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Carbohydrate Chemistry

VOLUME 20

Part I

Monosaccharides, Disaccharides, and Specific Oligosaccharides

ROYAL SOCIETY OF CHEMISTRY

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Carbohydrate Chemistry

Volume 20
Part I

A Specialist Periodical Report

Carbohydrate Chemistry

Volume 20

Part I
Monosaccharides, Disaccharides,
and Specific Oligosaccharides

A Review of the Recent Literature Published during 1986

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Preface

This report summarises the literature for 1986 available to us by March 1987. The format adopted in recent volumes has been maintained, in the absence of any recommendations for change.

I would like to thank my colleagues for all their hard work in assembling this report, and I am glad that I have been able to call upon an unchanged team for the endeavour. I would also like to thank Dr. P. G. Gardam and Mrs. R. H. Pape and their colleagues at the Royal Society of Chemistry for the production of this report in its final form.

April 1988 Neil R. Williams

R E P R I N T S

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

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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	trifluoroacetic 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 following chapters represent a survey of monosaccharide and selected oligosaccharide research reported in 1986. Whilst we have attempted to be comprehensive in our coverage of monosaccharide chemistry, certain topics embracing both carbohydrate and non-carbohydrate components have been selective for those papers reporting specific carbohydrate chemistry, and in some other areas it has been difficult to decide whether extensively modified derivatives can be regarded as being carbohydrate at all, and we have used our own judgement in deciding whether or not to include such papers. The trends in research interest established in our recent reports have been maintained, and, in particular, efficient methods for synthesizing glycosides have been widely applied to an increasing range of compounds of ever-increasing complexity. Natural products still have many surprises in store, as evidenced by the discovery of the antibiotic oxetanocin, a nucleoside analogue possessing a four-membered sugar ring; other antibiotics apparently contain novel thio-sugar components. We have reviewed about 1460 references for this report.

Reports on more general aspects of carbohydrates have included reviews on " the sweeter side of chemistry ",[1] synthetic control in the synthesis of carbohydrates,[2] the use of the hetero Diels-Alder reaction in synthesizing 1,4-difunctionalized pentoses and hexoses from furans,[3] the application of phase-transfer catalysis to carbohydrate chemistry,[4] and the use of stable isotopes in carbohydrate chemistry.[5]

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1 L.Hough, Chem. Soc. Rev., 1985, 14, 357.

2 T.Mukaiyama, Org. Synth.: Interdiscip. Challenge Proc. IUPAC Symp., 5th, 1984 (Pub. 1985), 237 (Chem. Abstr., 1986, 104, 110 023).

3 R.R.Schmidt, Acc. Chem. Res., 1986, 19, 250 (Chem. Abstr., 1986, 105, 227 145)

4 Yu.A.Zhdanov and Yu.E.Alekseev, Zh. Vses. Khim. O-va. im. D.I.Mendeleeva, 1986, 31, 188 (Chem. Abstr., 1986, 105, 134 244).

5 R.Barker and A.S.Serianni, Acc. Chem. Res., 1986, 19, 307 (Chem. Abstr., 1986, 105, 209 284).

2
Free Sugars

1 General and theoretical aspects

The reactions of monosaccharides in aqueous alkaline solution is the subject of a review covering initial transformations, alkaline degradation and the influence of reaction variables on product formation.[1]

Molecular orbital calculations have been carried out in an investigation of the mechanism of mutarotation of α-D-glucopyranose. The CNDO/2 results were in agreement with experiment for acid- and base-catalyzed processes.[2] A molecular dynamics simulation of the $^{1}C_{4}$ and $^{4}C_{1}$ conformations of α-D-glucopyranose *in vacuo* predicts very flexible rings. The mean dynamic structure was found to be close to the structure found in the crystal, but there was a deviation in the C-5 - O-5 region.[3]

A far-reaching communication has concluded that there is an intrinsic energy difference between enantiomeric chemical species. The results, from an *ab initio* calculation, depend on "parity-violating weak interactions" due primarily to the electron-neutron potential component of the weak neutral current present in atomic nuclei. Application to the model sugar, hydrated glyceraldehyde, indicated that the D-enantiomer is of lower energy, which, if taken as a free energy difference, corresponds to an enantiomeric excess of $\sim 10^{6}$ molecules per mole. The suggestion is that this difference is the cause of the preference for D-sugars in nature.[4]

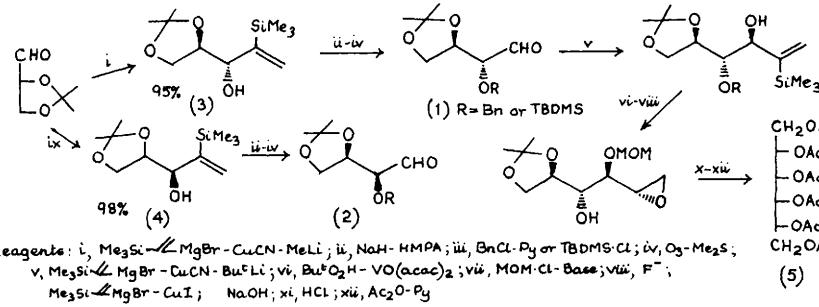
2 Synthesis

A review on asymmetric epoxidation of allylic alcohols by the Sharpless method includes discussion of its use for the *de novo* synthesis of sugars and polyols and for further extension of sugar-derived allylic alcohols for chiral synthesis from sugars.[5]

The one-step synthesis of straight chain carbohydrates from formaldehyde and syngas (hydrogen and carbon monoxide in a 2:1 ratio) has been described. The process involves heating paraformaldehyde in pyridine and tertiary amine in the presence of bistriphenylphosphine-

carbonyl rhodium chloride under an atmosphere of syngas in an autoclave. The product contained up to 60% total carbohydrate which consisted of straight chain sugars with between two and six carbon atoms. The results are thus different from those obtained in the formose reaction which gives a large proportion of branched-chain products.[6] The formose reaction in the presence of fructose and the alkaline degradation of fructose in the presence of formaldehyde have been investigated and compared. The study was prompted by the observation that formaldehyde added for microbiological control in the sugar industry is decomposed in the presence of invert syrup during the liming process. It was concluded that aldolization and retroaldolization reactions are of major importance and that there is no essential mechanistic difference between the two reactions.[7] Pentoses and hexoses are formed in 48 hours from glyceraldehyde on sodium montmorillonite clay at 40° in aqueous dispersion. The sugars were formed in the interlamellar regions of the clay and the resultant intercalates were found to be stable to 250° C.[8]

A convenient preparation of L-(S)-glyceraldehyde acetonide from L-ascorbic acid en route to glycerol acetonide is described more fully in Chapter 24.[9] An alternative method to that of Dondoni et al. (see Vol. 19, p.4) for the homologation of D-glyceraldehyde to prepare derivatives of D-erythrose (1) and D-threose (2) has been described; with appropriate reagents, either the erythro-epimer (3) or the threo-epimer (4) could be obtained as the major product (Scheme 1). Application of a further reaction sequence to the acetonide (1) yielded allitol hexa-acetate (5).[10]

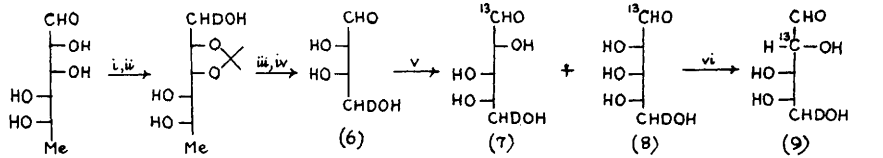


Scheme 1

Two convenient methods for the synthesis of L-erythrose from D-ribono-1,4-lactone have come from the same laboratory. In the first, the 2,3-O-isopropylidene derivative is subjected to sequential

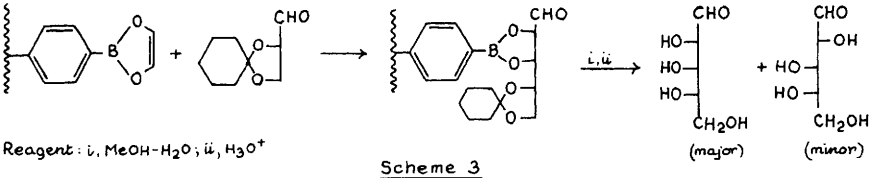
reduction to the ribitol, periodate oxidation, and deprotection.[11] second route similarly utilized 3,5-O-benzylidene-D-ribono-1,4-lactone.[12]

L-[4-^{2}H]Erythrose (6), L-[1-^{13}C, 5-^{2}H]arabinose (7), L-[1-^{13}C,5-^{2}H]ribose (8) and L-[2-^{13}C,5-^{2}H]arabinose (9) have been synthesized from L-rhamnose as shown in Scheme 2.[13] Condensations



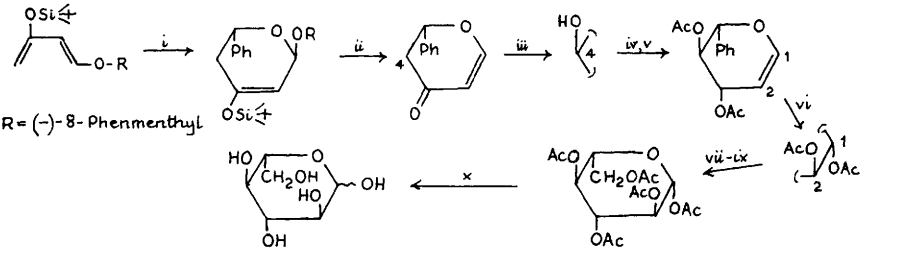
Scheme 2

using 2-substituted 1,3,2-dioxaboroles provide a means for extending the chain length of a sugar by two carbon atoms. The reagent was most conveniently used by attachment to a polymer. The application of the method to 2,3-O-cyclohexylidene-L-glyceraldehyde is shown in Scheme 3.[14]



Scheme 3

L-Glucose has been synthesized by the route shown in Scheme 4.



Scheme 4

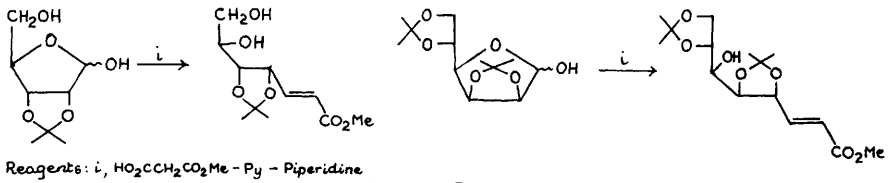
The Diels-Alder reaction of the substituted butadiene and benzaldehyde proceeded under asymmetric induction due to the sub-

stituted menthyl moiety.[15]

Conversion of alditols to aldoses without the need to protect all hydroxy groups has been achieved by monotosylation of one primary hydroxy group, displacement with azide ion and photolysis in methanol to yield the aldimine, which was then hydrolyzed to the aldose. The procedure was illustrated using 3,4-O-isopropylideno-D-mannitol to produce D-mannose.[16] The synthesis of D-[U-^{14}C]galactose from methyl α-D-[U-^{14}C]glucopyranoside *via* aqueous bromine oxidation to the 4-uloside, reduction by sodium borohydride and hydrolysis has been described, along with the isolation of D-glucuronic acid and methyl α-D-mannopyranoside as by-products.[17]

The Knoevenagel-Doebner reactions of 2,3-O-isopropylidene-D-ribofuranose and 2,3:5,6-di-O-isopropylidene-D-mannofuranose have been studied (Scheme 5). The products were found to be epimerized at the original C-2 position.[18]

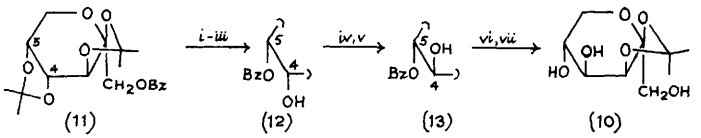
2,3-O-Isopropylidene-β-D-tagatopyranose (10) has been synthesized



Reagents: i, $HO_2CCH_2CO_2Me$ - Py - Piperidine

Scheme 5

from 1-O-benzoyl-2,3:4,5-O-isopropylidene-β-D-fructopyranose (11). The required inversion at C-4 was effected by oxidation - reduction of the 4-hydroxy derivative (12), but the reduction showed poor stereoselectivity and gave the C-4 epimers (12) and (13) in a 1:1 ratio. The regioselective 5-O-benzylation to generate (12) was achieved *via* a 4,5-O-dibutylstannylidene derivative (Scheme 6).[19]



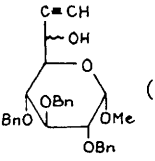
(11) (12) (13) (10)

Reagents: i, MeOH-H^+; ii, Bu_2SnO; iii, BnBr; iv, DMSO-$(CF_3CO)_2O$; v, $NaBH_4$; vi, H_2-Pd; vii, NaOMe-MeOH

Scheme 6

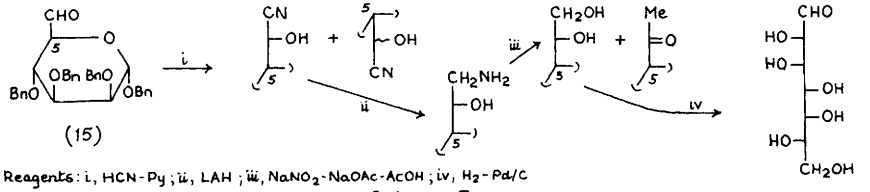
Synthesis of the higher sugars is currently attracting much interest and papers covering the range up to decoses have appeared. Reaction of D-mannose with nitromethane in the presence of sodium

methoxide followed by treatment with sulphuric acid gave D-glycero-D-galacto-heptose.[20] Sequential hydrogenation of the octynopyranose (14) using Lindlar catalyst and hydrogen, ozonolytic cleavage of the alkenyl products, and reduction of the ozonide gave methyl 2,3,4-tri-O-benzyl-α-D- and -L-glycero-D-gluco-heptopyranosides.[21]
Cyanide addition to the manno-dialdose (15) has been used in the syn-



(14)

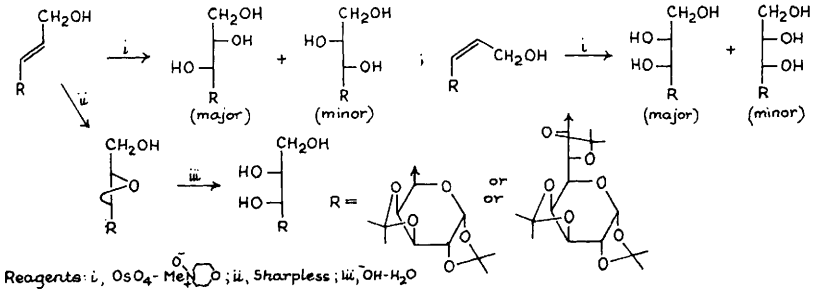
thesis of D- and L-glycero-D-manno-heptose. The addition was accompanied by epimerization at C-5, presumably by β-elimination and addition (Scheme 7).[22] L-glycero-D-manno-Heptose, a constituent of the inner region of lipopolysaccharides, has also been synthesized



Reagents: i, HCN-Py; ii, LAH; iii, $NaNO_2$-NaOAc-AcOH; iv, H_2-Pd/C

Scheme 7

by chain-extension of 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose using dithiane, the corresponding alditol being inverted to the required heptose by standard reactions.[23]



Reagents: i, OsO_4-Me; ii, Sharpless; iii, $OH-H_2O$

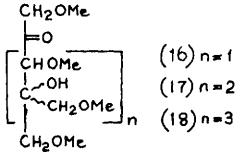
Scheme 8

A review on the occurrence and preparation of D-mannoheptulose has appeared.[24] Full papers have been published by Brimacombe's group

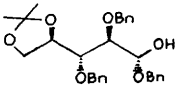
on their syntheses of octoses and decoses by ω-chain extension of dialdose derivatives to alkenyl derivatives which were then subjected to stereospecific hydroxylation procedures.[25-27] (See Vol. 19, p.6, refs. 14,15. Inadvertently the report indicated D-threo and L-erythro products as the major products; the correct data are shown in Scheme 8.)

