silica-based column.[38] 2-Deoxy-D-glucose and D-glucose in rat sera were assayed on a strong-anion-exchange resin column, using post-column reaction with *meso*-1,2-bis(4-methoxyphenyl)ethylenediamine in alkaline media and fluorescence detection.[39]

A review of h.p.l.c. methods for determining metabolites in bacteriology included a section dealing with the analysis of carbohydrates in fermentation broths, particularly the use of these as substrates by bacteria.[40] A model ethanol fermentation substrate composed of the sugars present in spent sulphite liquor (Glc, Gal, Man, Xyl, Ara), cellobiose and xylulose (which is likely to be formed if the non-fermentable xylose is to be utilized) were separated on a Pb^{2+}-form cation-exchange resin followed by post-column addition of NAD^+

buffer, splitting the eluant towards two enzymic reactors, and electrochemical detection of the NADH produced. The reactors contained mutarotase, glucose dehydrogenase, galactose dehydrogenase, and (in one of the two) xylose isomerase. Xylulose could thereby be determined in a co-eluting peak with mannose by difference between the responses of the two reactors, since it was only detected after isomerization to xylose.[41] An on-line clean-up procedure using four precolumns containing anion- and cation-exchange, amino-bonded silica, and hydrophobic packings, has been described for use in the analysis of carbohydrates present in broths during the fermentation of lignocellulosic material on a Pb^{2+}-form cation-exchange resin with RI-, u.v.- and immobilised enzyme post-column reactor detection systems.[42]

Palatinit, a sucrose substitute which is an equimolar mixture of 6-*O*-(α-D-glucopyranosyl)-glucitol and -mannitol, has been analysed along with its constituent monomers by h.p.l.c. on silica gel of their perbenzoylated derivatives.[43] The analysis of peracetylated aldononitriles and ketoximes (prepared by reaction of the free sugars with hydroxylamine then acetic anhydride in pyridine) has been investigated. Reversed-phase chromatography gave the best results, but the *N*-glycosylhydroxylamine peracetates that are inevitably present when this derivatization procedure is employed (Vol. 17, p. 230) were not discussed.[44] H.p.l.c. separations of partially phenylbenzylated or *p*-bromobenzoylated methyl glycosides have been reported in connection with Nakanishi's circular dichroic exciton chirality method for oligosaccharide structure determination.[45]

Reversed-phase separations have been reported for the following: sucrose monostearate isomers and homologues with different acyl chain,[17] the simultaneous analysis of ginsenosides and saikosaponins using a porous glass packing material,[46] ginsenosides on six commercial columns,[47] the anomers of 4-*O*-(D-glucopyranosyl)gallic acid and their analogues bearing a 6-sulphate on the sugar moiety (the β-anomer of which is a periodic leaf movement factor) on both an analytical and a preparative scale,[48] 41 cardiac glycosides whose retention characteristics correlated well with lipophilicity measurements and calculations,[49] and the cardiac glycoside digoxin and its metabolites as their per-*O*-(3,5-dinitrobenzoyl) derivatives with electrochemical detection.[50]

A review (with 10 refs) on the chromatographic separation of malto-oligosaccharides has been published.[51] The separation of an homologous series of 3-hydroxy-2-nitropyridinyl β-malto-oligosaccharides was used to exemplify the use of a new hydrophilic h.p.l.c. phase, "polyhydroxyethyl A" (which is silica coated with polysuccinimide into which ethanolamine has been introduced) for the chromatography of polar materials.[52] The sulphated oligosaccharides generated by enzymic hydrolysis of κ-carrageenan have been separated up to D.P. 8 (*i.e.*, 8 carrabiose residues) by both reversed-phase h.p.l.c. and size exclusion chromatography (on Bio-Gel P-6).[53]

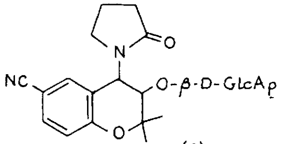
A variety of applications of h.p.l.c. on pellicular anion exchange resins with strongly alkaline eluants and pulsed amperometeric detection have been reported (see also references 28, 29 and 34). Mixtures of high-mannose type oligosaccharides [(Man*p*)$_x$-GlcNAc where x = 3-24] released enzymically from glycoproteins were very efficiently separated; retention increased linearly with size,[54] and individual components could be collected, derivatized and identified by FAB-m.s.[55] *N*- And *O*-linked sialyloligosaccharides that were released from glycoproteins then reduced ($NaBH_4$) could be separated preparatively and identified by ^{1}H-n.m.r. spectroscopy.[56] Comparison of chromatograms before and after neuraminidase treatment revealed the presence of sialic acid-containing oligosaccharides present in oligosaccharide mixtures released enzymically from glycoproteins.[57] The levels of neutral, amino and acidic monosaccharides released by hydrolysis from normal and diseased fibroblasts have been compared, and the levels of some constitutents were found to vary by 10- to 100-fold.[58]

Neutral and amino-sugars released by methanolysis of glycoproteins and polysaccharides have been assayed on a reversed-phase column with an evaporative light scattering detector.[59] *N*-Acetyl- and *N*-glycolyl-neuraminic acids released by hydrolysis of glycoconjugates were determined by per-*O*-benzoylation and reversed-phase h.p.l.c. analysis.[60] Unsaturated di- to hexa-saccharides released by enzymic digestion of hyaluronic acid and chondroitin sulphate have been assayed on a sulphonated polystyrene resin column in the Na^+-form, which acts in a gel permeation mode.[61]

Carbonyl-containing compounds generated during the Maillard reaction between D-glucose and glycine have been analysed as their 2,4-dinitrophenylhydrazones on a reversed-phase packing in a glass column.[62]

D-Glucosone in human and rat sera was assayed by h.p.l.c. on a 'ligand-exchange' column (Shodex SUGAR SP-1010) diluted with water.[63]

Reversed-phase h.p.l.c. assays have been reported for the antihypertensive agent cromakalin, its glucuronides (2) and other metabolites using a strong cation-exchange pre-column and direct injection of urine,[64] sulphadimethoxine and its *N*^{1}-glucuronide (3) and/or *N*^{4}-acetylated metabolites in human plasma and urine,[65] and the thioglucuronide (4) formed from the dithiol malotilate in rat hepatic microsomes.[66] Factors influencing the retention of phenyl, 4-nitro- and 4-amino-phenyl, and 8-hydroxyquinoline *O*-β-D-glucuronides and their aglycons on ion-pair reversed-phase h.p.l.c., including the type and level of ion-pair reagent, eluant buffer, organic modifier, and solid phase, have been investigated.[67] The *O*-β-D-glucuronide (5) of the epilepsy drug phenytoin has been assayed by ion-pair reversed-phase h.p.l.c.[68]



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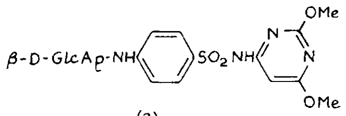

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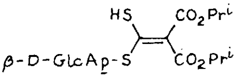

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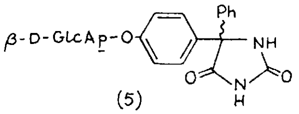