Conventional degradations of the appropriate octoses were also used to prepare L- and D-glycero-D-manno-heptose.[28] The preparation and identification of aldolization products formed by treatment of 1,3-dimethoxy-2-propanone with aqueous sodium hydroxide at 5°C has been reported. The products included the branched-chain pentose, heptose, and nonose derivatives (16) - (18).[29]

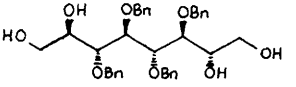
The synthesis of sugars by iterative, diastereoselective homologation of aldehydo-sugars with 2-trimethylsilylthiazole mentioned last year (see Vol. 19, p.5, ref. 11) has been extended up to nonose derivatives. The newly created chiral centre at C-2 invariably bore an erythro relationship to the C-3 substituent; thus, D-glyceraldehyde led to the D-allose derivative (19), and the meso-octitol (20) was obtained via the corresponding octose.[30]



(16) n=1
(17) n=2
(18) n=3

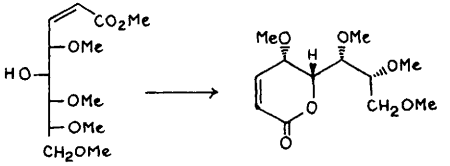


(19)



(20)

A Wittig reaction on aldehydo-2,4,5,6-tetra-O-methyl-D-glucose gave the Z-oct-2-enonic acid derivative (21), which yielded the lactone (22), an intermediate for synthesizing octoses.[31] Wittig

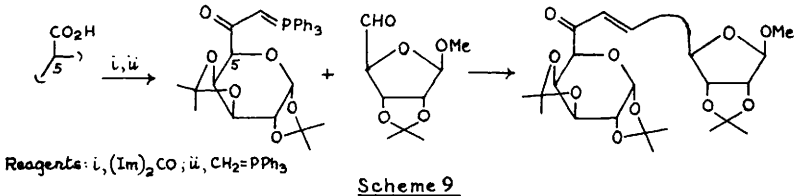


(21) (22)

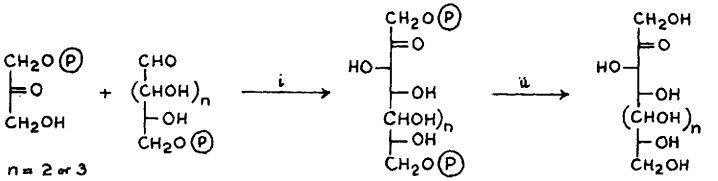
reagents prepared from sugars have also been used to synthesize potential intermediates for higher sugars; Scheme 9 illustrates such a synthesis, coupling two sugar units tail-to-tail, to give a dodecose derivative.[32]

Enzymic coupling of sugar phosphates by aldolase has been used to

prepare octoses and nonoses (Scheme 10). The method was shown to be suitable for coupling deoxy and amino-deoxy sugars.[33] The dianion

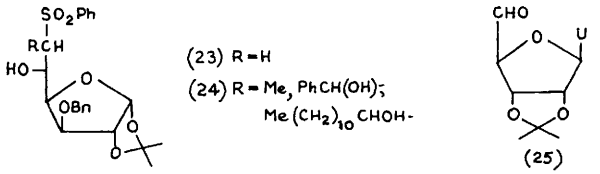


Scheme 9



Scheme 10

of the glucofuranosyl sulphone (23) has been reacted with carbon electrophiles to yield higher sugar sulphones (24). The same paper also reports chain extension of dialdehydo nucleosides such as (25) by means of Wittig reactions.[34]



Allosucrose, α-D-allopyranosyl-β-D-fructofuranoside, has been prepared from sucrose using an oxidation-reduction sequence to invert the C-3-hydroxy group.[35]

3 Physical measurements

The direct measurement of the rate of ring-opening of D-glucose by aldose reductase-catalyzed reduction has been reported. The results for this direct measurement of D-glucose and 5-thio-D-glucose support the prediction that base-catalyzed mutarotation proceeds primarily through the acyclic carbonyl intermediate for simple sugars.[36] The effect of cations on the anomeric equilibrium of D-glucose in aqueous solutions has been studied by Raman spectroscopy in the 950 - 800cm^{-1}

region. The calcium ion has a marked effect in shifting the equilibrium towards the α-anomer. The magnitude of this effect was found to decrease in the sequence $Ca^{2+} > Sr^{2+} \approx La^{3+} > Na^{+} \approx Zn^{2+} > Cd^{2+} \approx Mg^{2+} \approx K^{+}$ as determined by the proportion of the α-anomer present.[37] D-Idose in deuterium oxide exists as 13.5% α-furanose, 16.5% β-furanose, 35.9% α-pyranose, 33.4% β-pyranose, 0.5% aldehydrol and 0.1% aldehydo forms as measured with ^{13}C n.m.r. of ^{13}C-enriched compounds. For D-glycero-D-ido-heptose the corresponding proportions were 8.7, 15.5, 24.4, 50.8, 0.6, and 0.06%. The technique allowed the unidirectional rate constants for ring-opening and closing of the furanoses and pyranoses to be determined.[38] Isomer distribution of D-fructose in water, DMSO and pyridine has been determined by examination of ^{1}H n.m.r. intensities of the C-2 hydroxy protons. Experiments were carried out in [d_6]DMSO, or in other solvents by freezing the samples with liquid nitrogen and dissolving in DMSO with rapid determination of the n.m.r. spectrum. At 25° the β-furanose predominated in DMSO whereas in water and pyridine the most abundant form was the β-pyranose.[39] The rate constants for all the reactions in the interconversion of the pyranose, furanose, and aldehydo forms of 2-deoxy-D-erythro-pentose have been determined by n.m.r. methods.[40] Kinetic and thermodynamic parameters for the thermal and photochemical mutarotation of α-D-glucose in DMSO have been measured and a mechanism proposed.[41]

An investigation of the relationship between sweetness and structure of chlorinated sugars has been carried out using Fourier transform i.r. to examine the states of the hydroxy groups. It was concluded that the sweet compounds contained hydroxy groups which were not involved in hydrogen bonding and that chloro functions enhance sweetness by increasing lipophilicity.[42]

Enthalpies of solution of α-D-glucose, β-D-glucose, α-D-galactose, and α-D-mannose in water-DMF mixtures at 298.15K have been reported for the whole mol fraction region. Exothermic deviations from linear behaviour result from preferential hydrogen-bonding of functional groups and hydrophobic hydration of the apolar surfaces of the solute. Differences in solvation enthalpy of the four hexoses were related to differences in their conformations.[43] Results of calorimetric measurements of mean molar heat capacities of sugars have been reported. Derivatives of D-galactopyranose, DL-2,3,4-trideoxy-glycero-hex-2-enopyranose, and DL-ribopyranose were studied, and the heat capacity contributions of the pyranose rings in these sugars confirmed the existence of different energy levels found previously

from semi-empirical calculations for the different conformations of the pyranose ring.[44] Conformation entropies for a series of mono- and higher saccharides including O-methyl derivatives have been predicted from rotational prohibition rules and found to agree satisfactorily with known entropies of D-aldohexopyranoses.[45] The heats of dilution of aqueous solutions of cellobiose, maltose, trehalose, and melizitose have been determined by flow microcalorimetry, and the influence of urea in these solutions was studied. In some cases 'excess' thermodynamic properties could be determined.[46] Pyrolysis of glucose, maltose, cellobiose, amylose, and cellulose has been studied by thermogravimetry between 250 - 400° under helium at atmospheric pressure.[47] The mechanism of cryoprotection in living cells and liposome dispersions by mono-, di-, and tri-saccharides has been investigated by differential scanning calorimetry and Raman spectroscopy of aqueous sugar solutions at low temperatures, methods which determine the amount of 'unfreezable water' bound to the sugars.[48]

A kinetic study of the acetone-sorbose reaction on an ion-exchange resin, KU-23, showed that the reaction could be interpreted in terms of two types of water in the catalyst; one of these blocks the active sites while the other is involved in diluting the reactants.[49] A dielectric study of sorbed water on galactose has been carried out using a depolarization thermocurrent method on compressed pellets of hydrated galactose. The modes of binding of water molecules in the temperature range 80 - 300K and water contents between 2.2 and 20.8% were investigated; measurements revealed two dielectric dispersion regions, one attributed to reorientation of sorbed water. Three discrete relaxation mechanisms contribute to second dispersion at higher temperatures.[50] The hydrophobic properties of sugars and their implications in nutrition and food science have been reviewed.[51]

^{13}C-N.m.r. spin-lattice relaxation has been used to study the molecular motion of sucrose in water. Conformations of the sugar, which tumbles anisotropically, change with temperature and there are distinctly different rates and activation energies for the internal rotations of the three hydroxymethyl groups.[52] Two experiments on the crystallization of sucrose in cosmic space have been described. In one, the growth of single crystals was found to be eight times the rate on Earth,[53] while the other used zonal fusion with a temperature gradient to study the kinetics and the microtopography of sugar crystals compared to conditions on Earth.[54]

The nature of ester formation between borate and D-mannitol, D-glucitol, D-fructose, and D-glucose in aqueous solution at pH 6 - 12 has been elucidated using ^{11}B- and ^{13}C-n.m.r. spectroscopy.[55] Sugars have been transported against a concentration gradient in the artificial membrane system shown in Figure 1. The transportation is mediated by phenylboronic acid and a pH difference is used to drive accumulation of the sugar from the alkaline to the acid side. The sugars are carried through the dichloromethane 'membrane' as a boronate complex with a quaternary ammonium counter-ion.[56] Per-

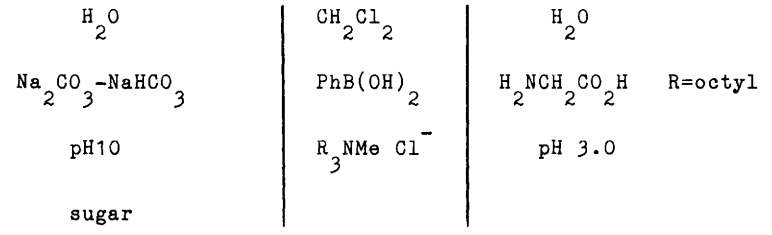


Figure 1

meations of glucose, lactose, and raffinose through poly(butylmethacrylate)-poly(L-glutamic acid) co-polymer membranes have been shown to be pH dependent. At low pH, glucose permeated faster than lactose, with raffinose slower still. Implications for sugar transport through biomembranes were mentioned.[57] Partition coefficients for partition of sugars between a polystyrene gel and aqueous solvents have been measured. The differential partition of monosaccharides was attributed to the hydrophobicity of the sugars, which increases in the order D-gal < D-glc < D-man < D-ara, D-xyl < D-rib, consistent with the order based on the free energy change for transfer of sugar molecules from water to 1-butanol.[58] The kinetics of the cathodic reduction of D-glucose have been determined using a rotating disc electrode.[59]

4 Isomerizations

There has been a ^{1}H n.m.r. study of the conversion of 2,3-*erythro*-aldoses into 2,3-*threo*-aldoses by methanolic potassium carbonate. The reactions proceed through hemiacetals.[60] D-Glucose, D-quinovose, and L-(or D-)rhamnose are rapidly epimerized at C-2 in the presence of $[Ni(H_2O)_2(tmen)_2]Cl_2$ (tmen = *N*,*N*,*N*'-trimethylethylenediamine). The

reaction was complete in 3 to 4 minutes at 60° in methanol. The manno-products (D-mannose, D-rhamnose) formed nickel(II) complexes which were isolable by gel permeation chromatography on LH-20, and from which the sugar could be released by acid hydrolysis.[61] The effects of several variables on the chemical changes undergone by D-glucose and D-fructose in acidic media, under conditions where 5-hydroxymethylfurfural is formed, have been studied. Reversion and degradation products were found.[62] Potassium hydroxide-catalyzed isomerization of D-[1-^{13}C]mannose under anaerobic conditions gave D-[1-^{13}C]glucose and D-[1-^{13}C]fructose as expected, but [6-^{13}C]glucose, [6-^{13}C]mannose, and [6-^{13}C]fructose were also found, possibly formed *via* 3,4-enediolates. Evidence for the latter came from observation of [1-^{13}C]sorbose and [6-^{13}C]sorbose in the reaction mixture.[63] A study of the adsorption of carbohydrates on anion exchangers, useful for conversion of glucose to fructose and lactose to lactulose, has been carried out. The ionization data, adsorption coefficients and heats of adsorption were determined.[64] A further paper details the diffusion coefficients on IRA 401, a gel type exchanger, and on IRA 938, a macroreticular type exchanger.[65] Sodium salts of epimeric 1-deoxy-1-nitro-octitols, obtained from nitromethane and D-*glycero*-D-*galacto*-heptose, on treatment with hydrogen peroxide-ammonium molybdate gave D-*erythro*-L-*gluco*- and D-*erythro*-L-*manno*-octose. Molybdate-catalyzed epimerization of the latter gave a mixture in which the former predominated. Both normally occur as pyranoses in aqueous solution, but complexation with molybdate induces furanoid structures.[66] A disadvantage of molybdate epimerization reactions is that there are often side-reactions in which C-3 epimers are produced in admixture with the desired C-2 epimers. These side-reactions may be controlled by using the paramolybdate form of an anion exchange resin together with the formate form of the same resin. The latter scavenges unbound molybdate and paramolybdate anions that appear to be responsible for the side-reactions.[67]

5 *Oxidation*

A review on metal-ion oxidations of reducing sugars and kinetic approaches to mechanisms has appeared.[68]

The kinetics of the oxidation of hexoses, pentoses, hexitols and pentitols by vanadium(V), cerium(IV), manganese(III) and thallium-(III) in aqueous acidic media have been claimed to proceed *via* a

free radical mechanism. The kinetics and mechanism of the cerium(IV) oxidation of glucose and sorbose in aqueous acid have been described.[70] The oxidation of D-altrose by cerium(IV) perchlorate in perchloric acid medium is first order in sugar and oxidant; there is a positive salt effect but no evidence for initial complexation was found.[71] The kinetics and mechanism of the thallium(III) oxidation of melibiose in the presence of sulphuric acid in aqueous acetic acid at constant ionic strength have been studied. The reaction, which is second order overall and shows a primary salt effect, produces gluconic acid and galactose.[72] A study of the kinetics of the oxidation of ribose by potassium bromate in an acid medium has been carried out and a mechanism proposed.[73]

Pyridinium fluorochromate oxidized D-glucose to yield D-arabinose and formic acid in a second order reaction catalyzed by acid. The rate of oxidation of the produced arabinose is insignificant under kinetic conditions.[74] The kinetics of oxidation of D-galactose by *N*-bromosaccharin in aqueous acetic acid show the reaction to be first order in oxidant and sugar; the product is D-galactonic acid.[75]

Electrolytic oxidation of sucrose, maltose and glucose on a lead-(II) oxide-coated titanium mesh electrode has been studied in connection with electrochemical treatment of effluents.[76] Hydroxide radicals are the effective oxidant in the stepwise photoanodic oxidation of D-glucose to carbon dioxide on a polycrystalline zinc oxide electrode in alkaline solution.[77] The electrocatalytic oxidation of D-glucose at a glucose oxidase-immobilized benzoquinone-mixed carbon paste electrode has been studied and the importance of various concentration parameters on the oxidation examined.[78] A comparative study of the electrocatalytic influence of underpotential heavy metal adatoms on the anodic oxidation of monosaccharides on platinum in acid solutions has been carried out.[79] In water at neutral pH, D-fructose is oxidised photochemically in the presence of iron(III) and manganese(II) ions. The main product is D-erythrose.[80]

Gamma radiation damage in solid glucose and lactose has been studied by i.r. and u.v. spectral methods and a mechanism for radiolytic oxidation proposed.[81]

Bacterial oxidation of L-mannitol and L-glucitol has been used to prepare L-fructose and D-sorbose respectively. The bacterium called MD 13 contains a novel polyol dehydrogenase which preferentially oxidizes L-alditols. The reaction was also applied to pentitols.[82]

Two methods of ozonolysis of glucose, kinetic-static and ozone-bubbling, have been compared for kinetic measurements and the former

found to be the most suitable.[83]

The platinum-catalyzed oxidation of isosorbide is referred to in Chapter 18.

6 Other aspects

Anomers of D-glucose, xylose, galactose, mannose, arabinose, maltose, and cellobiose have been separated by HPLC on cation-exchange resin columns in the calcium ion form using water as eluent at 1.5°C. In each case the 1,2-cis-diol had longer retention times due to complexation.[84]

Various methods for enriching tetroses, pentoses and hexoses with oxygen isotopes have been described. Approaches included exchange between $H_2{}^{18}O$ and the aldehyde group of an aldose, exchange of O-1 with O-2 of both of the 2-epimeric aldoses formed by molybdate resin epimerization, and chain extension using cyanide addition. All sixteen aldohexoses enriched at five out of six oxygen atoms and all eight aldopentoses enriched at two out of four oxygen atoms were prepared and characterized by g.c.-mass spectroscopy.[85]

Hydrolysis of sugar cane bagasse with hydrochloric acid promoted by metal cations has been investigated. Lithium chloride was found to be very effective with commercial grade hydrochloric acid in the hydrolysis of prehydrolysed sugar cane bagasse, most of the sugar oligomers being hydrolyzed to monomers in 10 - 20 minutes. Longer times lead to decomposition and reversion products. Zinc chloride is a milder promoter which requires post hydrolysis even after 30 min at 50°C but does not decompose the sugars. Prolonged reaction time and post-hydrolysis gave the highest sugar yields. Iron(III) chloride was largely ineffective in the hydrolysis of cellulose but was a good promoter of hydrolysis of sugar oligomers.[86]

Irradiation of D-glucose or lactose with ultrasound produced malonaldehyde which can polymerize if the conditions are neutral or acidic. The process may be important in food manufacture where ultrasound is used to produce cavitations.[87]

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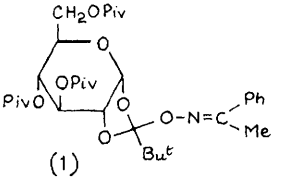
3
Glycosides and Disaccharides

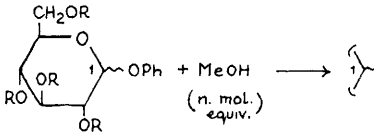
1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.- A very useful review has appeared on newer methods for glycoside formation, particularly those based on O-alkylation and on the use of glycosyl trichloroacetimidates, sulphonium salts and fluorides.[1] A shorter paper has dealt with the use of silicon-containing compounds as glycosylation catalysts.[2]



(1)

The interesting new glycosyl donor (1), obtainable by silver ion catalysed condensation of acetophenone oxime and tetra-O-pivaloyl-α-D-glucopyranosyl bromide, is an improved glycosylation reagent of the orthoester type. Together with catalytic boron trifluoride, it affords excellent access to β-D-glucopyranosides of a range of complex alcohols.[3] A more unconventional route to glycosides uses aryl glycosides and their substituted derivatives which react with alcohols under mild electrolytic conditions. Acetonitrile and lithium perchlorate were used as solvent and electrolyte; oxidation potentials of aryl glycosides are 1-2 v, and slightly higher voltages were used to effect the displacement reactions. Some results are illustrated in Scheme 1. Secondary and tertiary



	R		n.	Yield	α : β
1.	Ac	β	1·4	79%	3 : 97
2.	Bn	β	1·6	92%	35 : 65
3.	H	β	1·0	77%	75 : 25
4.	H	α	1·3	93%	79 : 21

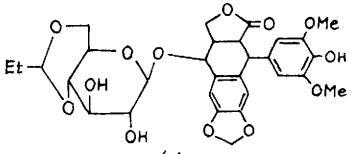
Scheme 1

alcohols react with less efficiency; α- and β-1,6-linked disaccharides were however produced in 65% yield but with poor

anomeric selectivity.

Phase transfer reaction of unsubstituted anomeric hydroxy compounds with dimethyl sulphate gives α,β-ratios of methyl glycosides which are determined by the relative acidities of the anomeric sugars. Alcohols in the solvent cause the formation of increased proportions of β-anomers in the D-glucose and D-galactose series.[5]

2,3,4,6-Tetra-O-benzyl-α-D-glucose treated with alcohols, pyridine and trimethylsilyl triflate gave good yields of α,β-anomeric glycosides in various solvents. Alternatively, 2,3,4-tri-O-benzyl-D-glucose gave good α-selectivity in dichloromethane, methyl 2,3,4-tri-O-benzyl-β-D-glucoside affording 72% of the α,β-1,6-linked disaccharides in the ratio 6:1.[6] 2-Amino-2-deoxy-4,6-O-ethylidene-α- and β-D-glucosyl-, the 2-methylamino-L-analogue and the 3-amino-3-deoxy-4,6-O-ethylidene-β-D-glucopyranosyl- and other analogues of etoposide (2), an anticancer podophyllotoxin compound, have been made by coupling (BF_3 catalysis) the partially protected aglycone with the appropriate sugar derivatives having a free-hydroxy group at C-1.[7,8]



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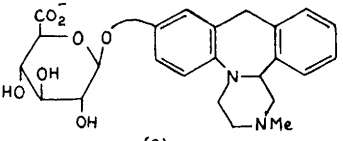


(3)

α-Glycosidation of anthracycline aglycones has been effected with 3-N-trifluoroacetyl-1,4-bis-O-(p-nitrobenzoyl)-L-daunosamine using trimethylsilyl triflate as catalyst,[9] and a β-glucoside of (-)-steganol has been made by a transglycosylation process with boron trifluoride as catalyst.[10]

The trichloroacetimidate method has been employed in the preparation of the glucosides of 1,2-dipalmitin,[11] sphingosine,[12] digitoxigenin[13, 13A] and of the glucuronide (3) of the antidepressant mianserin and its 6-aza analogue.[14]

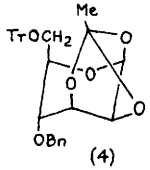
1-Thio compounds continue to attract attention as glycosylating agents. Thioglycosides can be activated under mild conditions by use of copper(II) bromide and catalytic tert-butyl ammonium bromide to give high yields of either 1,2-cis- or 1,2-trans-glycosides from primary or secondary alcohols. Nitromethane or 1,2-dichloroethane were used as solvents.[15] Perbenzylated glucosyl xanthates, made conventionally from the 1-hydroxy compound, on treatment under vacuum with alcohols and catalytic boron trifluoride gave glycosides in very high yields. Reactive alcohols gave α,β-mixtures, but less

reactive alcohols afforded mainly α-products. Small amounts of methyl 1-thioglycosides were formed as by-products.[16]

4-O-Benzyl-1,2-O-(1-cyanoethylidene)-β-L-rhamnose, with an exo-cyano group, can be prepared in 4 stages from a methyl L-rhamnopyranoside derivative, and is useful in the synthesis of O-antigenic polysaccharides of Shigella flexneri.[17] Also in the area of glycosylating agents based on bicyclic systems, α-D-glucopyranose cholesteryl orthoacetate has been employed to cause glucosylation of the steroidal epoxydammaranetriol.[18]

A review has appeared on the synthesis of fluorinated carbohydrates including glycosyl fluorides and their use in the preparation of O- and C-glycosides.[19] The use of tri-O-benzyl-α- and β-L-rhamnopyranosyl fluoride in the presence of tin(II) chloride or silver perchlorate as glycosylating agents have been examined. Both anomers gave α-linked disaccharide products with secondary monosaccharide alcohols.[20]

In connection with studies of the carbohydrate part of bleomycin [2-O-(3-O-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose], several key D-mannose compounds have been prepared including the orthoester (4) and the glycosyl chloride (5).[21] Other glycosyl chlorides have been used in the preparation of the glycosides (6)[22] and (7).[23]



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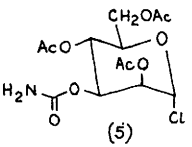

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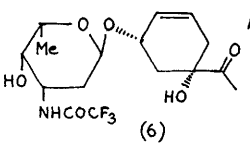

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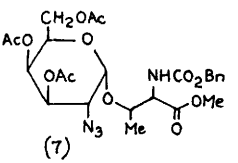
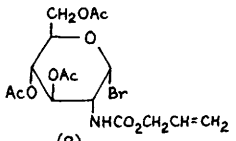


(7)

Glycosyl bromides continue to hold primary place as glycosylation reagents; Tl^{+}, Co^{2+} and Cd^{2+} salts of zeolites 4A and 3X are suitable solid phase promoters of glycosylation as alternatives to Ag^{+} and Hg^{2+} salts.[24] Comparisons have been carried out on the effects of silver carbonate, silver triflate and silver tetrafluoroborate as promoters of condensation between tetra-O-acetyl-α-D-glucopyranosyl and -galactopyranosyl bromide and simple alcohols and 8-methoxycarbonyloctanol. Optimum yields of β-glycosides were obtained using the tetrafluoroborate alone or in the presence of s-collidine in acetonitrile.[25] Benzoylated 2-deoxy-β-D-glycosyl bromides used with silver zeolite as catalyst gave 54-84% yields of deoxydisaccharides and 2-deoxysteroidal glycosides; α,β-ratios varied from 0.25 to 1.18.[26] An improvement in the oxazoline and phthalimido methods of making β-glycosides of 2-amino-2-deoxy-D-glucopyranose has been made by use of compound (8) together with

mercury(II) cyanide; yields were greater than 80% including with sugar alcohols.[27]



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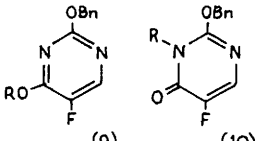


(9) (10)

R = tetra-O-Ac-β-D-Glc-p

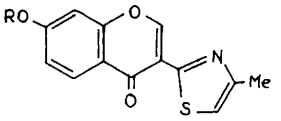
Relatively simple glycosides to have been made are trifluoromethyl tetra-O-methyl-D-glucopyranoside, by use of tris(dimethylamino)sulphonium trifluoromethoxide and the glycosyl bromide,[28] and the β-glucopyranoside (9) of 2-O-benzyl-5-fluorouracil by use of acetobromoglucose and a phase transfer catalyst. It however was formed together with the N-substituted isomer (10).[29]

Koenigs Knorr glycosylations of several natural products have been reported: steroidal alcohols by use of tetra-O-pivaloyl and tetra-O-(o-toluoyl)-α-D-glucopyranosyl bromide, the former giving β-glucosides with no orthoesters and therefore to be preferred;[30] β-sitosterol,[31] 4-hydroxyestriol (3-, 4-, 16- and 17-glucuronides) and 4-hydroxyestradiol (17-glucuronide);[32] a partially protected flavone (to give pedalin, 3',4',5,6-tetrahydroxy-7-methoxyflavone-6-O-β-D-glucopyranoside);[33] dammarane triterpenoids;[34] and 18-β-glycyrrhetol (3- and 30-β-D-glucuronosides).[35] A review on "recent developments in the total synthesis of macrolide antibiotics" includes references to several types of glycosylations applied in this field.[36] Several 3-O-β-D-furanosides of digitoxigenin, including those involving 5-amino-5-deoxy-D-ribose, 3,6-anhydro-D-glucose and 3,6-dideoxy-3,6-imino-D-glucose, have been reported. The compounds showed weak to moderate cardiotonic activity.[36a]

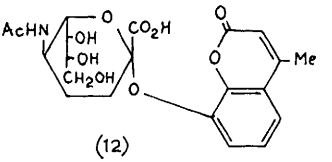
Several reports have appeared on the synthesis of aryl glycosides; a method using 3,4,6-tri-O-acetyl-2-deoxy-α-D-arabino- or -lyxo-hexopyranosyl dialkyldithiophosphate (obtainable from tri-O-acetyl-D-glucal and -galactal) was used to obtain o-nitrophenyl and p-nitrophenyl 2-deoxy glycosides.[36b] Optimum conditions for preparing 1,2-trans-related pyranosyl compounds using phosphoric acid or sugar peracetates have been determined using ^{13}C n.m.r. methods,[37] and furanosyl phenyl and p-nitrophenyl trans-related glycosides of D-glucose, D-galactose, L-arabinose and D-ribose have been obtained from 1,2-trans-related acetylated glycosyl fluorides using the sodium phenates in ethanol.[38] p-Nitrophenyl β-D-galactofuranoside has been made from D-galactono-1,4-lactone tetrabenzoate via the sugar pentabenzoate.[39] 2,3,4,6-Tetra-O-benzyl-D-glucose, activated

with DCC, offers general access to aryl glucopyranosides.[40]

Acetobromoglucose condensed with 2,4-dihydroxybenzaldehyde gave the 4-substituted, β-linked product from which 3-methoxy-4-(2'-nitro-vinyl)phenyl β-D-glucoside was produced as a potential chromogenic substrate for use as a glucosidase assay substrate.[41] β-D-Glucosides of a range of hydroxybenzoic and hydroxycinnamic acids found in berries and vegetables have been prepared and quantitatively assayed in their natural sources.[42] During the reaction of salicylic acid with a D-glucuronic acid-based glycosyl bromide, both the phenyl glycoside and the product of substitution at the carbohydrate were formed.[43] Acetylated glycosides of 2-hydroxy-1,4-naphthoquinone have been made as potential fungicides.[44] The glycosides (11)[45] and (12)[46] have been synthesized; the latter, the



(11) R = β-D-Glc,-Gal,-Ara



(12)

4-methylumbelliferyl α-glycoside of N-acetyl-4-deoxyneuraminic acid, is resistant to bacterial sialidases.

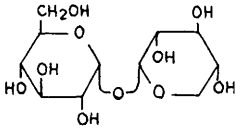
Specific, simple O-glycosides to have been reported are allyl β-D-mannopyranoside (from 4,6-di-O-acetyl-2,3-O-carbonyl-α-D-mannopyranosyl bromide)[47] and formylmethyl α-D-galactopyranoside (by reductive ozonolysis of the allyl glycoside) which was coupled to chitosan to give a high viscosity product.[48] A further product from alteration of the aglycone is O-β-D-xylopyranosyl-L-serylglycyl-L-isoleucine-glycine which was made from an N-protected O-β-D-xylopyranosyl-L-serine.[49]

Transglycosylation using a β-galactosidase from *Aspergillus oryzae* from phenyl β-glycosides gave β-glycosides of racemic α-phenylethanol and related glycols. The diastereomers produced were separable by chromatographic methods.[50]

1.2 Synthesis of Disaccharides and Their Derivatives.- Reference is made to the synthesis of disaccharides from thioglycosides in Section 2 of this Chapter. In the area of non-reducing disaccharides, a set of sucrose derivatives have been prepared by enzymic methods as follows: i) 1'-azido-1'-deoxysucrose from 1-azido-1-deoxy-D-fructose and UDPG with a sucrose synthetase, ii) 6'-deoxy-6'-fluorosucrose and 6'-deoxysucrose from 6-modified D-glucoses and UDPG with glucose isomerase and sucrose synthetase, and

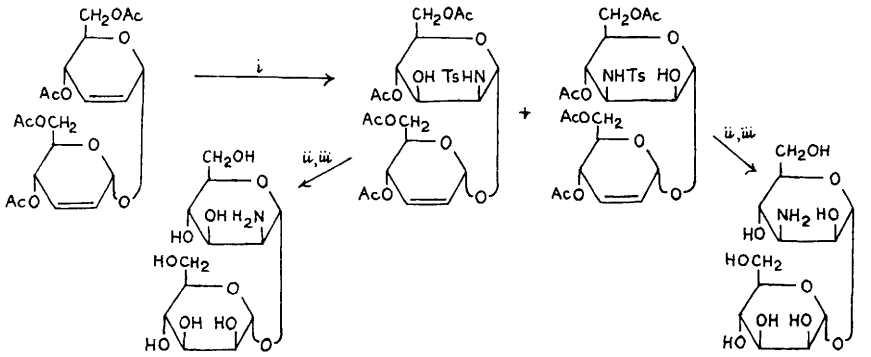
iii) 4'-deoxy-4'-fluorosucrose from 4-deoxy-4-fluoroglucose with kinase, followed by isomerase and phosphatase to give 4-deoxy-4-fluoro-D-fructose, which was treated with sucrose synthetase. The binding of the modified sucroses to a sucrose carrier protein was investigated.[51]

The anomeric geometries of 6-O-methanesulphonyl-2,3,4-tri-O-methyl-α-D-glucopyranosyl 6-O-methanesulphonyl-2,3,4-tri-O-methyl-α-D-glucopyranoside and its β,β-anomer were compared with data for 13 analogous non-reducing disaccharides in a paper reporting the X-ray structures of these two named compounds.[52] Trehalase has been found to catalyse the condensation between β-D-glucopyranosyl fluoride and α-D-xylopyranose to give the α,α-linked compound (13). α-D-Glucopyranosyl fluoride underwent simple hydrolysis.[53]



(13)

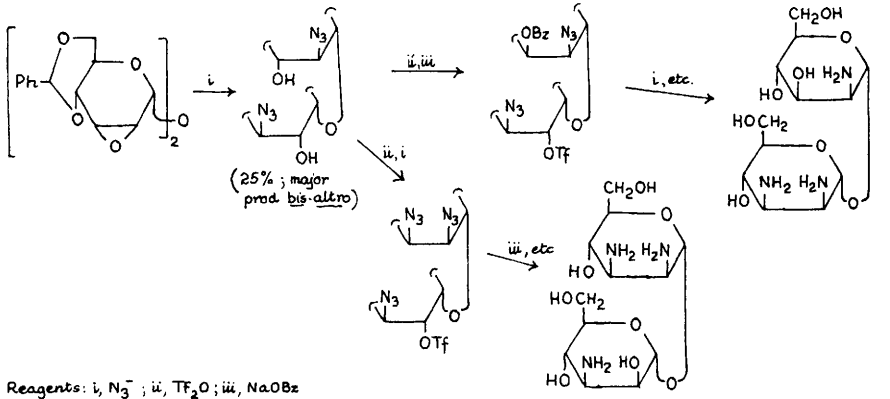
Aminosugar-containing non-reducing disaccharides have been produced from unsaturated and epoxy-containing precursors as indicated in Schemes 2[54] and 3.[55]