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Ion-pair reversed-phase h.p.l.c. methods have been used to separate various *myo*-inositol mono- to tetra-phosphates. The influence of major variables on the retention of five common inositol phosphates, and the retention behaviour of some common nucleotides and sugar phosphates that are likely to co-occur in biological samples, were established.[69] The use of the novel counter ion *N*-methylimipramine[70] and of the micelle-forming ion-pair reagent hexadecyltrimethylammonium hydroxide[71] was investigated, and applications in the separation of radiolabelled material with scintillation detection were reported. For the determination of D-*myo*-inositol 1,2,6-triphosphate, post-column ligand exchange and fluorescence detection in which the analyte displaces methylcalcein blue from its Fe(III) complex and the released, strongly fluorescent dye is detected, has been used. A detection limit of 3-10 ng was attained. In combination with an ion-pair formation based preconcentration technique, low-ppb concentrations can be determined.[72]

Ascorbic acid and dehydroascorbic acid have been determined by reversed-phase h.p.l.c., post-column reduction of dehydroascorbic acid to ascorbic acid with dithiothreitol, reaction of excess reagent with *N*-ethylmaleimide, and electrochemical detection.[73] Ascorbic acid and its 2-phosphate were determined by h.p.l.c. on an aminopropyl bonded-phase silica column. Dehydroascorbic acid could also be determined by the increase in the ascorbic acid content after reduction with dithiothreitol. The method was applied to raw apple and potato to which these compounds are added to prevent browning.[74]

The following antibiotics have been determined: the aminoglycoside tobramycin by chromatography on a pellicular anion-exchange resin, post-column addition of alkali, and pulsed amperometric detection;[75] pseudouridine with 5-fluorouridine as an internal standard on a reversed-phase column with post-column periodate oxidation, derivatization with *meso*-

1,2-bis(4-methoxyphenyl)ethylenediamine, and fluorescence detection;[76] methyl 1-thiolincosaminide in fermentations by pre-column fluorescence *N*-derivatization with 4-chloro-7-nitrobenzofuran and reversed-phase h.p.l.c.;[77] and clindamycin, its 2-*O*-phosphate, and the related antibiotics lincomycin and lincomycin B, by ion-pair reversed-phase chromatography with electrochemical detection.[78]

A number of reports on the h.p.l.c. analysis of nucleosides have appeared. A fully-automated analyser that tolerates the direct and repetitive injection of biological fluids, that has been used for the analysis of ribonucleosides and their nucleotides, utilised a coupled dual column system.[79] Adenosine and adenine, and separately their nucleotides, have been determined in blood by the use of direct injection, a column switching technique, and post-column fluorescence derivatization with bromoacetaldehyde. After passage through a hydrophobic-phase precolumn, adenosine and its base were absorbed on a reversed-phase minicolumn then analysed on a size-exclusion matrix.[80] The separations of nucleosides, nucleotides and bases on a weakly hydrophobic vinyl alcohol copolymer gel column was compared to those obtained on a reversed-phase silica column. While the primary mechanism for separation was through hydrophobic interactions in both cases, the former column was useful for separating the three classes of compounds using isocratic elution.[81]

A variety of other reversed-phase h.p.l.c. analyses of nucleosides have been reported. A strong linear correlation was observed between reversed-phase h.p.l.c. capacity factors and the log partition coefficients determined by a shake-flask method, for 25 nucleoside analogues of interest as chemotherapeutic agents.[82] Nucleosides and their adducts with carcinogens could be determined to femtomole levels by derivatization with 1-anthroylnitrile and laser-fluorescence detection.[83] A new reversed-phase column packing had improved performance for the separation of 16 purine nucleosides, nucleotides and bases, and could be applied in the study of purine metabolism in hearts for transplantation.[84] An enzyme-reactor composed of co-immobilized purine nucleoside phosphorylase, guanase, and xanthine oxidase generated hydrogen peroxide from purine nucleosides and bases in the h.p.l.c. eluant, and this was used to generate a fluorescent compound for detection.[85] Reversed-phase separations have been reported for the analysis in biological fluids of 3′-azido-3′-deoxythymidine (AZT) alone[86] or with its glucuronide metabolite,[87,88] 2′,3′-dideoxyinosine,[89] 2′,3′-dideoxycytidine,[90] all three of the aforementioned deoxynucleosides together with 3′-deoxy-3′-fluorothymidine,[91] and modified nucleosides associated with cancer patients.[15] The preparative separation (2.5 g scale) of AZT 5′-phosphate prepared by direct phosphorylation of AZT has also been reported.[92]

Ion-pair reversed-phase h.p.l.c. assays of purine nucleosides, nucleotides and bases in mitochondria using a microbore column (2.0 mm i.d.)[93] and in intestinal mucosa,[94] and of 2′,3′-dideoxyinosine in biological fluids with 2′-deoxyguanosine as an internal standard,[95] have been reported. The reversed phase h.p.l.c. behaviour of nucleosides, nucleotides and their bases when α-, β- or δ-cyclodextrins are present in the eluant, has been studied.[96]

The hydrophobic properties of a series of 5-alkyl-, 5-alkenyl- and 5-alkynyl-substituted deoxyuridines were defined from their retention behaivour on silica and reversed-phase columns.[24] Zeatin and its riboside were determined in plant tissues by solid-phase extraction and cation-exchange h.p.l.c.[16] Sugar and nucleoside H-phosphonates have been separated by anion-exchange h.p.l.c., and by flow injection analysis in which the components are hydrolysed, oxidised and the orthophosphate so generated is detected colorimetrically.[97]

Pre-column fluorimetric derivatization of adenosine and its cyclic monophosphate with chloroacetaldehyde,[98] and pre-column chemiluminescence derivatization of 5-fluoropyrimidines with 7-diethylamino-3-(4-iodoacetamidophenyl)-4-methylcoumarin,[99] have yielded derivatives suitable for reversed-phase h.p.l.c. analysis.

Applications of h.p.l.c.-m.s. techniques to the characterisation of nucleosides in synthetic mixtures and RNA hydrolysates,[100] and to a glycopeptide,[101] have been reported. Related applications are discussed in Chapter 22. Preparative h.p.l.c. of sphingolipid derivatives is discussed earlier in this Chapter (see ref. 8).

Column Chromatography:- Size exclusion chromatography has been used to isolate individual *N*-deacetylated chito-oligosaccharides of D.P. up to 15, and mixtures of oligomers up to D.P. 40, following conc. HCl hydrolysis of chitosan.[102]

The triterpene disaccharide glycyrrhizic acid was purified from 80% to >99% on a 20 mg scale using an 'internal-surface reversed-phase' packing material prepared from C_{18}-silica such that its external surfaces are wettable with water.[103] The hexoses, mainly galactose and glucose, released on hydrolysis of photographic gelatin were separated chromatographically as their borate complexes.[104]

Preparative separations of *myo*-inositol bis- and tris-phosphate isomers, yielding mg amounts of pure materials, were achieved by fractionations first on a cation- then on an anion-exchange resin.[105] Stepwise elution of inositol mono- through hexa-phosphates from a strong-base anion-exchange resin in the formate form was demonstrated and used for the separation of ^3H- and ^{32}P-radiolabelled cellular constituents.[106]

Other applications are discussed earlier in this Chapter (see refs. 27 and 35).