Reagents: i, OsO_4-chloramine T; ii, OsO_4; iii, Na-NH_3(l)

Scheme 2

Reducing disaccharides are now treated according to the non-reducing moiety. Tetra-O-acetyl-β-D-glucopyranosyl fluoride with titanium tetrafluoride affords mainly β-linked products when condensed with, e.g., 1,2:3,4-di-O-isopropylidene-α-D-galactose. The benzylated analogue gives mainly β-products in acetonitrile, but α-anomers in ether. Various other glycosyl fluorides were also studied in disaccharide synthesis.[56] (See also ref.20). Glucosyl-ation of methyl 4,6-O-benzylidene-α- and -β-D-glucopyranoside with

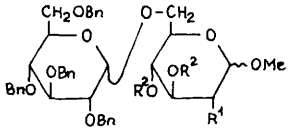


Scheme 3

tetra-O-benzyl-α-D-glucopyranosyl bromide gave α-products linked through 0-2 and 0-3 in the ratio 1:1.6 for the α-glycoside and 1:1.1 for the β-anomer.[57] Reaction between acetylated 1,2-O-cyanoethylidene derivatives of 6-O-methyl and 6-deoxy-α-D-glucopyranose and 3-O-trityl- and 4-O-trityl-D-glucose tetracetates in the presence of catalytic trityl perchlorate gave mixtures of the 3- and 4-linked compounds, respectively, with unexpectedly high proportions of α-bonded disaccharides. In the case of 3-O-trityl-α-D-glucopyranose tetraacetate the α-(laminaribiose) and β-(nigerose) linked products were obtained in the ratio 64:36 (77% yield), and the isomeric β-starting material gave analogous disaccharides in the ratio 54:46.[58]

The properties and some uses of dodecyl β-maltoside which has a meso phase identical to that of the corresponding glucoside have been discussed.[59] Studies of the coupling of substituted α-D-glucopyranosyl and -galactopyranosyl bromides with 3-O-acetyl-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose in the presence of insoluble silver salts indicate that the galactosyl bromides lead to higher proportions of β-disaccharides. 4-O-Acyl groups in the glycosylation reagents also increases β,α-ratios relative to 4-O-alkyl groups, whereas 3- and 6-O-acyl functions reduce this ratio.[60] The 8-methoxycarbonyl glycoside of 4-O-(3,6-di-O-methyl-β-D-glucopyranosyl)-2,3-di-O-methyl-α-L-rhamnose has been prepared using the Koenigs Knorr and Helferich methods, and a related compound has been bound to bovine serum albumin for serological studies.[61] In related work the following methyl ethers of 4-O-β-D-glucopyranosyl-L-rhamnose were synthesized as precursors of trisaccharide units of phenolic glycolipid antigens of *Mycobacterium leprae*: 2,3,3',6-tetramethyl, 2,3,6'-trimethyl, 2,3-dimethyl.[62] The 1,6-α-linked

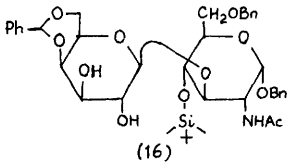
glycoside (14) has been synthesized by use of the β-1-thioglycoside



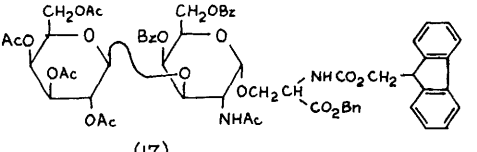
	R^1	R^2
(14)	OBn	Bn (β-anomer)
(15)	NHAc	Me (α-anomer)

and dimethyl(methylthio)sulphonium triflate[63] and the amino-compound (15) by DCC activation of 2,3,4,6-tetrabenzyl-D-glucose.[40]

2-O-α-D-Galactopyranosyl-L-rhamnose and 2-O-α-D-galactopyranosyl-D-mannose have been synthesized,[64] and the disaccharide (16), a synthon for H, A and B-type I blood group oligosaccharides, has been prepared by selective glycosylation of benzyl 2-acetamido-6-O-



(16)



(17)

benzyl-2-deoxy-α-D-glucopyranoside.[65] In related work the disaccharide derivative (17) has been used in glycopeptide synthesis. The N- and C-aminoacid termini can be released selectively to produce peptides carrying β-D-Galp-(1→3)-α-D-GalpNAc units.[66]

In the area of 1→4 linked compounds, the 3-O-methyl, 3-C-methyl and 3-deoxy derivatives of methyl 4-O-α-D-galactopyranosyl-β-D-galactopyranoside have been made by glycosylation of methyl 6-O-benzyl derivatives prepared from the corresponding 4,6-O-benzylidene acetals.[67] Acetobromogalactose and benzyl 2-acetamido-6-O-benzyl-2-deoxy-α-D-glucopyranoside gave 49% of the 1→4, β-linked disaccharide and 7% of the 1→3 linked analogue.[68]

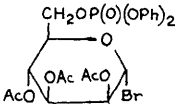
Condensation between tetra-O-acetyl-β-D-galactofuranosyl chloride and allyl 2,3,6-tri-O-benzyl-β-D-galactofuranoside gave access to 5-O-β-D-galactofuranosyl-D-galactofuranose, the carbohydrate moiety of the helminthosporoside from Helminthosporium sacchari.[69]

2,3-Epoxypropyl O-β-D-galactopyranosyl-(1→6)-β-D-galactopyranoside has been prepared as a potential affinity label for 1,6-linked-β-D-galactopyranan-binding monoclonal antibodies.[70]

Methyl 2-O-, 3-O-, and -4-O-α-D-mannopyranosyl-α-D-mannopyranoside and related compounds have been prepared by enzymic methods,[71] and 8-methoxycarbonyloctyl 2-O-α-D-mannopyranosyl-α-D-mannopyranoside and related substances by use of tri-O-acetyl-1,2-O-(1-methoxyethylidene)-β-D-mannopyranose.[72] 2-O-(3-O-Carbamoyl-α-D-mannopyranosyl)-L-gulose, the carbohydrate moiety of bleomycin, has been made by use of 2,4,6-tri-O-acetyl-3-O-carbamoyl-α-D-mannopyranosyl

chloride and 1,6-di-O-acetyl-3,4-di-O-benzyl-β-L-gulose; several related compounds were also obtained including 1,6-di-O-acetyl-3,4-di-O-benzyl-2-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-L-gulose, which is a precursor for decarbamoyl bleomycin.[73]

Reports on the synthesis of methyl 3-O-α-[74] and β-[75] D-mannopyranosyl-α-D-mannopyranoside have appeared, the former also describing p-nitrophenyl and allyl analogues. Unusually, a glycosyl bromide incorporating a protected phosphate ester (18) has

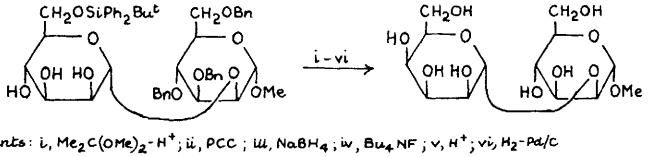


(18)

been used to obtain 1,3- and 1,6-linked D-mannopyranosyl disaccharide 6-phosphates.[76] p-Chlorophenyl and p-nitrophenyl 6-O-β-D-mannopyranosyl-β-D-mannopyranoside and the β-1,2-linked isomers have been isolated as by-products from the hydrolysis of the corresponding aryl β-D-mannosides with β-mannosidase from guinea pig liver.[77]

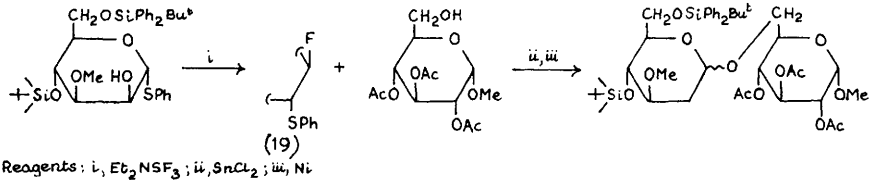
A procedure for obtaining methyl 2-O- and 3-O-α-D-talopyranosyl-α-D-mannopyranoside from derivatives of the dimannose analogues is illustrated in Scheme 4.[78]

A highly novel and potentially very useful approach to 2-deoxy-sugar disaccharides depends on compound (19), the preparation and application of which are illustrated in Scheme 5. Steric control



Reagents: i, $Me_2C(OMe)_2$-H^+; ii, PCC; iii, $NaBH_4$; iv, Bu_4NF; v, H^+; vi, H_2-Pd/C

Scheme 4

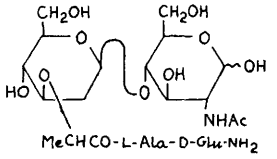


Reagents: i, Et_2NSF_3; ii, $SnCl_2$; iii, Ni

Scheme 5

was possible by choice of solvent, ether at -15°C affording the β-linked product in high yield, dichloromethane at the same temperature giving the α-analogue in high yield.[79] The specific 2-deoxy disaccharide peptide (20), which is a part of a bacterial cell wall peptidoglycan, has been reported.[80]

Methyl 2-O-α-L-rhamnopyranosyl-α-L-rhamnopyranoside, and the L-lyxo- and -L-mannopyranosyl analogues have been prepared,[81] and glycosylation of 1,2-O-cyanoethylidene-β-L-rhamnopyranose gave the α-1,4- and α-1,3-linked O-α-L-rhamnopyranosyl-1,2-O-cyanoethylidene-β-L-rhamnopyranoses in 41 and 20% yield, respectively, together with a small proportion of the disubstituted product.[82] Standard methods have been used to obtain 3-O-α-L-rhamnopyranosyl-β-L-arabino-pyranoside and 5-O-α-L-rhamnopyranosyl-β-L-arabinofuranoside.[83]



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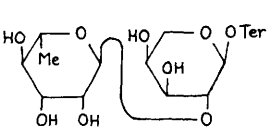

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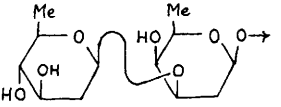
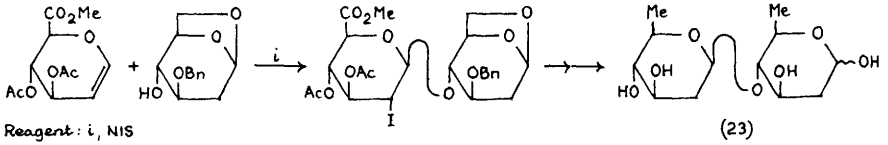


(22)

Thermal degradation of the L-rhamnose-containing disaccharide unit (21) in a triterpenoid glycoside gives the same products of sugar-aglycone and sugar-sugar bond cleavage as would be produced by acidic hydrolysis.[84]

Disaccharides having 2,6-dideoxyhexose units at the non-reducing termini are important because of their occurrence in antibiotics. The disaccharide unit (22) of mithramycin has been shown by Koenigs Knorr synthesis and 2D-n.m.r. analysis to be the β-1,3-linked compound.[85] During this work the 1,4-linked isomers were also produced and the analogue (23), the terminal disaccharide of the

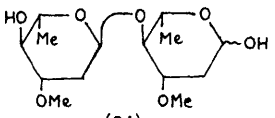


Reagent: i, NIS

(23)

Scheme 6

orthosomycins, has been prepared as indicated in Scheme 6.[86] The controlled degradation of avermectin B_{1a} gave compound (24).[87]



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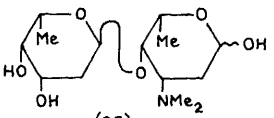
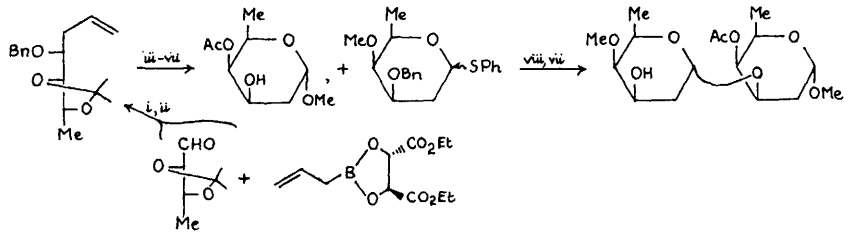


(25)

The L-sugar disaccharide (25), found in the anthracycline musettamycin, has been synthesized,[88] and a related D-compound, the AB disaccharide unit of olivomycin A, has been obtained as outlined in Scheme 7.[89]

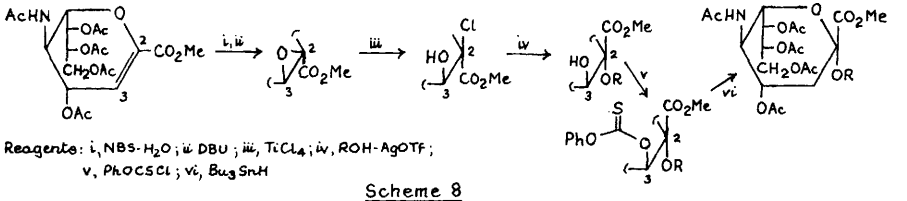
N-Acetylneuraminic acid has been glycosidically linked to O-6 of



Reagents: i,(-78°c); ii, BnBr-NaH; iii, H^+; iv, O_3; v, MeOH-H^+; vi, Ac_2O-Py; vii, H_2-Pd/C; viii, NBS

Scheme 7

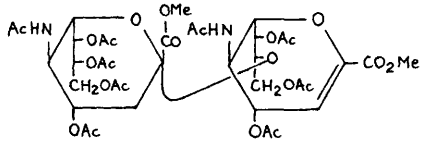
methyl β-D-galactopyranoside,[90] 0-5 of 2,3-0-isopropylidene-D-ribono-γ-lactone and 0-5' of 2,3-0-isopropylidene-D-ribofuranosyl nucleosides.[91] In general α,β-mixed products were obtained. An ingenious method of making α-glycosides is illustrated in Scheme 8;[92]



Reagents: i, NBS-H_2O; ii DBU; iii, $TiCl_4$; iv, ROH-AgOTf; v, PhOCSCl; vi, Bu_3SnH

Scheme 8

the paper described various disaccharide derivatives while in a preceding paper compound (26) and its 9-bonded isomer are noted as having been prepared by this method.[93]



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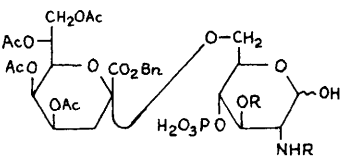
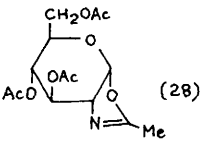


(27) R = C_{14}-O-C_{14} or C_{14}-O-C_{12} lipids

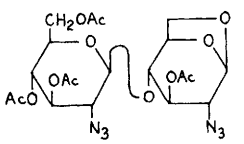
The tetraacetyl-3-deoxy-D-manno-2-octulosonic acid (KDO)-D-glucosamines (27), which are analogues of lipid A, have been synthesized and shown to have mitogenic activity like that of lipid A.[94]

Compound (28) is a key glycosylating reagent for making disaccharides having 2-amino-2-deoxy-D-glucose at the non-reducing end;

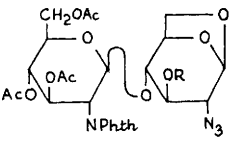


(28)

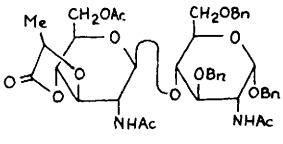
a new method of preparing it starts with the peracetate which is treated with trimethylsilyl triflate.[95] A range of such disaccharides (or precursors) have been reported, several having modified 2-amino-2-deoxy-D-glucose units at the reducing ends also. These include compounds (29),[96] (30),[97] (31) and (32),[98] (33),[80] (34)[99] and (35), which is an intermediate for lipid A synthesis.[100]



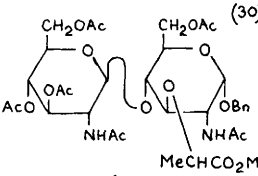
(29)



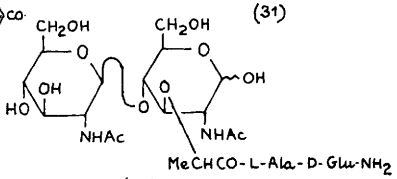
(30) R=MeO-C6H4-CO-



(31)



(32)



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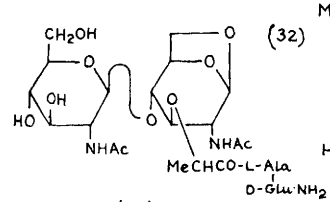

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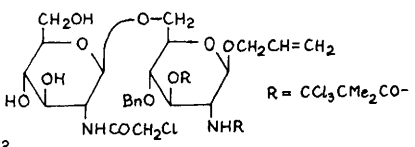


(35)

Other glucosamine-based compounds to have been described are: 6-O-(2-deoxy-2-N-octanoylamino-β-D-glucopyranosyl)-D-galactose,[101] 1-O-acetyl-2-O-(3-O-acetyl-4,6-di-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3,4-di-O-benzoyl-α-L-rhamnopyranose,[102] and 4-O-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-D-ribitol.[103]

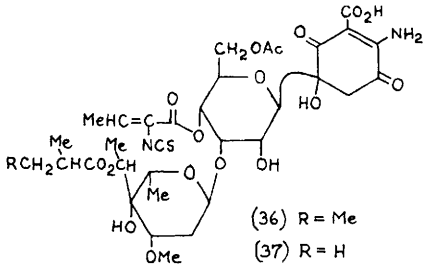
Disaccharides with amino-sugar non-reducing termini other than D-glucosamine to have been reported are: 4-O-(2-azido-2-deoxy-D-xylopyranosyl)-2-azido-2-deoxy-D-xylopyranose [104] and phenyl 2-O-(3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)-β-D-glucopyranoside.[105]

^{13}C N.m.r. spectroscopy has been used to confirm the structures of the aldobiouronic acids 2-O-β-D-glucopyranosylurono-D-mannose and 6-O-β-D-glucopyranosylurono-D-galactose.[106]

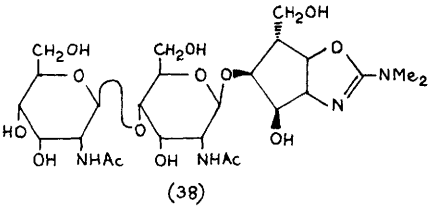
Pentose derivatives to have been reported are p-nitrophenyl 6-O-α- and 6-O-β-D-xylopyranosyl-β-D-glucopyranoside,[107] methyl β-D-xylobioside (a 2D n.m.r. study),[108] and six of the eight possible methyl 3- or 4-O-α- or β-L-arabinopyranosyl-α- or β-L-arabinopyranosides.[109]

1.3 O-Glycosides Isolated from Natural Products.- As always, only compounds having notable features in the carbohydrate portions are noted.