2 Electrophoresis

The separation of neutral sugars, uronic acids and their oligomers by electrophoresis on silylated glass-fibre paper has been investigated. The support is inert so that aggressive chemical reagents can be used for staining, and it has only a small electroendosmotic flow. With a borate buffer, neutral sugars form negatively charged complexes, and both neutral and acidic sugars can be separated, as well as mono- and oligo-saccharides in the same run.[107] Using barium, cadmium or zinc acetate buffers the four uronic acids (GlcA, GalA, GulA and ManA) commonly encountered in acidic polysaccharides were separable.[108]

Capillary zone electrophoresis has been used for the separation of malto-oligosaccharide derivatives prepared by reductive amination with 2-aminopyridine,[109] and of products arising from the Maillard reaction of D-ribose or D-glucose with free amino-acids.[110] In the latter case, it was noted that such products had resisted other analytical approaches, and that derivatization with phenyl isocyanate or 2,4-dinitrophenylhydrazine could be used to test for the presence of free amino-groups or carbonyl groups, respectively, in the resolved components. Capillary zone electrophoresis with indirect fluorescence detection has been extended to the separation of aldoses, sucrose and fructose at pH 11.5 with the use of visible light and coumarin 343 as fluorophore.[111]

3 Other Analytical Methods

A spot-test on anion-exchange resin beads and a colorimetric assay for reducing sugars using 1-chloro-2,4-dinitrobenzene as reagent have sensitivities in the ppm range, and result in complete removal of interferences from ketones that give similar colour to sugars with other reagents.[112] A new colorimetric assay for the selective determination of glucosone in the presence of D-glucose and D-fructose, and in biological materials such as serum, used a phenazine methosulphate and nitroblue tetrazolium reagent.[63] A simple colorimetric assay for 2-keto-L-gulonic acid based on its condensation with 2-thiobarbituric acid in hot aqueous acid has been developed, and conditions have been established to allow the determination to be conducted in the presence of L-sorbose.[113]

Ribonucleosides and ribonucleotides, and also reducing sugars, produce fluorescence (340 nm excitation, 470 nm emission maxima) when heated in acidic solution with *meso*-1,2-bis(4-methoxyphenyl)ethylenediamine or related materials, permitting detection to 60-500 pmol ml^{-1}.[114] The fluorimetric determination of sugars and amino-acids, using their Hantzsch reaction with 2,4-pentanedione and formaldehyde, has been reviewed in Japanese.[19]

A trinitrobenzene sulphonate ion-selective electrode has been used for the kinetic determination of glucose and fructose during the reaction of an excess of these sugars with trinitrobenzenesulphonic acid in alkaline solution at 45-60°C.[115]

Treatment of D-glucose oxidase with tetrathiafulvene modified the enzyme such that it could be directly oxidized at a metallic electrode and could thereby be used to assay D-glucose.[116] Related amperometric D-glucose electrode sensors based on D-glucose oxidase have used enzyme immobilized on a collagen membrane with glutaraldehyde and the Ugi reaction,[117] and determination of sugar concentration by measuring the amount of byproduct hydrogen peroxide formed using its reduction by ruthenium(II) ions.[118] D-Fructose in fruits has been determined by an electrochemical method in which D-fructose dehydrogenase is immobilised behind a dialysis membrane on a carbon paste electrode, and a current is generated by *p*-benzoquinone mediated bioelectrocatalytic oxidation of the sugar.[119]

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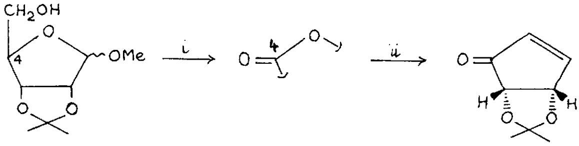
24

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

1 Carbocyclic Compounds

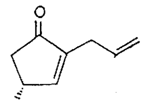
The useful cyclopentenone synthon (1) can be prepared easily from D-ribose, as outlined in Scheme 1.[1] The enantiomer of (1) can be made in the same way from D-lyxose derivatives, but it is instructive to compare this present work[1] with earlier studies from the same laboratory, in which the enantiomer of (1) (as the cyclohexylidene analogue) was prepared from D-ribonolactone (see Vol. 21, p. 157 and 197). A full account has been given of the formation of chiral 4-hydroxycyclopentenones from D-glucose, and an additional similar example is included, leading to the synthesis of (2).[2]



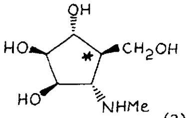
(1)

Reagents: i, PCC; ii, $LiCH_2P(O)(OMe)_2$

Scheme 1



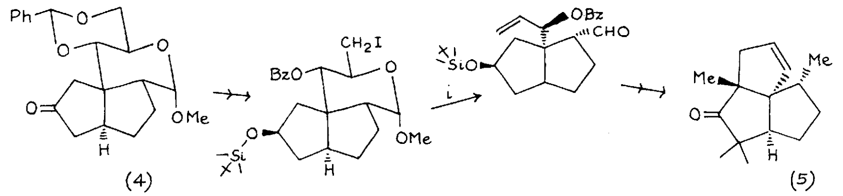
(2)



(3)

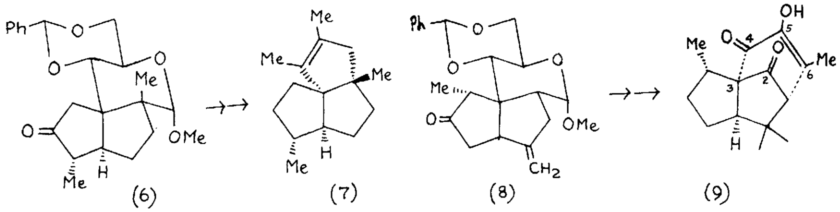
The cyclopentane (3), a potent α-mannosidase inhibitor, has been prepared from a previously-known intermediate made by intramolecular nitrone-alkene cycloaddition (see Vol. 13, p. 152); an epimerization at the carbon atom indicated was effected at the aldehyde oxidation level.[3]

Fraser-Reid's group have described further examples of the use of serial radical cyclization to prepare di- and triquinane natural products. The previously-reported intermediate (4) (Vol. 23, p. 264) has been ring-opened by a Vasella-Bernet reaction, and hence converted to the triquinane (5) with the silphinene skeleton (Scheme 2).[4] Similar initial steps were involved in the conversion of (6) into silphiperfolene (7),[4] and to transform (8) (Vol. 23, p. 265) into (-)-α-pipitzol (9) (mannose carbons numbered).[5]

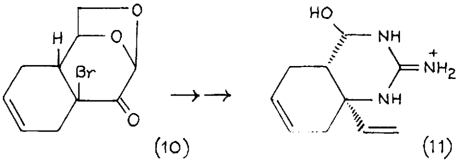


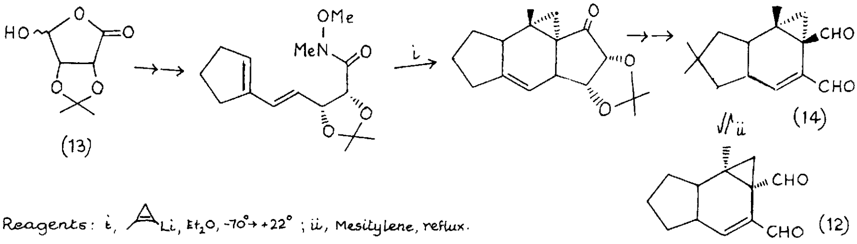
Reagents: i, Zn(Hg); EtOH

Scheme 2



A Diels-Alder reaction between 3-bromo-levoglucosenone and butadiene gives rise to adduct (10), which could be converted into (11), which represents the guanidinium part of tetrodotoxin.[6] An interesting intramolecular Diels-Alder reaction (Scheme 3) was a key step in a synthesis of (+)-isovelleral (12) from the L-erythuronic acid derivative (13) which is accessible from D-ribonolactone. The synthesis produced firstly the diastereomer (14) of (+)-isovelleral (12), but the two were thermally interconvertible by an ene-type opening and closing of the three-membered ring.[7] An intramolecular Diels-Alder reaction of (15) gave tricycle (16)

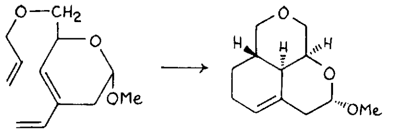


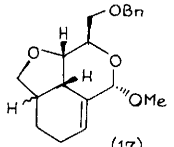


Reagents: i, △Li, Et$_2$O, −70°→+22° ; ii, Mesitylene, reflux.

Scheme 3

stereospecifically, whilst a similar reaction of a 4-*O*-allyl ether gave the mixed isomers (17).[8] Reaction of diene (18) with maleimide gave adduct (19) as the major isomer (4:1); in a number of similar reactions it was found that the dienophile has a strong preference for addition to the face of the diene opposite to the anomeric centre, even when, as in (18), the steric effect of the allylic substituent opposes this.[9]


(15) (16)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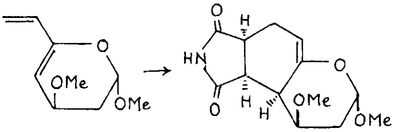
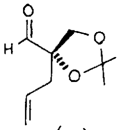

(18) (19)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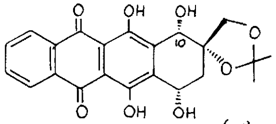
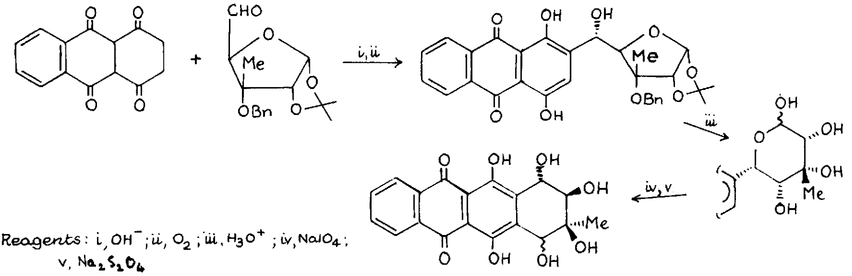

(21)

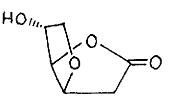
Condensation of the aldehyde (20), derived from α-D-isosaccharino-lactone, with leucoquinizarin has led to the synthesis of the anthraquinone (21), and its C-10 epimer.[10] A further report from Shaw's laboratory has described the synthesis of some anthracyclinones with a tertiary methyl carbinol in ring A, as indicated in Scheme 4 (the reporter has amended the stereochemistry of the final product from that indicated in the paper).[11]


Reagents: i, OH^-; ii, O_2; iii, H_3O^+; iv, $NaIO_4$; v, $Na_2S_2O_4$

Scheme 4

2 γ- and δ-Lactones

Various furanone chirons such as (22)-(24), and their C-5 epimers, have been prepared in optically-pure form from the dibromide (25) and its C-5 epimer; these in turn are easily accessible from L-ascorbic and D-isoascorbic acids.[12] Baeyer-Villiger oxidation of levoglucosenone leads to the formation of the unsaturated lactone (26), with loss of C-1 of the precursor;[13] similar oxidation of the product (27) from dimethyl cuprate addition to levoglucosenone gave a γ-lactone convertible to (+)-whisky lactone (28), (+)-cognac lactone (29), and eldanolide (30).[14]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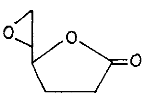
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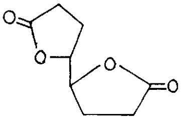
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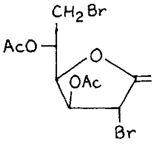
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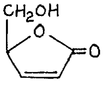
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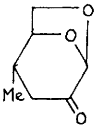
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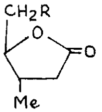
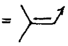
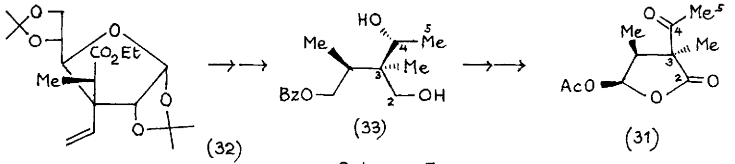

(28) R = $C_3H_7^n$
(29) R = $C_4H_9^n$
(30) R =


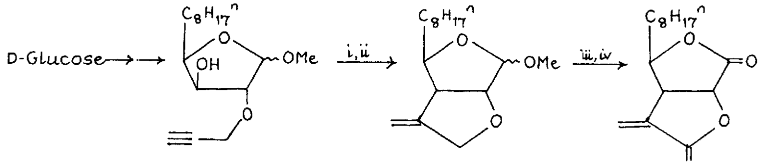
In a multistep synthesis of (-)-acetomycin (31), which served to confirm its absolute configuration, the doubly-branched furanose (32) (Scheme 5), produced from D-glucose by a stereoselective Claisen rearrangement (Vol. 23, p. 150), was degraded to the intermediate (33), which was subsequently elaborated to the target (glucose carbons indicated).[15]



Scheme 5

There has been a further glucose-based synthesis of the popular target avenaciolide (34), in which a free-radical cyclization was the key step (Scheme 6).[16] Radical cyclization was also involved in a synthesis of isoavenaciolide and ethisolide,[17] in a manner that is conceptually very similar to that reported for (-)-avenaciolide by other workers (Vol. 22, p. 261), and (-)-isoavenaciolide has also been prepared in a multi-step procedure from a known derivative of quebrachitol (Vol. 23, p. 7).[18]

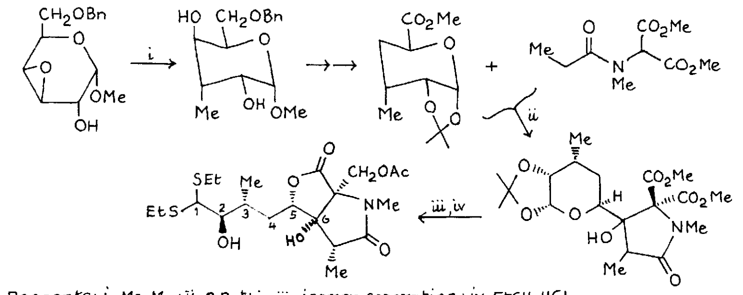
In a total synthesis of neooxazolomycin, the chiral array of the 'right-hand side' of the molecule was assembled from a 3,4-anhydrogalactoside as



Reagents: i, NaH, CS_2, MeI ; ii, Bu_3SnH, AIBN ; iii, HOAc, H_2O, HCl ; iv, CrO_3, py

Scheme 6

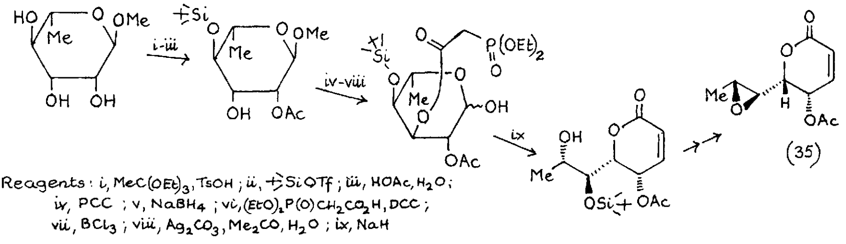
outlined in Scheme 7; the key formation of the pyrrolidinone ring led to two separable isomers, both with hydroxyl and methyl groups *cis*.[19]