The paulomycins A and B have been shown to be (36) and (37), i.e., to contain a D-allose and a branched-chain sugar within their



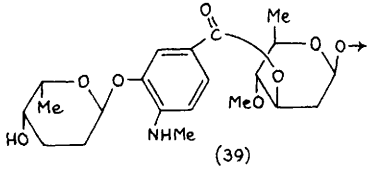
(36) R = Me
(37) R = H



(38)

structures. Structural elucidation depended on an X-ray analysis of a derivative of the former from which the unsaturated ester group had been cleaved.[110] The insect chitinase inhibitor allosamidin (38) has been isolated from a Streptomyces.[111]

Another Streptomyces metabolite, the antifungal notonesomysin A, is a macrocyclic lactone carrying the unusual side chain (39).[112]



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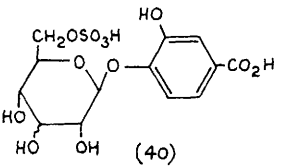
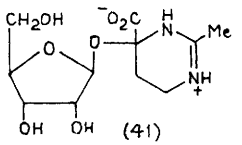


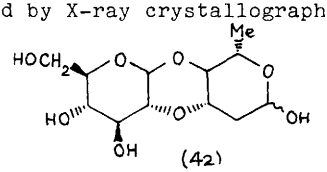
(40)

A further set of aromatic glycosides to have been encountered (from the honey locust), and synthesized, are 6-sulphates of D-glucosides or D-allosides, e.g., (40).[113]

Rhizolotine (41), an unusual nucleoside analogue, has been isolated from root nodules of Iotus tenius inoculated with Rhizobium loti, and characterized by X-ray crystallography.[114]



(41)

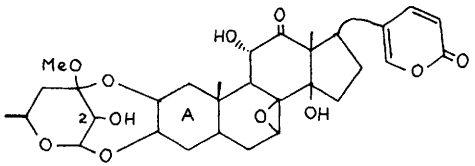


(42)

The novel disaccharide anhydride wilforibiose (42) has been isolated from the acidic hydrolysate of a plant glycoside. The structure previously reported (Vol.18, Chapter 12, ref. 2) has been corrected on the basis of the X-ray analysis of the α-tetra-acetate.[115]

S. African plant toxins have been found to have the novel

glycosidic structures (43)[116] and (44).[117] Several related com-



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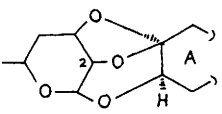


(44)

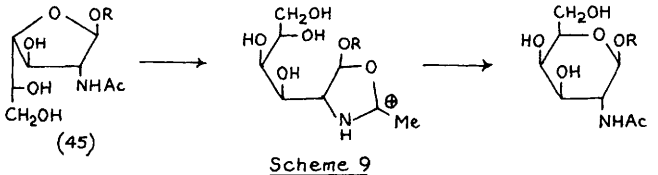
pounds were also characterized; in some cases the carbohydrate carbon-2 of (43) was present as a ketone function.

1.4 Hydrolysis and Other Reactions and Features.- A linear relationship exists between bond lengths and ease of hydrolysis for a wide range of unsymmetrical acetals, including aryl α-D-glucosides (the C-1–O-1 bond in these cases).[118]

By use of labels at C-1 (^{2}H and ^{13}C), C-2 (^{2}H), C-5 and the leaving group (^{2}H and ^{18}O), kinetic isotope effects have been measured for the perchloric acid catalysed hydrolysis of methyl α- and β-D-glucopyranoside, and these and other studies were used to describe unimolecular transition states in a thorough and detailed analysis.[119] The hydrolysis of cellobiose as a model for cellulose has been examined in the region 160-250°C and in the pH range 2-7. Conventional acid catalysis occurs at pH 2-3, but hydrothermolysis, i.e., hydrolysis which takes place in the absence of added mineral acid following the formation of degradation acids, occurs above pH 3.2.[120] A report has appeared on the kinetics of oxalic acid-catalysed hydrolysis of melibiose.[121] 2-Trimethylsilylethyl glycosides give 1,2-trans-related glycosyl acetates on treatment with acetic anhydride and boron trifluoride, and hydrolyse to the free sugars with the latter reagent alone.[122]

An examination of the mechanism of anomerization of the methyl glucopyranosides in DMSO/perdeuteriomethanol catalysed by $^{2}H_{2}SO_{4}$ showed that the reaction was zero order in methanol but that it depended on the presence of the alcohol. It was reasoned that the solvent played a dominant role and that important transition state interactions occur between the substrate and the solvent cage molecules.[123]

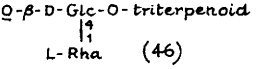
Ring expansion occurs specifically when the amino-sugar furanosides (45) are exposed to strong acid ion exchange resin in water (Scheme 9). The method assists in a synthesis of the β-pyranosides. The α-anomers are obtainable in 70% yield from them by use of boron trifluoride catalysis.[124]



(45)

Scheme 9

The kinetics of alkaline degradation of methyl β-D-xylopyranoside and several oligosaccharide methyl glycosides based on wood xylans have been examined as models for the processes occurring in the alkaline treatment of wood pulp.[125] Alcohols containing a trace of water and dissolving metallic sodium or potassium can cause separate cleavage of all of the glycosidic bonds of saponins, e.g., (46).[126]



(46)

Two very different studies depended to a degree on theoretical methods. Consistent free field calculations for methyl 2-deoxy-β-D-erythrofuranoside led to a conformational model consistent with that measured by n.m.r. methods.[127] Secondly, computer simulation has been used to modify the mechanism of the formations of the glycosides during the methanolysis of D-galactose. Various rate constants, equilibrium constants and activation energies were assigned.[128]

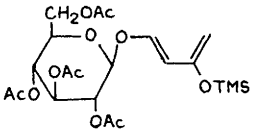
The selective deuteration of methyl pyranosides and furanosides over Raney nickel in D_2O has shown that exchange rates are not highly regioselective, but conditions were found for the selective labelling of methyl β-D-fructopyranoside at C-5, methyl β-D-fructofuranoside at C-3 and methyl β-D-galactopyranoside at C-3 and C-4.[129] The behaviour of sucrose under similar conditions has been examined using ^1H and ^2H n.m.r. methods. The samples studied by the latter method were examined in potassium laurate liquid crystal, the signals were assigned and the quadrupole splittings for each position were used to deduce conformational data.[130]

Further studies on sucrose (and starch) involved the determination of the water uptake as a function of humidity by a modified "inverse frontal g.c." method.[131]

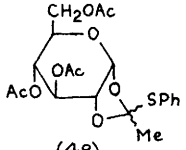
Chain extended sucroses involving C-methylation at C-6 and at C-1 by oxidation and Grignard methylation have been reported.[132]

Diene (47) displays notable diastereofacial discrimination in Diels-Alder reactions which has been ascribed to a reacting conformation determined by the exo-anomeric effect on the basis of an

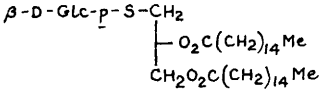
X-ray structure and n.O.e. nmr studies.[133]



(47)



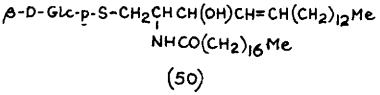
(48)



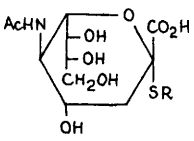
(49)

2 S-Glycosides

A review has appeared on the synthesis and applications in synthetic carbohydrate chemistry of 1-thioglycosides (in Polish),[134] and the same authors have developed a phase transfer catalysed preparation of 1-thioglycosides from glycosyl bromides. Tetra-O-acetyl-β-glucopyranosyl chloride, under these conditions, with thiophenol gave the mixed orthothioesters (48).[135] Syntheses have been reported for the thioglycosides (49)[136] and (50),[137] the analogous neuraminic acid glycosides (51),[138] and disaccharide (52) and related compounds.[139]

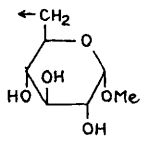


(50)



(51) R = hexyl, dodecyl, octadecyl

(52) R =

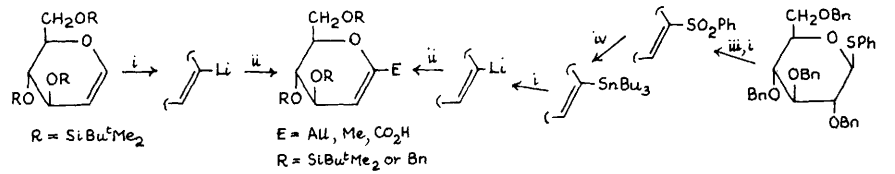


Dimethyl(methylthio)sulphonium triflate activates thioglycosides as glycosyl donors and permits the synthesis of β-1,2-, 1,3-, 1,4- and 1,6-linked disaccharides in high yield.[140] Several examples of this reaction are noted earlier in this Chapter. A very interesting alternative approach to the same objective uses copper(II) bromide as activating reagent in the presence of tetrabutyl ammonium bromide in nitromethane or 1,2-dichloromethane. Yields in excess of 80% are obtained using secondary carbohydrate alcohols and 1,2-α- and β-linked products were described.[15]

3 C-Glycosides

3.1 Pyranoid Compounds.- The use of glycosyl fluorides in the synthesis of C-glycosides has been covered in a review on fluorinated carbohydrates,[19] and the work of Sinay's group on C-glycoside synthesis from 1-lithio derivatives and from glycosyl phenylsulphones has appeared in the form of a published lecture.[141]

Extensions of this work have appeared (Scheme 10).[142] Related work

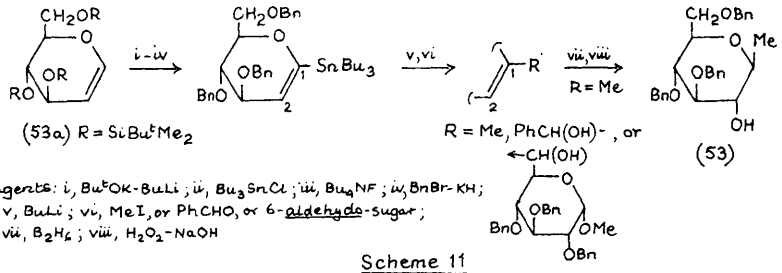


R = SiBu^{t}Me$_2$ E = All, Me, CO_2H R = SiBu^{t}Me$_2$ or Bn

Reagents: i, BuLi (-78°→0°); ii, E^+; iii, MCPBA; iv, Bu_3SnH

Scheme 10

has led to the methyl β-C-glycoside (53) and related compounds (Scheme 11).[143]

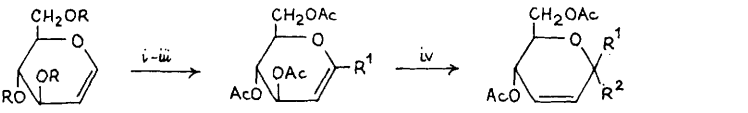


(53a) R = SiBu^{t}Me$_2$ R = Me, PhCH(OH)-, or -CH(OH) (53)

Reagents: i, Bu^{t}OK-BuLi; ii, Bu_3SnCl; iii, Bu_4NF; iv, BnBr-KH; v, BuLi; vi, MeI, or PhCHO, or 6-aldehydo-sugar; vii, B_2H_6; viii, H_2O_2-NaOH

Scheme 11

Nicolaou et al. have used the glycal triether (53a) in related manner and have developed routes to unsaturated "glycosides" carrying geminal carbon substituents at the anomeric centre (Scheme 12).[144] Details have been given for the palladium diacetate induced preparation of C-glycosides from glycals. The



R = SiBu^{t}Me$_2$ R = All or Me R^2 = Me, Et, CN, All, or C≡CMe

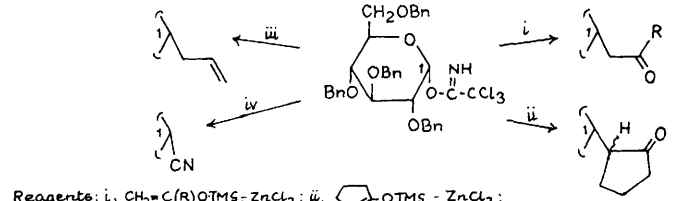
Reagents: i, BuLi-CuI-All.Br or MeI; ii, Bu_4NF; iii, Ac_2O-Py; iv, $AlMe_3$-$TiCl_4$ or Et_3Al, or TMS-R^2

Scheme 12

reaction occurs by an addition-elimination process and requires a good leaving group at C-3; the absence of such a group leads to hydride elimination and palladium-containing products. Furanoid and pyranoid glycal derivatives were examined.[145]

A set of C-glycosides have been made from a trichloroacetimidate (Scheme 13).[146] Acetobromoglucose with acrylonitrile or methyl vinyl ketone in the presence of vitamin B_{12} gives the adducts (54) and (55) together with tri-O-acetyl-D-glucal.[147]

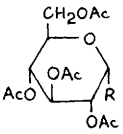
Benzylated glycosyl fluorides react with trimethylsilyl cyanide



Reagents: i, $CH_2=C(R)OTMS$, $ZnCl_2$; ii, - $ZnCl_2$; iii, TMS·Allyl - $ZnCl_2$; iv, TMS·CN – TMS·OTf

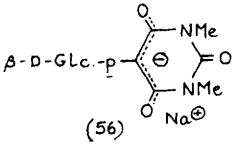
Scheme 13

and boron trifluoride to give initially the isonitriles which then rearrange to the glycosyl cyanides. While the β-D-ribofuranosyl compound gave both cyanides, the α-D-glucopyranosyl cyanide was



(54) R = CH_2CH_2CN

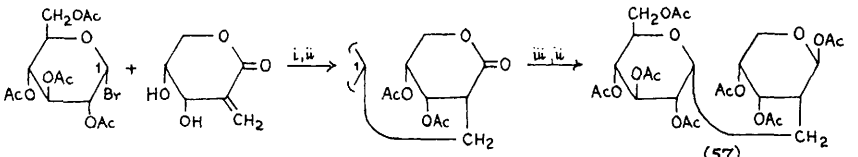
(55) R = CH_2CH_2COMe



(56)

obtained in 85% yield. With allyltrimethylsilane and the same catalyst the β-allyl C-riboside was obtained in 93% yield, and the α- and β-allyl C-glucosides in 72 and 22% yields, respectively [148] (*c.f.* K.C. Nicolaou *et al.*, Vol.18, p.31). Reduction of 1-bromo-β-D-glucopyranosyl cyanide tetra-acetate with zinc-acetic acid or sodium borohydride gave both glycosyl cyanides with the α-predominating; tributyltin hydride gave the β-isomer - again with low selectivity.[149] Acetylated glycosyl cyanides have been converted, via the glycosyl carboxylates, into the corresponding diazomethyl ketones, which are useful as affinity labels.[150]