Reagents: i, Me_2Mg; ii, 2 Bu^tLi; iii, isomer separation; iv, EtSH, HCl

Scheme 7

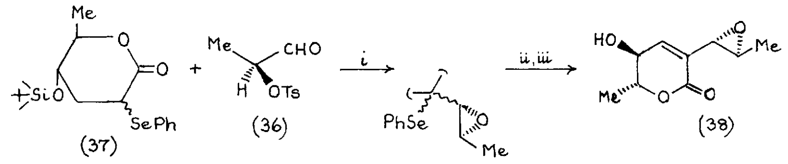
An intramolecular Wadsworth-Emmons reaction was a key step in the synthesis of (+)-asperlin (35) outlined in Scheme 8,[20] and a full account has



Reagents: i, $MeC(OEt)_3$, TsOH; ii, Bu^tMe_2SiOTf; iii, HOAc, H_2O; iv, PCC; v, $NaBH_4$; vi, $(EtO)_2P(O)CH_2CO_2H$, DCC; vii, BCl_3; viii, Ag_2CO_3, Me_2CO, H_2O; ix, NaH

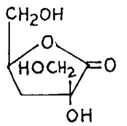
Scheme 8

been given of a synthesis of the (6*R*, 7*S*)-diastereomer of (35) (see Vol. 22, p. 201-2).[21] Optically-pure aspyrone (38) has been prepared from lactone (37), formed by Ferrier rearrangement from diacetyl-6-deoxy-D-glucal, and the aldehyde (36), synthesized from 3,4-*O*-isopropylidene-D-mannitol, as indicated in Scheme 9.[22] The quaternary centre of α-D-isosaccharinolactone (39) has been transformed into the equivalent position of (-)-malyngolide (40).[23]



Reagents: i, $LiN(TMS)_2$; ii, H_2O_2; iii, Bu_4NF

Scheme 9



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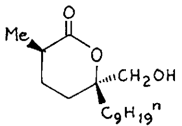
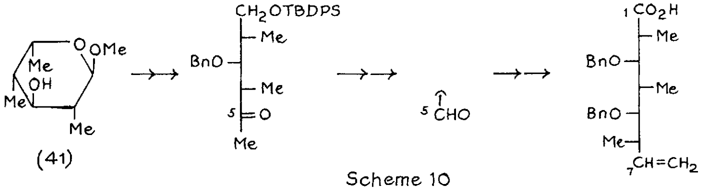


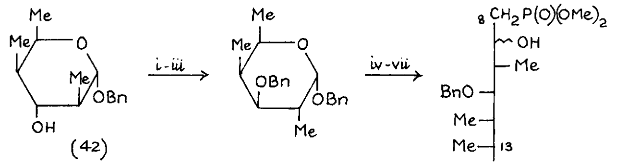
(40)

3 Macrolides, Macrocyclic Lactams, and their Constituent Segments

Yonemitsu's group has described the completion of their synthesis of erythronolide A by macrolactonization of a seco-acid made from glucose-derived fragments.[24] A fragment corresponding to C(1)-C(7) of oleandolide has been prepared from the doubly-branched glycoside (41) (Vol. 22, p. 150) via the key intermediates indicated in Scheme 10, whilst a C(8)-C(13) segment was prepared from the enantiomeric benzyl glycoside (42) as indicated in Scheme 11.[25] The Moscow group has described the synthesis of two units (43) and (44), corresponding respectively to C(1)-C(7) and to C(8)-C(15) of lankanolide. The chiral array at C(2)-C(4) in (43) and at C(12)-C(14) in (44) (macrolide numbering) was derived by ring opening of levoglucosan epoxides, whilst much of the remaining stereochemistry was put in place by stereocontrolled aldol condensations.[26] Levoglucosan was also the precursor for the unit (45), corresponding to C(2)-C(9) of rosaramycin, C(2)-C(7) of the macrolide corresponding with C(6)-C(1) of D-glucose.[27] The synthon (46, R=H), representing C(4)-C(9) of 16-ring macrolides such as carbomycin, could be obtained by deoxygenation of (46, R=OH), which in turn was prepared by regiospecific opening of an epoxide.[28] The unit (47), representing C(11) - C(17) of mycinolide V, has been prepared from D-ribose; in a key step, the



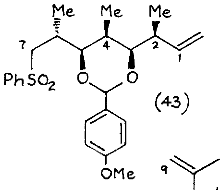
Scheme 10



Reagents : i, $BF_3.Et_2O$; ii, B_2H_6, H_2O_2; iii, BnBr ; iv, H_3O^+ ; v, PDC ; vi, $MeP(O)(OMe)_2$, BuLi ; vii, LAH

Scheme 11

enolate of (48) was alkylated by ICH_2OBn, produced in situ from $CH_2(OBn)_2$ and TMSI. Both stereomers of (49) were produced, but each could be separately manipulated to give (47).[29]



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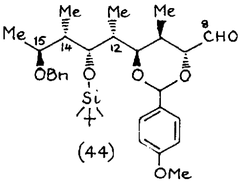

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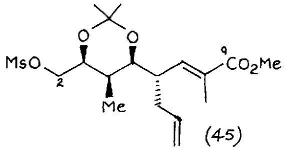

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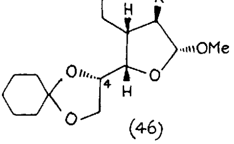

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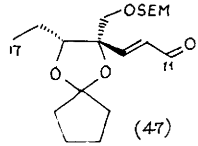

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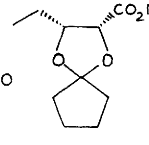

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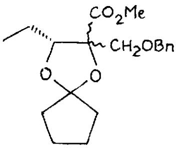


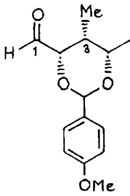
(49)

Two total syntheses of the important immunosuppressant FK-506 have been reported. Danishefsky's group has described a synthesis of the C(22) - C(27) unit (50) from tri-*O*-acetyl-D-galactal (sugar carbons indicated), with the C(3)-methyl group being introduced by opening of a 2,3-D-*talo*-epoxide with Li_2Me_2CuCN.[30] The same team has given an expanded account of their galactose-based route to a C(10)-C(19) chiron (see Vol. 23, p. 269),[31] and the two units, together with another synthon not derived from a carbohydrate, have been linked to complete the synthesis.[32] Meanwhile, Schreiber's team has described in full the preparation of their L-arabinitol-derived C(10)-C(18) unit (see Vol. 23, p. 269), and linked it with other chiral entities to complete the FK-506 molecule.[33]

Mootoo and Fraser-Reid have given full accounts of their synthesis of a chiral unit corresponding to the ansa-chain of streptovaricin A (see Vol. 23, p. 270),[34,35] and Tatsuta and Kinoshita's group has reported in full on the total synthesis of rifamycin W, using an ansa-chain unit constructed from D-glucose-derived starting materials (*Bull. Chem. Soc. Jpn.*, 1985, 58, 3457), but with some improved procedures.[36]

4 Other Oxygen Heterocycles

A full account has been given of the synthesis of the enantiomers of botryodiplodin and epibotryodiplodin (see Vol. 21, p. 265).[35] The marine natural product (51) has been prepared from D-glucose (sugar carbons numbered); the tetrahydrofuran ring was made by cyclization of a 5-*O*-tosyl derivative.[38] The fragment (52) of the polyether antibiotic tetronasin has also been made from glucose (carbons numbered), with a sequence of Wittig



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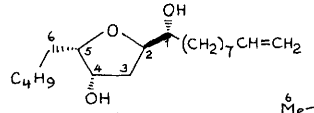

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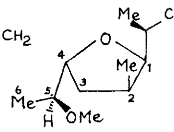

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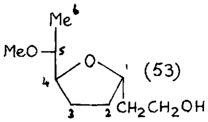
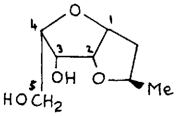


(53)

reaction-intramolecular cyclization being used to introduce the remaining carbons, non-stereospecifically with regard to the exocyclic chiral centre.[39] The same chiron (52) has also been made from L-rhamnal (same sugar numbering), as has the unit (53) of tetronasin, where the stereochemistry of L-rhamnal was inverted at both C-4 and C-5 by a sequence of epoxide formation and cyclization.[40] Previous work on the synthesis of the bis(tetrahydrofuran) unit of (+)-asteltoxin from D-glucose (Vol. 22, p. 263) has been modified and extended to the synthesis of the complete mycotoxin.[41] The hexahydrofuran unit (54) of erythroskyrin has been prepared from diacetone glucose by way of D-*gulo*- and L-*lyxo*-intermediates (sugar carbons numbered). The three remaining carbons were introduced by a Wittig reaction, which was followed by two intramolecular cyclizations which occurred with good stereocontrol.[42] Wittig reactions were also important in the use of 2,3-*O*-ethylidene-D-erythrose for the preparation of the model system (55) for the pseurotins.[43,44]



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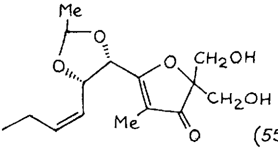
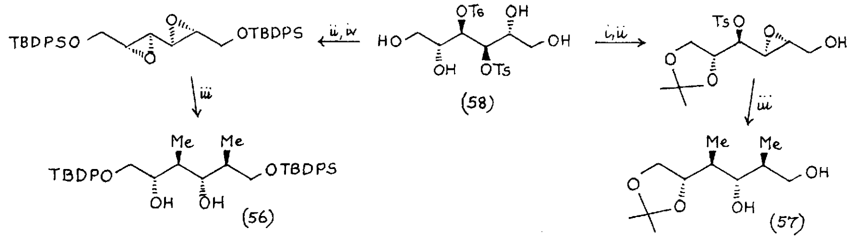


(55)

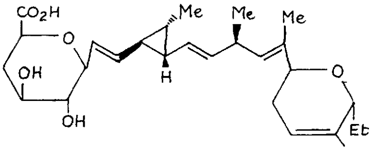
The two units (56) and (57) which are differentially-protected versions of a chiral array found in ionophoric antibiotics such as zincophorin, have been prepared from the D-mannitol-derived ditosylate (58) by means of regioselective openings of epoxides (Scheme 12).[45]



Reagents : i, $(MeO)_2CMe_2$, TsOH ; ii, K_2CO_3, MeOH ; iii, $Me_2CuCNLi_2$; iv, TBDPSCl, imidazole

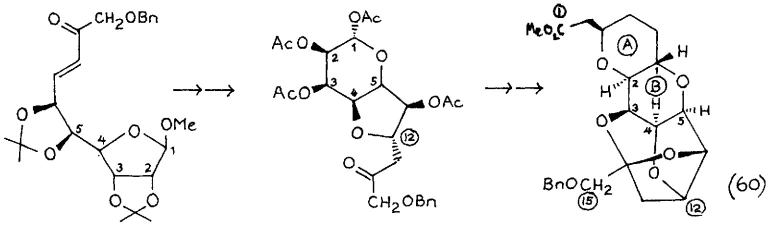
Scheme 12

In the first total synthesis of (+)-ambruticin (59), the left-hand ring was derived from methyl α-D-glucoside, with the β-*C*-vinyl glycoside link being established by coupling of a *trans*-vinylalane with a glycosyl fluoride.[46]



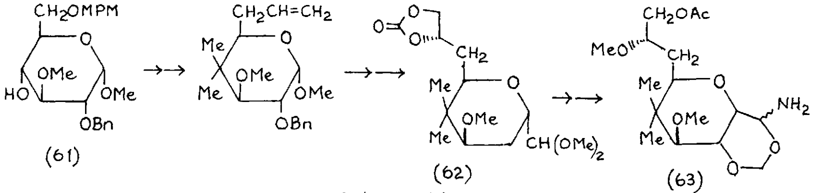
(59)

By means of the key intermediates indicated in Scheme 13, D-ribose has been built up into the unit (60) representing the C(1) - C(15) portion of the halichondrins, incorporating rings A and B and the intramolecular ketal (halichondrin numbering circled). The initially incorrect stereochemistry at C-12 was inverted by an elimination-addition process.[47]



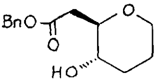
Scheme 13

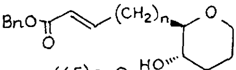
In a total synthesis of mycalamide B, the aminal unit (63) was prepared from glucose derivative (61) via the key intermediates indicated in Scheme 14. Amongst much ingenious chemistry, the introduction of the axial dimethyl acetal grouping into (62) by the use of propargyl trimethylsilane-TMSOTf, followed by ozonolysis and acetalization, is noteworthy. Hydroxylation of the allyl group involved asymmetric osmylation; the synthesis was completed by acylation of (63) with a non-sugar-derived acid unit, and mycalamide A was made by a variation on the route.[4]

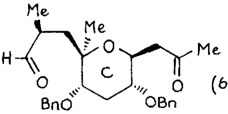


Scheme 14

Nicolaou's group has continued its assault on brevetoxin B (see Vol. 23, p. 270-271). In model studies, tri-*O*-acetyl-D-glucal was converted to the tetrahydropyrans (64)-(66), which were converted to macrodithiolactones which could be reductively linked between the carbon atoms of the thiolactones.[49] The *C*-glycoside derivative (67) has been converted into the BCD ring system of brevetoxin B,[50] whilst 2-deoxyribose has been transformed into the ABC ring unit (68) and the FG system (69) by second-generation syntheses amenable to larger-scale operation (sugar carbons numbered).[51]


(64)


(65) n = 0
(66) n = 1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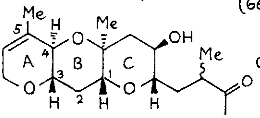
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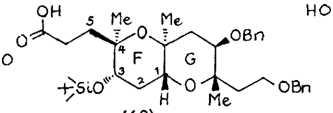
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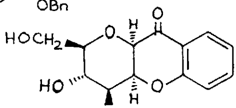
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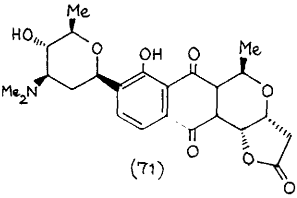
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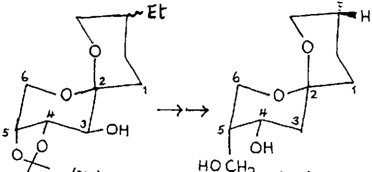
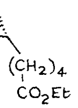

(72) (73)


(74)