Other syntheses include C-β-D-glycopyranosylmethylamines derived from lactose, cellobiose and maltose, produced by ferrous hydroxide reduction of the previously reported glycosylnitromethanes (Vol.16, p.42, ref.186),[151] C-glycosylbarbiturates, *e.g.*, (56), produced by reaction of free sugars in aqueous solution with barbituric acids,[152] and the C-linked disaccharide (57) synthesized by a novel radical addition reaction (Scheme 14).[153]

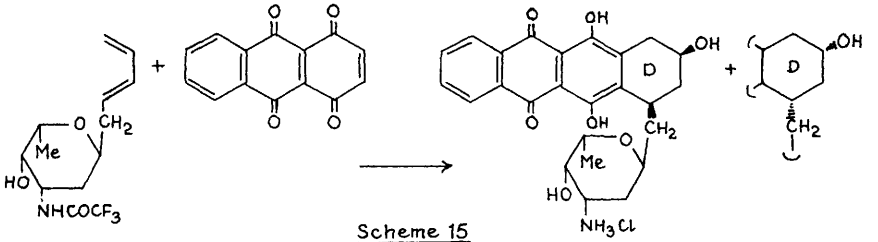


Reagents: i, Bu_3SnH - AIBN; ii, Ac_2O-Py; iii, $NaHAl(OEt)(OCH_2CH_2OMe)_2$

(57)

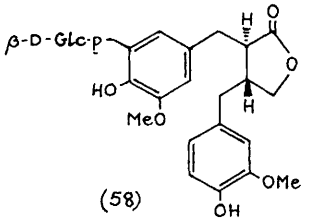
Scheme 14

C-Glycosides of anthracyclines have been made by improved procedures (Scheme 15),[154] and compounds (58) and (59) have been

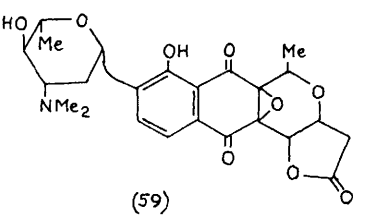


Scheme 15

isolated from natural sources. The former is the first C-



(58)

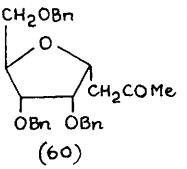


(59)

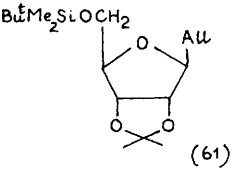
glucoside of a lignan to have been found,[155] and the latter is a microbiological antibiotic.[156]

3.2 Furanoid Compounds.- N.O.e. experiments have shown that the anomeric configuration of C-furanosides can be determined by this method.[157]

Both anomers of tri-O-benzyl-D-ribofuranosyl fluoride with 2-trimethylsilyloxypropene and boron trifluoride gave a very high yield of the acetone compound (60),[158] and both anomers of the



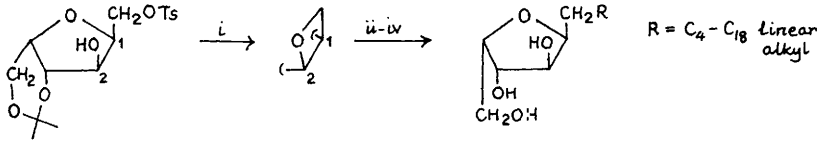
(60)



(61)

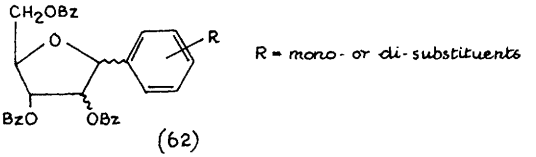
corresponding ribofuranosyl acetate with allyltrimethylsilane and zinc bromide afforded the β-allyl compound (61) under all conditions. Anomeric ratios were high (16:1) in nitromethane, whereas in less polar solvents they were about 2:1.[159] A new set of thermotropic liquid crystals are based on the reactions indicated in Scheme 16.[160]

The aryl glycosides (62) have been obtained using arylmagnesium bromides with acylated pentofuranosyl halides.[161] Intramolecular reaction of substituted-benzylated glycosyl acetates in presence of



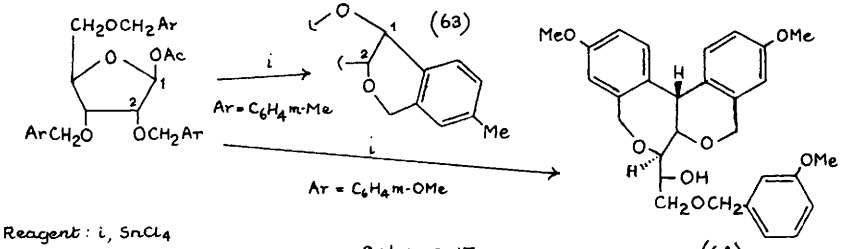
Reagents: i, NaOMe ; ii, HC≡CR'-BuLi ; iii, H^+ ; iv, H_2-Pd/C

Scheme 16



(62)

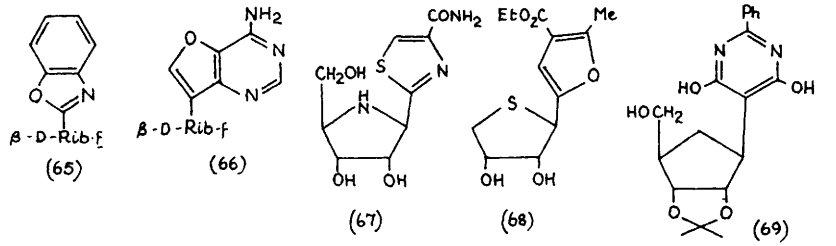
stannic chloride led to the C-glycoside (63) and a 1,1-diarylalditol (64) (Scheme 17).[162] Appropriately substituted D-ribofuranose



Reagent: i, $SnCl_4$

Scheme 17

derivatives with [chloro(alkoxycarbonyl)methylene]triphenylphosphorane gave the C-β-D-furanosyl glycosides which were used in the synthesis of C-nucleosides, e.g., showdomycin.[163] Other papers report the heterocyclic C-glycosides (65)[164] and (66),[165] and the furanose ring analogues (67),[166] (68)[167] and (69).[168]



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4
Oligosaccharides

1 General

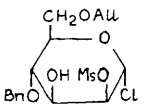
As before, this Chapter deals with specific tri- and higher oligosaccharides; most references relate to their syntheses by specific chemical methods. It does not deal with compounds made by the oligomerization of monosaccharide derivatives, nor does it deal with the cyclodextins. The synthesis of, e.g.,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

A review has been published on the total synthesis of biologically active heparin fragments,[1] while a more general treatment of the strategy for oligosaccharide synthesis has appeared as a published lecture.[2]

The observation of negative n.O.e. effects following irradiation of inter-unit anomeric protons on the glycosylated carbon atom signals of the adjacent units suggests a method for oligosaccharide sequencing.[3]

Preferred conformations of some D-mannose and 2-acetamido-2-deoxy-D-glucose-containing oligosaccharides related to the N-glycosyl proteins which interact with concanavalin A have been calculated by empirical potential energy methods.[4]

Compound (1) is a 3,6-di-O-glycosyl acceptor and a β-D-manno-



(1)

pyranosyl donor useful in the synthesis of the core parts of glycoproteins,[5] and several protected L-rhamnopyranose derivatives have been prepared for use in the synthesis of oligosaccharides related

to the O-antigenic polysaccharide of Shigella flexneri.[6]

2 Trisaccharides

2.1 Linear Homotrisaccharides.- 1- And 2-O-α-D-cellotriosyl-3-deoxy-2(R)- and -2(S)-glycerols[7] and the corresponding disaccharide glycosides[8] have been synthesized to allow the determination of the complete stereochemistry of rhynchosporoside, the host selective phytotoxin of Rhynchosporium secalis. Maltotriose is effective as a side-chain donor and acceptor and, in consequence, several isomeric hexasaccharides are formed by use of an isoamylase from Pseudomonas. It also can be used to introduce branches into cyclomalto-oligosaccharides.[9]

Silver triflate-promoted Koenigs Knorr reactions have been used in the preparation of the β-(1 → 3), β-(1 → 4) and β-(1 → 4), β-(1 → 3)-linked D-glucopyranose trimers.[10]

In the D-galactopyranose series, the β-(1 → 3)-[11] and β-(1 → 6)-[12,13] linked trimers have been reported. In both reports on the latter compound higher oligomers were also described in illustrations of the use of 2,3,4-tri-O-acetyl-6-O-(bromoacetyl)-α-D-galactopyranosyl chloride and bromide, respectively.

2.2 Linear Heterotrisaccharides.- A β-galactosidase of E. coli has been used to transfer a β-D-galactopyranose unit to the primary position of the D-glucose moiety of sucrose and thus give "isoraffinose",[14] and the corresponding trimer having α-D-galactopyranosyl uronic acid as the sucrose substituent has been made from raffinose by use of D-galactose oxidase followed by hypoiodite oxidation of the resulting aldehyde. Mild acid-catalysed hydrolyses then gave α-D-GalpUA-(1 → 6)-D-Glc (melibiouronic acid).[15] Neokestose, which has a β-D-fructofuranosyl group at O-6 of the D-glucose unit of sucrose, is produced by an enzyme of Penicillium oxalicium by transfer of the fructosyl substituent from one sucrose molecule to another.[16]

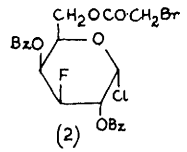
Reducing compounds of this class (and their derivatives) are now dealt with first according to their reducing termini and then according to the adjacent moieties.

O-α-D-Glcp-(1 → 2)-O-α-D-Galp-(1 → 3)-α-D-Glcp-OMe has been made by use of methyl 1-thioglycoside glycosylating agents,[17] and the trimeric antigenic determinant of the capsular polysaccharide of Klebsiella type 73, i.e., O-β-GlcUAp-(1 → 3)-O-β-D-Galp-(1 → 4)-D-

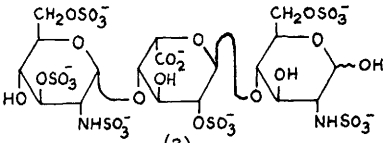
Glc, has also been synthesized.[18]

Lactose-based trisaccharides having N-acetylneuraminic acid linked α- and β- to O-6 of D-galactose have been reported,[19,20] as have the analogues linked through O-3[20,21] and other isomeric trisaccharides.[20] A related compound having two neuraminic acid units linked to glucose, O-β-D-NeuAc-(2 → 8)-O-β-D-NeuAc-(2 → 6)-α-D-Glcp-OMe, has also been produced.[22]

O-β-D-Galp-(1 → 6)-O-3-deoxy-3-fluoro-β-D-galactopyranosyl-(1 → 6)-β-D-Galp-OMe has been synthesized using the glycosylating reagent (2),[23] and the D-mannose terminating trisaccharide β-D-GlcNAc-(1 → 2)-α-D-Manp-(1 → 6)-β-D-Man has been obtained as the 8-methoxycarbonyloctyl glycoside.[24]



(2)



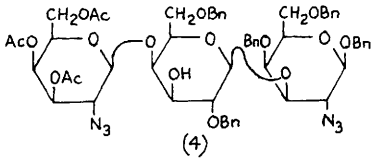
(3)

O-α-NeuAc-(2 → 6)-O-β-D-Galp-(1 → 4)-GlcNAc (6'-N-acetylneuraminyllactosamine) has been prepared by use of immobilized enzymes;[25] the same compound and the 3'-linked isomer have been isolated from pregnancy urine.[26] The binding of the related O-α-L-Fucp-(1 → 2)-O-β-D-Galp-(1 → 4)-β-D-GlcNAc-OMe by lectin I of Ulex europaeus has been examined in a study of H-type 2 human blood group determinant.[27]

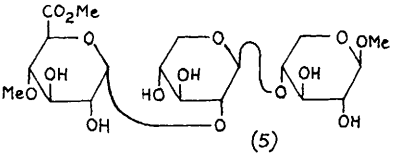
Methyl α-L-iduronosiduronic acid 2-sulphate prefers the $^{1}C_{4}$ conformation, but the acid, as part of the trisaccharide (3) and of larger sections of the heparin molecule, adopts a considerably distorted mean ring shape near the $^{2}S_{0}$ skew-boat conformation. These ^{1}H n.m.r.-based conclusions were compared with those of force-field calculation results.[28] In related studies of heparin sulphate catabolism by sulphatases, O-α-D-GlcpNH$_2$-(1 → 4)-O-α-L-IdopUA-(1 → 4)-2,5-anhydro-D-[1-^{3}H]mannitol has been synthesized.[29]

Conventional synthetic methods have been used to obtain the desialylated human Cad-antigenic determinant O-β-D-GalpNAc-(1 → 4)-O-β-D-Galp-(1 → 3)-D-GalpNAc,[30] the synthetic precursor (4) of this compound[31] and the trisaccharide unit of the capsular polysaccharide of Streptococcus pneumoniae Type 4, O-β-D-ManpNAc-(1 → 3)-O-α-L-FucpNAc-(1 → 3)-D-GalNAc.[32]

The aldotriouronic acid (5), a derivative of a component of 4-O-methyl-D-glucurono-D-xylans, and related branched trisaccharide and associate aldobiouronic acid derivatives have been studied by

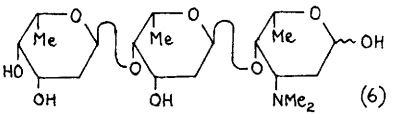


(4)



(5)

detailed nmr methods (including 2D).[33] Other trisaccharide syntheses reported include the fragment of Shigella flexneri O-specific polysaccharide, O-α-D-Glcp-(1 → 3)-O-α-L-Rhap-(1 → 3)-α-L-Rhap-OMe,[34] the determinant of the enterobacterial common antigen, O-β-D-ManpNAcUA-(1 → 4)-O-α-D-GlcpNAc-(1 → 3)-α-D-FucpNAc-O(CH$_2$)$_8$CO$_2$Me,[35] and the aminated trisaccharide (6), which is the sugar unit of the anthracycline marcellomycin.[36]



(6)

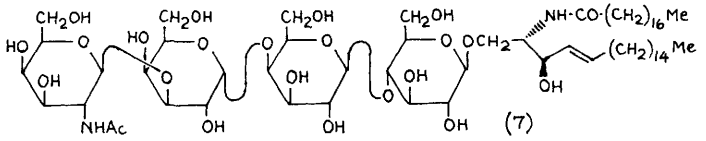
2.3 Branched Heterotrisaccharides.- Compounds of this category to have been reported are: O-β-D-Galp-(1 → 4)-O-[α-L-Fucp-(1 → 3)]-D-Glc, (3-fucosyl-lactose),[37] O-α-L-Fucp-(1 → 2)-O-[α-D-GalpNAc-(1 → 3)]-β-D-Gal-OMe,[38] O-α-L-Fucp-(1 → 2)-O-[α-D-Galp-(1 → 3)]-β-D-Galp-OMe (antibody binding studies),[39] O-α-L-Fucp-(1 → 2)-O-[α-D-Galp-(1 → 3)]-1,6-anhydro-β-D-Galp,[40] O-α-Fucp-(1 → 3)-O-[β-D-Galp-(1 → 4)]-α-D-GlcpNAc-OPO$_3$H,[41] O-α-D-Fucp-(1 → 4)-O-[β-D-Galp-(1 → 3)]-D-GlcNAc,[42] O-α-D-Glcp-(1 → 3)-O-[β-D-ManpNAc-(1 → 4)]-L-Rha[43] and O-[3,6-di-O-Me-β-D-Glcp-(1 → 4)]-O-[2,3-di-O-Me-α-L-Rhap-(1 → 2)]-3-O-Me-α-L-Rhap-O-Pr.[44]