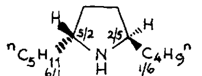
Pyrano[3,2-*b*]benzopyrans such as (70) have been made by reaction of 1-nitroglycals with 2-hydroxybenzaldehyde, and reductive removal of the anomeric nitrogroup using Bu_3SnH.[52] A synthesis of medermycin (71) has ben reported in which the *C*-aryl glycoside was formed by interaction of an *o*-lithioaromatic with a sugar lactone derived from D-rhamnal; the fused pyran ring was introduced by means of methods developed earlier by the same group (Vol. 19, p. 259) in their synthesis of kalafungin.[53]

Wittig reactions were used to convert 2,3: 4,5-di-*O*-isopropylidene-β-D-fructopyranose into the separable isomers (72), one of which could be converted to (-)-talaromycin A (sugar carbons indicated). Acid treatment of (73) gives talaromycin B, the epimer at C-5 (fructose numbering), with C-6 of the sugar now endocyclic.[54]

The terminal epoxyester (74) has been prepared from L-arabinal, the chiral centre corresponding with C-4 of the sugar,[55] and a full account has been given of the synthesis of the polyene epoxide AK-Toxin-II from L-ascorbic acid (see Vol. 21, p.264).[56]

5 Nitrogen Heterocycles

The ant venom alkaloid (75) has been synthesized from D-mannitol (sugar carbons numbered) by a sequence involving deoxygenation at C-3 and C-4, and introduction of nitrogen by double inversion at C-2 and C-5.[57] Diacetone glucose has been converted into the iminoalditols and iminoacids (76)-(79) (sugar carbons indicated) by sequences involving introduction of nitrogen at C-5 or C-6, followed by cyclization onto C-2, with inversion of configuration.[58]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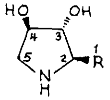
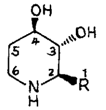
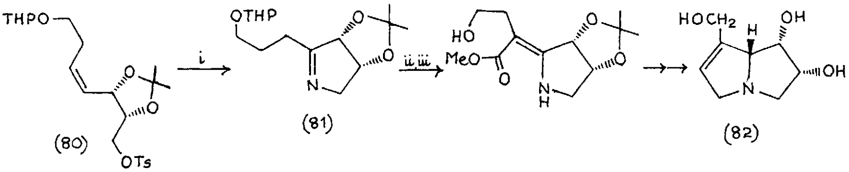

(76) R = CH_2OH
(77) R = CO_2H

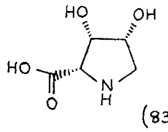

(78) R = CH_2OH
(79) R = CO_2H

In a synthesis of the pyrrolizidine alkaloid (+)-crotanecine (82) (Scheme 15), an intramolecular cycloaddition was used to convert (80), derived from 2,3-*O*-isopropylidene-D-erythrose (carbons numbered), into the Δ^1-pyrroline (81).[59] A similar intramolecular cycloaddition of an azide was also used in a preparation of the dihydroxyproline (83) from isopropylidene-D-erythrose,[60] and the same concept and starting chiron were used in a synthesis of (-)-swainsonine which has features in common with one reported last year (Vol. 23, p. 273).[61] The tetrahydroxypyrrolizidine (84) has been made from 2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptonolactone, by introduction of nitrogen at C-7, and subsequent double cyclization to C-1 and C-4.[62] The trihydroxypyrrolizidine (87), which can be regarded as a ring-contracted analogue of swainsonine, has been prepared as outlined in Scheme 16. The aldehyde (85) was made from isopropylidene-D-erythrose, and it was observed that the same product (86) was formed highly stereo-



Reagents: i, NaN_3, DMF; ii, LDA, $ClCO_2Me$; iii, PPTS, MeOH

Scheme 15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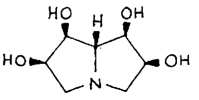
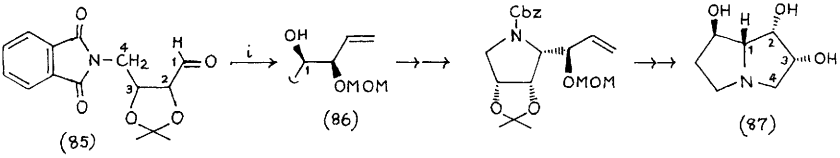
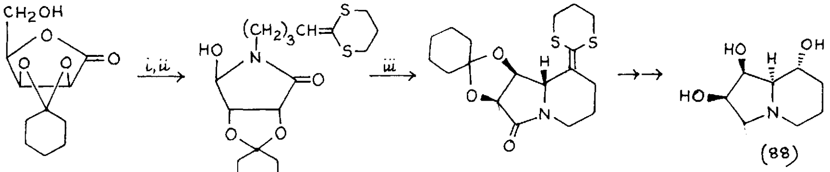

(84)

selectively in the reaction with the chiral borane, independent of which enantiomer of the reagent was employed, although the achiral reagent derived from 9-BBN gave lower selectivity.^{63} Key steps in a new synthesis of swainsonine (88) from D-lyxose are indicated in Scheme 17, and a similar approach was used to make castanospermine and 1,8a-diepicastanospermine from D-gluconolactone.^{64} 1,2-*O*-Isopropylidene-α-D-glucofuranurono-6,3-lactone can be converted in four steps into the ketal (89), which can then be used to prepare (+)-castanospermine (90) (glucose carbons numbered).^{65} A full account has been given of the synthesis of 6-epi- and 1,6-diepi-castanospermine from L-gulonolactone (Vol. 22, p. 265-6),^{66} and 1-deoxy-6-epi-castanospermine (91) and 1-deoxy-6,8a-diepicastanospermine have been prepared from 2,3: 4,5-di-*O*-isopropylidene-β-D-fructopyranose (sugar carbons indicated).^{67} The interesting α-mannosidase inhibitor kifenensine (92) has been synthesized from D-mannosamine, the carbons of which are



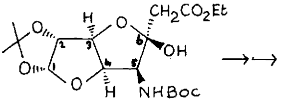
Reagent: i, MOMO⌒B(ipc)$_2$

Scheme 16



Reagents: i, $NH_2(CH_2)_3CH$=⟨dithiane⟩, MeOH ; ii, $Pb(OAc)_4$; iii, MsCl, Et_3N

Scheme 17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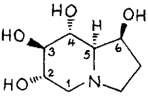
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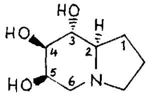
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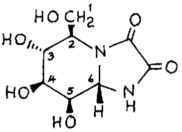
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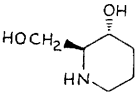
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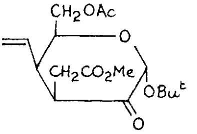
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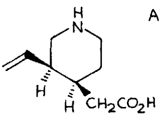
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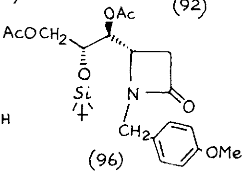

(96)

indicated.[68] Piperidine (93), representing the piperidine portion of swainsonine (88), has been made from methyl α-D-galactoside, but was not a significant inhibitor of mannosidases.[69] Some other references to iminoalditols are given in Chapter 19.