3 Tetrasaccharides

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

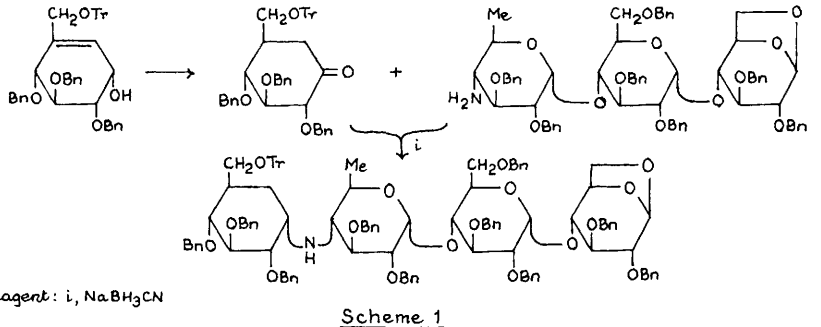
3.1 Linear Tetrasaccharides.- The following compounds having D-glucose at the reducing end have been reported: O-β-D-Glcp-(1 → 6)-O-β-D-Glcp-(1 → 3)-O-β-D-Glcp-(1 → 3)-D-Glc[45] and its three possible (1 → 3)(1 → 4)(1 → 4)-linked sequence isomers.[10] The first of these is a possible repeating unit of the extracellular

polysaccharide of the fungus Schizophyllum commune, while the others are the tetrasaccharide units of the linear chains of lichenan and cereal glycans. "Globoside", the major glycosphingolipid of human erythrocyte membrane, has structure (7),[46] and "dihydroacarbose", a



(7)

pseudo-tetrasaccharide with potent α-D-glucosidase inhibitor characteristics, has been synthesized as indicated in Scheme 1.[47]



Reagent: i, $NaBH_3CN$

Scheme 1

Glucosamine-containing members of this set to have been reported are: O-α-D-Manp-(1 → 6)-O-β-D-Manp-(1 → 4)-O-β-D-GlcpNAc-(1 → 4)-D-GlcNAc[48] and O-α-KDO-(2 → 4)-O-α-KDO-(2 → 6)-O-β-D-GlcpNH_2-(1 → 6)-D-GlcNH_2, which is a fragment of the R-mutant of Salmonella minnesota.[49]

L-Rhamnose-containing compounds have received particular attention in connection with bacterial polysaccharide studies. The following have been synthesized: O-β-D-GlcpNH_2-(1 → 2)-O-α-L-Rhap-(1 → 2)-O-α-L-Rhap-(1 → 3)-L-Rha,[50,51] 3-O-Me-O-β-L-Xylp-(1 → 4)-O-α-L-Rhap-(1 → 4)-O-α-L-Rhap-(1 → 2)-L-Rha,[52] and O-α-L-Fucp-(1 → 4)-O-α-L-Fucp-(1 → 3)-O-α-L-Rhap-(1 → 2)-L-Rha, carrying O-methyl substituents at positions 2 and 3 of both fucose residues.[53]

Units of the Malvaceae plant mucilage polysaccharides including the tetrasaccharide O-α-D-GalpA-(1 → 2)-O-α-L-Rhap-(1 → 4)-O-α-D-GalpA-(1 → 2)-L-Rha-itol, and higher members containing the central disaccharide repeated 1-3 times, have been examined by ^{13}C n.m.r. spectroscopy.[54]

3.2 Branched Tetrasaccharides.- The following compounds have been described:

1. D-Glucose reducing terminus: O-β-D-Glcp-(1 → 3)-O-β-D-Glcp-(1 → 3)-O-[β-D-Glcp-(1 → 6)]-D-Glc,[45] O-β-D-Glcp-(1 → 3)-O-[β-D-Glcp-(1 → 6)]-O-β-D-Glcp-(1 → 3)-D-Glc,[45] O-β-D-GlcpNAc-(1 → 3)-O-[β-D-GlcpNAc-(1 → 6)]-O-β-D-Galp-(1 → 4)-β-D-Glc-OMe,[55] O-β-D-Glcp-GlcpNAc-(1 → 3)-O-[β-D-GalpNAc-(1 → 4)]-O-β-D-Galp-(1 → 4)-β-D-Glc-OR[56] and O-α-D-NeupAc-(2 → 3)-O-[β-D-GalpNAc-(1 → 4)]-O-β-D-Galp-(1 → 4)-β-D-Glc-OR [57] (where R in the last two compounds is a ceramide derivative and the compound a glycosphingolipid).

2. D-Mannose reducing terminus: O-β-D-GlcpNAc-(1 → 2)-O-α-D-Manp-(1 → 6)-O-[α-D-Manp-(1 → 3)]-β-D-Man[24] and O-β-D-GlcpNAc-(1 → 6)-O-[β-D-GlcpNAc-(1 → 2)]-O-α-D-ManpNAc-(1 → 6)-D-Man.[58]

3. D-Glucosamine reducing terminus: O-α-L-Fucp-(1 → 2)-O-β-D-Galp-(1 → 3)-O-[α-L-Fucp-(1 → 4)]-D-GlcNAc,[59,60] O-α-L-Fucp-(1 → 2)-O-β-D-Galp-(1 → 4)-O-[α-L-Fucp-(1 → 3)]-D-GlcNAc[59] and O-β-D-Galp-(1 → 4)-O-β-D-Glcp-(1 → 6)-O-[β-D-Galp-(1 → 4)]-D-GlcNAc.[61]

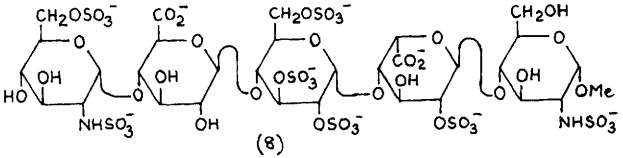
4. D-Glucuronic acid reducing terminus: O-β-D-Glcp-(1 → 2)-O-β-D-Galp-(1 → 4)-O-[α-D-Galp-(1 → 2)]-β-D-GlcUA.[62]

5. L-Rhamnose reducing terminus: O-α-L-Rhap-(1 → 2)-O-[α-D-Glcp-(1 → 3)]-O-α-L-Rhap-(1 → 3)-α-L-Rhap-OMe,[34] O-β-D-GlcpNAc-(1 → 2)-O-α-L-Rhap-(1 → 2)-O-[α-D-Glcp-(1 → 3)]-α-L-Rhap-OMe,[34] O-α-D-Glcp-(1 → 3)-O-α-L-Rhap-(1 → 2)-O-[α-D-Glcp-(1 → 3)]-α-L-Rhap-OMe[63] and O-α-D-Glcp-(1 → 4)-O-α-D-Glcp-(1 → 3)-O-[β-D-ManpNAc-(1 → 4)]-L-Rha,[43] all of them being bacterial polysaccharide components.

6. Pentose reducing terminus: the plant tetrasaccharides O-β-D-Xylp-(1 → 2)-O-β-D-Glcp-(1 → 4)-O-[β-D-Glcp-(1 → 2)]-α-L-Arap-O-terpene[64] and O-β-D-Xylp-(1 → 4)-O-[4-O-Me-α-D-GlcpA-(1 → 2)]-O-β-Xylp-(1 → 4)-D-Xyl.[65]

4 Pentasaccharides

The antithrombin-binding heparin-like pentasaccharide glycoside (8) has been synthesized,[66] and the corresponding free sugar sulphated at O-6 of the reducing moiety has also been prepared[67] (c.f., Sinay *et al.*, *Carbohydr. Res.*, 1984, **130**, 221 and an expanded account[68]). Glycoprotein work has led to the chemical/enzymic synthesis of O-α-D-Neu-Ac-(2 → 6)-O-β-D-Galp-(1 → 4)-O-β-D-GlcpNAc-



(8)

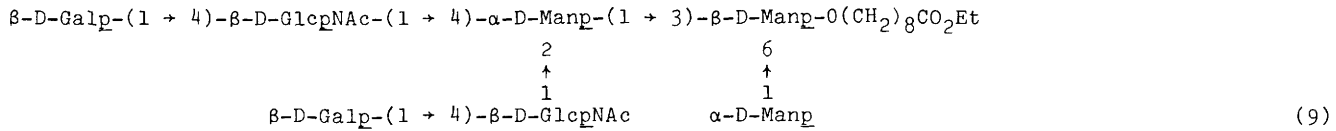
(1 → 3)-O-β-D-Galp-(1 → 4)-D-Glc and other closely related pentasaccharides[20] and to the conformational analysis of O-α-D-Manp-(1 → 3)-O-[β-D-GlcpNAc-(1 → 4)]-O-[α-D-Manp-(1 → 6)]-O-β-D-Manp-(1 → 4)-D-GlcNAc.[69]

5 Hexasaccharides

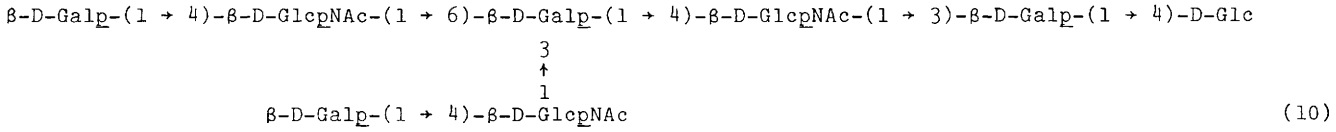
Maltotriose is effective as a side-chain donor and acceptor in the presence of a *Pseudomonas* isoamylase and gives a set of 6-O-α-maltotriosyl maltotrioses,[9] and in other enzymic work α-D-glucopyranosyl fluoride has been converted into approximately equal proportions of α- and β-cyclodextrins.[70] A heterohexasaccharide to have been synthesized is the Le^b antigen O-α-L-Fucp-(1 → 2)-O-β-D-Galp-(1 → 3)-O-[α-L-Fucp-(1 → 4)]-O-β-D-D-Glcp-NAc-(1 → 3)-O-β-D-Galp-(1 → 4)-β-D-Glcp-(1 → 1)-O-ceramide.[71]

6 Higher Saccharides

The following higher saccharides have been described: compound (9), a heptasaccharide hapten;[72] (10)[73] and (11),[74] octasaccharide parts of glycolipids; and (12), an undecasaccharide component of glycoproteins.[75] These were produced by chemical synthesis, apart from the third which was obtained from spermatazoa of a bivalve and characterized by 2D ^1H nmr spectroscopy.



(9)



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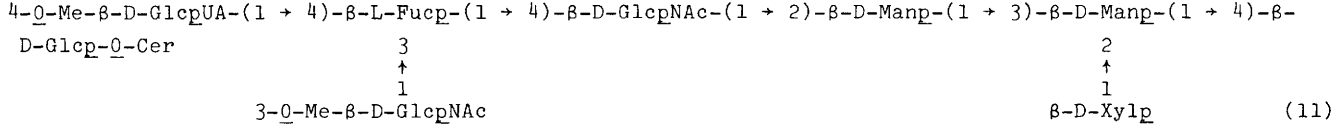

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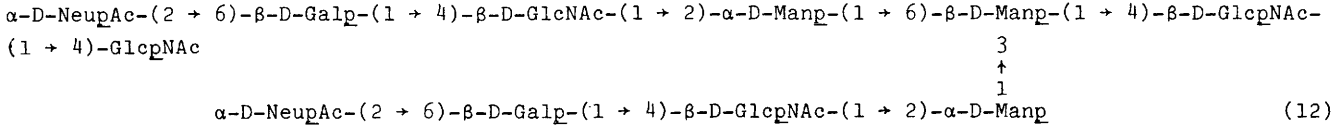

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5
Ethers and Anhydro-sugars

1 Ethers

Methyl and Trifluoromethyl Ethers.- Echinoside A, an antifungal triterpene tetrasaccharide isolated from a sea cucumber, has a 3-O-methyl-β-D-glucopyranosyl moiety at the non-reducing terminus.[1] Crossasteroside, a steroidal glycoside from the starfish Crossaster papposus, has a 3-O-methyl-2-O-(4-O-methyl-β-D-xylopyranosyl)-β-D-xylopyranosyl moiety.[2]

A mixture of 6-O-methyl-D-fructose and 6-O-methyl-L-sorbose has been isolated in high yield on a 4-20 mmole scale from the sequential enzyme catalyzed condensation of racemic 3-O-methyl-glyceraldehyde and dihydroxyacetone phosphate [the latter being generated in situ from fructose 1,6-diphosphate], followed by cleavage of a phosphate ester in the product by acidic or enzymic hydrolysis. 6-O-Methyl-L-sorbose was unaffected by glucose isomerase, but 6-O-methyl-D-fructose was brought into a 40:60-equilibrium with 6-O-methyl-D-glucose, which was isolated chromatographically.[3,4] Application of this methodology to the synthesis of other sugars is covered in Chapter 12.

5-O-Methyl-D-galactofuranose was obtained in six steps from D-galactono-1,4-lactone via its 2,3,5-tri-O-acetyl-6-O-trityl derivative; detritylation with (5 → 6) acetyl migration was followed by methylation (CH_2N_2-BF_3.OEt_2) and reduction (disiamylborane).[5] 3,6-Di-O-methyl-glucose, required for the synthesis of mycobacterial oligosaccharides, has been obtained from D-glucurono-6,3-lactone via its 1,2-O-isopropylidene-5-O-(tetrahydropyran-2-yl) or -(1-methoxyethyl)-derivatives, which were reduced ($LiAlH_4$) and methylated.[6] 2'-O-Methyl, 2'-O-benzyl, and 2',6'-di-O-methyl ethers of lactose were obtained by alkylation of the two products of isopropylidenation of lactose with acidic 2,2-dimethoxypropane (see Chapter 6).[7]

Various conditions have been investigated for the partial methylation of methyl 2-deoxy-α- and β-D-threo-pentopyranosides,

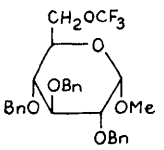
the mono-methyl ethers of the β- but not the α-anomer being chromatographically separable.[8] Mixtures containing all possible mono- to tri-O-methyl ethers of methyl α-L-arabinopyranoside (using Me_2SO_4 - 30% NaOH)[9] and methyl α-L-fucopyranoside (using MeI-Ag_2O-MeOH)[10] have been prepared and separated by preparative chromatography, the ^{13}C-n.m.r. spectra of the components being reported. Regioselective methylation (CH_2N_2-$SnCl_2$) of methyl α-L-fucopyranoside has been studied as a function of solvent and reaction time, the 3-mono- and 2,3-di-ethers, and to a lesser extent the 2,4-di-ether, being the major products; data for eight partially methylated derivatives of methyl α- and β-L-fucopyranoside were given.[11]

In the permethylation analysis of trehalose glycolipids such as cord factor and 6-O-mycolyl-α,α-trehalose, various standard reagents proved unsatisfactory due to ester cleavage, but the method of Ciucanu and Kerek (Vol.18, p.50; powdered NaOH-MeI-DMSO) gave excellent results, only lower acyl groups such as acetyl being cleaved. 6,6'-Di-O-methyl-α,α-trehalose was obtained from the 2,3,4,2',3',4'-hexaacetate by use of methyl triflate - 2,6-di-*tert*-butylpyridine as methylating reagent.[12]

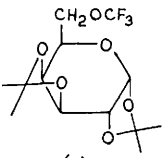
Trimethylsulphonium hydroxide in the presence of Mg^{2+} or Ca^{2+} ions has been used for selective 2'-O-methylation of ribonucleosides with limited success (see Chapter 20).[13]

De-O-methylation at O-1 (in aqueous media) or at O-3 (in anhydrous media) of methylated 2-acetamido-2-deoxy-D-hexitol moieties has been observed during the acid cleavage of permethylated oligosaccharides containing such end groups; the problem was studied using the corresponding glucitol, galactitol and mannitol derivatives as models.[14]

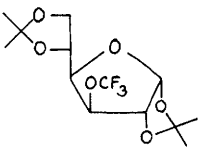
O-(Trifluoromethyl)ethers (1)-(3) have been obtained (in the indicated yields) by displacement of trifluoromethanesulphonyloxy



(1) 76%



(2) 52%



(3) 16%

groups using tris(dimethylamino)sulphonium trifluoromethoxide; these were then conventionally deprotected to the trifluoromethyl derivatives of the corresponding free sugars. Competitive formation of the corresponding C-fluoro-derivatives (from the

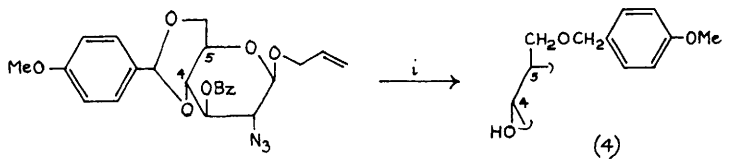
presence of F^- due to reagent breakdown) accounted for the rest of the product. The O-trifluoromethyl group is expected to confer interesting biological properties, since it is both more electron withdrawing and more lipophilic than O-methyl.[15]

Other Alkyl and Aryl Ethers.- Procedures for the selective removal of allyl ether in the presence of allyloxycarbonyl ester protecting groups, or vice versa, using palladium and iridium catalysts have been published in full (cf. Vol.19, p.15).[16] A reference to ester migration during O-allylation is covered in Chapter 7.