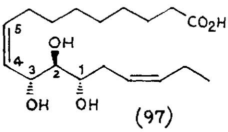
The doubly-branched sugar (94) can be made by cuprate addition-enolate alkylation from the 3,4-ene-2-one; subsequent manipulation has led to (+)-meroquinene (95), an important synthetic precursor for quinine and cinchonamine.[70]

There has been a further report concerned with the synthesis of (+)-sesbanimide, in which a popular intermediate derived from D-xylose (see Vol. 19, p. 268) has been manipulated in a novel manner, involving a tricyclic intermediate.[71]

A route to chiral oxazolidinones reported last year (Vol. 23, p. 272) has been extended to the preparation of chiral β-lactams such as (96), which are potential precursors of carbapenems; the oxazolidinones were opened reductively to β-aminoacids and then recyclized using 2-chloro-1-methylpyridinium iodide.[72]

6 Acyclic Compounds

The C_{18}-acid (97), a constituent of rice plants suffering from rice blast disease, has been prepared from D-ribose (sugar carbons numbered). The 4,5-ene (ribose numbers) was initially generated as a terminal alkyne from a 5-chloro-5-deoxyribose derivative by base-catalysed elimination (see Vol. 23, p. 275).[73] A similar elimination was used to introduce the 1,2-alkyne (sugar numbering) in a synthesis of the triyne carbonate L-660,631 (98) from D-glucose.[74] The hydroxyester (99) has been synthesized from L-arabinose (sugar carbons numbered), in order to confirm the structure and absolute configuration of the product formed from (*Z*,*Z*,*Z*,*E*)-5,8,11,13-eicosatetraenoic acid by the action of 12-lipoxygenase.[75]



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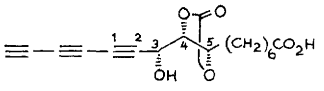

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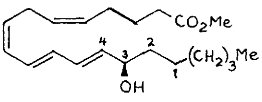
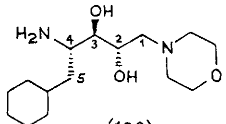


(99)

The dipeptide mimic (100), a constituent of the orally-active renin inhibitor BW-175, has been prepared from 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-allose (sugar carbons numbered).[76]

The chiral divinyl glycol (101) has been synthesized from D-mannitol. The monobenzyl ether could be prepared using stannylene chemistry, and this in turn could be converted by orthoester-Claisen rearrangement to the known precursor (102) of lipoic acid (mannitol carbons indicated).[77] The 5,6-acetonide of L-ascorbic acid has been degraded to both diastereomers of



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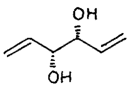

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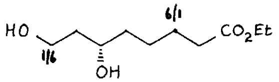
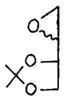


(102)

epoxide (103); epoxide opening and glycol cleavage then gave access to long-chain α-hydroxyacids for cerebroside synthesis.[78] Simple routes have been reported to both enantiomers of 1,2,4-butanetriol from L-ascorbic and D-isoascorbic acids,[79] and branched-chain compounds of type (104) have been prepared by Grignard additions to the 2-keto-compound, obtained from 5,6-*O*-isopropylidene-L-ascorbate.[80] Efficient methods have been described for *in situ* trapping of (*R*)- or (*S*)-isopropylidene glyceraldehyde by stabilized Wittig reagents to give chiral enones and enoates.[81] Degradation of *N*-BOC-D-glucosamine has been used to prepare *N*-BOC-L-serinal.[82] A report on the synthesis of γ-hydroxynorvalines is discussed in Chapter 16.

7 Carbohydrates as Chiral Auxiliaries

Kunz has reviewed Lewis-acid catalysed stereoselection on carbohydrate templates, with particular reference to his group's work on *O*-acylated glycosylamines as chiral auxiliaries.[83] A full and expanded account has been given of the synthesis of (+)-bostricin using a Diels-Alder reaction of a glucosyl diene (see Vol. 23, p. 276).[84] Compounds of type (105) can be formed with good diastereoselectivity by alkylation of the glucosyloxy-cyclohexadienyl anion, and used as precursors for chiral 2-alkylcyclohexanones.[85]



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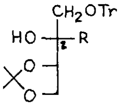

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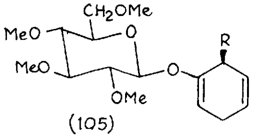

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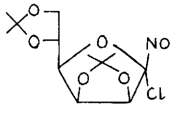

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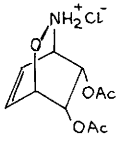

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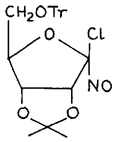

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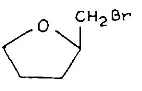

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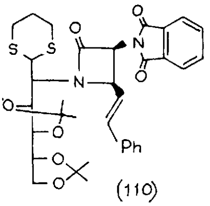
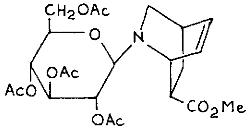


(110)

Cycloaddition of the D-mannose-derived chloronitrosocompound (106) with *meso*-5,6-diacetoxy-1,3-cyclohexadiene gave rise to the chiral dihydro-oxazine (107), which could be converted to various aminocyclitols. Use of the ribose-derived chloronitroso species (108) gave products in the enantiomeric series.[86]

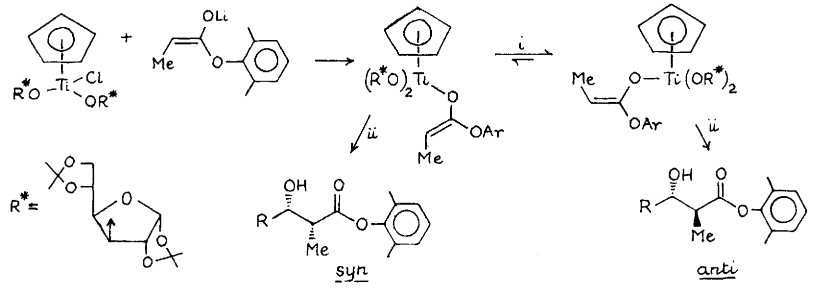
When 4-pentenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside was treated with NBS, the bromomethyl tetrahydrofuran (109) was formed with 80% e.e. The corresponding β-D-glucoside gave the enantiomer of (109), but only with 20% e.e., and various related cases were also studied.[87]

Ketene-imine cycloaddition involving an imine derived from cinnamaldehyde and a D-glucosamine derivative led stereoselectively to the β-lactam (110); the chiral auxiliary could be disconnected from the β-lactam by base treatment.[88] Cycloaddition of methyl acrylate and an *N*-glycosyl dihydropyridine gave adduct (111) and its diastereomer in the azabicyclic ring system. Removal of the chiral auxiliary from each diastereomer then gave the enantiomeric isoquinuclidines.[89]



(111)

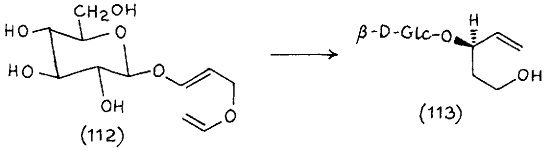
The titanium-based chiral auxiliary reported last year (Vol. 23, p. 276-7) has been used in enantio- and diastereo-selective routes to aldol products as outlined in Scheme 18, and related enolates derived from *N*-acyloxazolidinones behaved similarly.[90]



Reagents: i, Δ (-30°c) ; ii, RCHO, -78°

Scheme 18

The vinyl glycoside (112) undergoes rapid Claisen rearrangement in water, to give, after borohydride reduction, (*R*)-diastereomer (113) and the separable (*S*)-isomer. The chiral auxiliary can be removed using β-glucosidase.[91]



(112) (113)

The chiral borohydride formed from 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranoside, 9-BBN, and potassium hydride gives good chiral induction in reactions with ketones; reduction of acetophenone led to (*R*)-methyl phenyl carbinol in 77% e.e.[92] Aminoalcohols derived from D-glucose can catalyse enantioselective Michael additions of arylthiols to cyclohexenone.[93]

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