The synthesis of 2'-O-benzyl-lactose has been reported.[7] All isomers of the monobenzyl and monotrityl ethers of tetra-O-acetyl-D-glucopyranose have been synthesized, their ^1H- and ^{13}C-n.m.r. spectra completely assigned, and the chemical shifts induced by such substituents examined.[17] O-Benzyl groups can be replaced by O-acetyl groups by acetolysis (Ac_2O-$FeCl_3$), a process which shows some selectivity. Thus benzyl ethers at O-6, O-3, and O-2 of D-glucopyranose derivatives were replaced with relative rates of 125:24:1 respectively.[18] O-Debenzylation in the presence of 2-phenyl-1,3-dioxanes and 2-alkyl-1,3-dioxolanes, but not 2-phenyl-1,3-dioxolanes, has been effected by catalytic transfer hydrogenation over palladium-on-charcoal catalyst using hydrazine hydrate as hydrogen donor.[19] In the catalytic transfer hydrogenolysis (Pd/C-Me_2CHOH) of 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-hexopyranoses, the benzyl groups can act as hydrogen donors. Thus 1,6-anhydro-3-O-benzoyl-β-D-galacto- and -manno-pyranose were obtained in 70 and 40% yield respectively, and 1,6-anhydro-2-O-benzoyl-β-D-gulopyranose in 40% yield. A cis-vicinal arrangement of benzyloxy substituents appears to be required, since no benzoates were obtained from the glucose analogue.[20] In a related fashion it has been found that oxidative debenzylation (Pd cat. - EtOH, Δ) can be effected if a second ligand, e.g., a methoxy-group, is available to bind the catalyst. While simple benzyl ethers do not react, 1-benzyloxy-3-methoxypropane and a methyl 3-O-benzyl-2,4-dideoxy-α-D-erythro-pyranoside derivative were debenzylated, an alkene in the latter compound not being reduced.[20a] The preparation of per-O-benzylated glycosyl fluorides is covered in Chapter 8.

Many examples of the selective deprotection of benzyl, 4-methoxybenzyl (MPM), and 3,4-dimethoxybenzyl (DMPM) protected hydroxy groups have been detailed. Benzyl ethers but not MPM or DMPM ethers are cleaved on hydrogenolysis (H_2 - Raney Ni), while DMPM

ethers are more rapidly cleaved than MPM ethers by benzylic oxidation with DDQ.[21] The 6-O-(4-methoxybenzyl) group has been introduced as illustrated in Scheme 1 in such a way that the result-



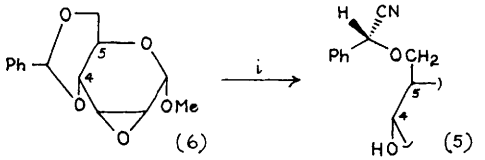
Reagents: i, $NaBH_3CN$-HCl

Scheme 1

ing 2-azido-2-deoxy-sugar derivatives of glucose [e.g.,(4)] or galactose are suitable for glycosylation at O-4; O-6 can be deprotected with DDQ without affecting the azido-group.[22] Separable mixtures of 2'- and 3'-O-(4-methoxybenzyl)-nucleoside derivatives have been obtained from the stannous chloride catalyzed reaction of N-acylated nucleosides with 4-methoxyphenyldiazomethane.[23]

2-Pyridylmethyl, 2-quinolylmethyl, and 3-methyl-6-nitro-3H-indol-2-ylmethyl ethers have been prepared by phase-transfer catalyzed alkylation of 1,2:3,4-di-O-cyclohexylidene-D-galactopyranose and 1,2:5,6-di-O-cyclohexylidene-D-glucofuranose.[24]

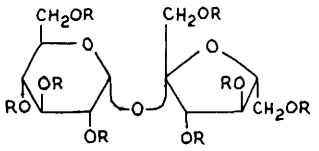
The α-cyanobenzyl ether (5) was obtained as the major isomer on cleavage of the benzylidene acetal (6), the 2,3-epoxide moiety not being cleaved even with excess reagent (Scheme 2).[25]



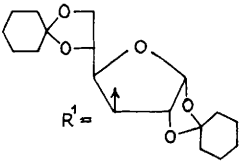
Reagents: i, Me_3SiCN-BF_3OEt_2

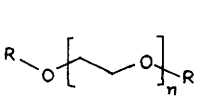
Scheme 2

Crown ethers and their acyclic analogues, incorporating sugar units, continue to receive attention. A review covering the stereospecific synthesis of macrobicyclic and macropolycyclic polyethers has appeared.[26] Polyoxygenated ethers (7) of sucrose have



(7) R = $-(CH_2CH_2O)_nMe$ (n = 1-5)

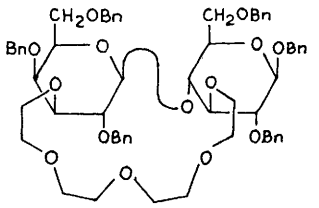




(8) R = R^1, n = 2-4

(9) R = Ts

been synthesized by conventional alkylation and shown to be somewhat less effective than dibenzo-18-crown-6 in catalyzing certain model reactions.[27] The bis(glucos-3-yl) ether (8) has been obtained by coupling the sugar alcohol precursor to the ditosylates (9). Selective hydrolysis of the 5,6-acetals, and periodate cleavage of the released diol moieties, provided bis(dialdehyde) derivatives.[28] Reductive cleavage ($LiAlH_4$-$AlCl_3$) of the benzylidene acetal moieties in a bis(methyl 4,6-O-benzylidene-α-D-glucopyranosido)-18-crown-6 macrocycle [Vol.16, p.55, compound (11)] gave mostly the bis(4-O-benzyl) ether derivative in agreement with analogous reactions on monosaccharide derivatives. Other conventional reactions applied to this macrocycle included hydrolysis to the tetraol or hexahydroxy-compound, and bromination (NBS) to a 6,6'-dibromo-4,4'-di-O-benzoate.[29] O-Benzylated lactose derivatives 3,3'-, 3,2'-, or 3,2':3',4'-O-bridged by 3,6,9-trioxaundecan-1,11-diyl moieties, e.g. (10), have been synthesized by coupling partially benzylated lactose derivatives having a free hydroxy group in each ring with



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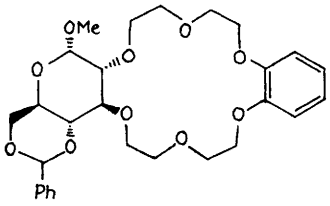


(11)

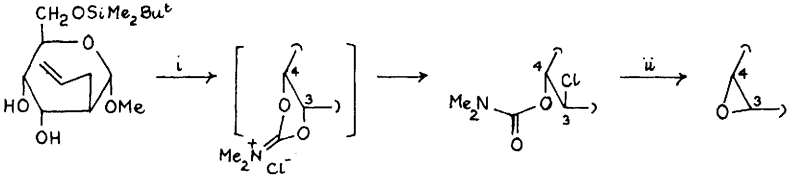
α,ω-ditosylated polyethers, and shown to form host-guest complexes with benzylammonium thiocyanate.[30] These macrocycles, when complexed to potassium bases (e.g., $KOBu^t$), induced an enantiomeric excess in the products from Michael condensation reactions, such as that between methyl (2-phenyl)acetate and methyl acrylate.[31] Synthesis of nine benzo-18-crown-6 ethers incorporating carbohydrate 1,2-diol units, e.g., (11), have been reported, and their complexing behaviour with alkylammonium salts, especially α-aminoacid esters, has been studied; chiral recognition factors (D:L) of up to 2.3 were recorded.[32]

Selective O-detritylation with formic acid in diethyl ether has been shown to be effective in the presence of benzylidene, isopropylidene, and t-butyldimethylsilyl protecting groups, and even tetrahydropyranyl ethers survive partially.[33]

Silyl Ethers.- A new method for introducing 3'-O-trisopropylsilyl groups into 2'-deoxyribonucleosides is covered in Chapter 20.

2 Intramolecular Ethers (Anhydro-sugars)

Oxirans.- Epoxides can be synthesized directly from certain diols by addition of an equivalent of tosyl chloride to the diol under phase-transfer conditions (e.g., $BnNEt_3^+.Cl^- - CH_2Cl_2$ - sat.aq. NaOH). In this way high yields of 5,6-anhydro-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose and related 5,6-anhydrides were obtained. On exposure of methyl 4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside to similar phase-transfer conditions, the corresponding 2,3-anhydromannoside was obtained in 91% yield.[34] Treatment of cis-diols with Viehe's salt generates trans-chlorocarbamates (c.f., Vol.16, p.84), and where a trans-diaxial arrangement of these substituents can be achieved, treatment with base can lead to epoxides as exemplified in Scheme 3.[35] Four sucrose epoxide derivatives

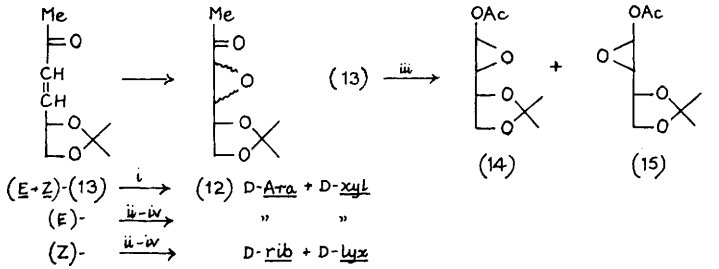


Reagents: i, $Cl_2C{=}NMe_2Cl$; ii, MeLi

Scheme 3

have been synthesized from the products of selective pivaloylation of sucrose by treatment of O-mesyl derivatives with methoxide.[36]

The four isomers of the 3,4-anhydro-1-deoxy-D-hex-2-ulose derivative (12) have been isolated by chromatographic separation of mixtures obtained from the enone (13) as shown in Scheme 4.



Reagents: i, H_2O_2-NaOH ; ii, $NaBH_4$; iii, MCPBA ; iv RuO_4

Scheme 4

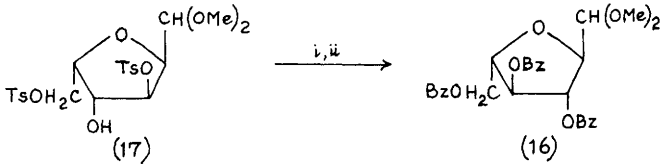
Epoxidation with MCPBA led to concomitant Baeyer-Villiger oxidation to yield the 1,2-anhydrotetrose hydrate derivatives (14) and (15).[37] Polymerization of 1,6:2,3-dianhydro-4-O-methyl-β-D-mannopyranose led to a stereoregular polymer with novel (2 → 3)-linked 4-O-methyl-D-glucose units.[38] Other references to epoxides can be found in

Chapters 14 and 16.

Other Anhydrides.- The synthesis and Lewis acid catalyzed ring-opening polymerization reactions of 1,4-anhydro-2,3-di-O-benzyl-α-L-arabinofuranose,[39] and of 1,6-anhydro-2,4-di-O-benzyl-3-O-octadecyl-β-D-glucopyranose,[40] have been detailed.

The stereoselectivity achieved in the synthesis of C-6 chirally deuterated hexopyranoses by sequential C-6 photobromination - tributyltin deuteride reduction applied to the eight isomeric 1,6-anhydro-2,3,4-tri-O-benzyl-D-hexopyranoses has been reported.[41] A variety of 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose derivatives, of potential as glucosamine monomers in oligosaccharide synthesis, have been synthesized from 1,6-anhydro-β-D-mannopyranose. The procedure of Georges and Fraser-Reid (Vol.18, p.55) for the one-pot conversion of mannose to its 1,6-anhydride has been made reliable and scaled-up for the production of 35 g lots of the anhydride in 56% yield.[42]

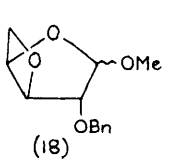
2,5-Anhydro-L-mannose dimethyl acetal derivative (16) has been synthesized from the D-glucose derived 2,5-anhydro-3,6-di-O-tosyl-L-idose dimethyl acetal (17) (Scheme 5) and converted to C-nucleosides.[43]



Reagents: i, NaOBz; ii, BzCl-Py

Scheme 5

Methyl 2-O-benzyl-3,5-anhydro-α,β-D-xylofuranoside (18) has been synthesized in five steps from methyl 3,5-O-isopropylidene-α,β-D-xylofuranoside, anhydride formation involving conventional intramolecular tosylate displacement.[44] 4,6-Anhydro-α-D-galactopyranosyl 6-O-mycoloyl- and -corynomycoloyl-α-D-galactopyranoside, analogues of trehalose glycolipids, have been synthesized by sequential introduction and displacement of tosylate groups from C-6 and C-6' of a 2,3,2',3'-tetra-O-benzyl-protected galactosyl galactoside.[45]



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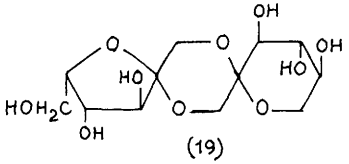

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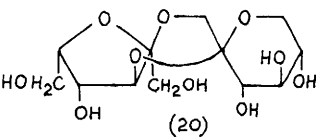

(20)

L-Sorbose has been converted into a mixture of six disorbose dianhydrides (two of which were previously known) by treatment with anhydrous hydrogen fluoride, L-sorbofuranosyl fluoride being the intermediate. Five of the dianhydrides were 1,2':2,1'-isomers [e.g., compound (19)] differing in ring size and anomeric configuration, while the sixth was the 2,1;3,2'-dianhydride (20). Such dianhydrides were also formed on treatment of L-sorbose with other acids ($MeOH-H_2SO_4$ or CF_3CO_2H).[46]

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6
Acetals

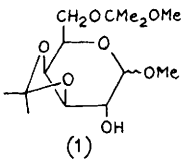
The reactions of carbohydrate acetals with particular emphasis on acid catalyzed migrations and the conversion of acetals to halogen derivatives form the subject of a review in Hungarian.[1] From a ^{1}H-n.m.r. study and examination of X-ray structures of pyranoid rings fused to dioxolan rings in acetylated D-gluco- and D-galactopyranose derivatives, it was concluded that the configuration of the dioxolan ring influences the conformation of the pyranoid ring in D-glucose but not in D-galactose derivatives.[2]

1 Isopropylidene acetals

Sugar isopropylidene acetals have been prepared by ultrasonic irradiation of a suspension of the sugar in propanone in the presence of 98% sulphuric acid or 70% perchloric acid. The sugar dissolves within 30 minutes and the acetals are isolated after neutralization with sodium or potassium carbonate. Cyclohexylidene acetals were prepared in a similar manner.[3]

Aldehydo-2,3:4,5-di-O-isopropylidene-D-xylose has been prepared in 52% yield by direct acetalation of D-xylose with 2-methoxypropene in the presence of tosic acid.[4] Direct isopropylidenation of free sugars has also been carried out by means of iodine in propanone. D-mannose yielded the 2,3:5,6-di-O-isopropylidene furanose in 25 min at room temperature whereas L-arabinose gave the 1,2:3,4-diacetal of the pyranose in 2 hours at room temperature and 20 min at reflux. In both cases yields of 85% were obtained.[5] Treatment of either anomer of methyl D-galactopyranoside with 2,2-dimethoxypropane in the presence of tosic acid and propanone gave a 50 - 70% yield of the corresponding diacetal (1), useful for synthesis of 2-,6-, or 2,6-substituted galactose derivatives.[6] The reaction of 3,6-anhydro sugars with acetonating agents has been investigated. Propanone-sulphuric acid with 3,6-anhydro-D-glucose yielded 3,6-anhydro-1,2-O-isopropylidene-D-glucofuranose (2) whereas anomers of the open chain diacetal (3) were obtained when 2,2-dimethoxypropane was used. Complex reactions occurred when 3,6-anhydro-D-mannose

was treated with propanone-sulphuric acid, although the acyclic 1,2:4,5-diacetals were identified. Anomeric acyclic 3,6-anhydro-1,2:4,5-di-O-isopropylidene-D-mannosides (4) were obtained from methyl 3,6-anhydro-α-D-mannopyranoside with propanone-sulphuric acid.[7] Terminal



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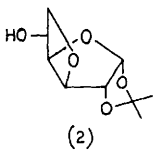

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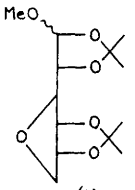

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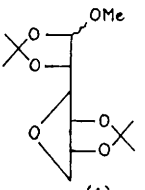
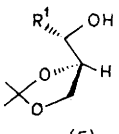


(4)

1,3-dioxolans (5) were obtained when the corresponding 1-C-substituted-D-erythro-glycerols reacted with propanone-sulphuric acid.[8] The 3,6:4,5-di-O-isopropylidene derivative (6), a minor product in the isopropylidenation of 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal, has been isolated and characterized by X-ray crystallography.[9]



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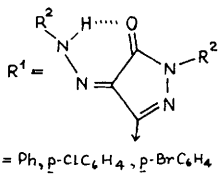
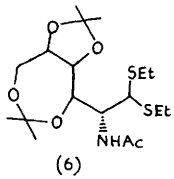




(6)

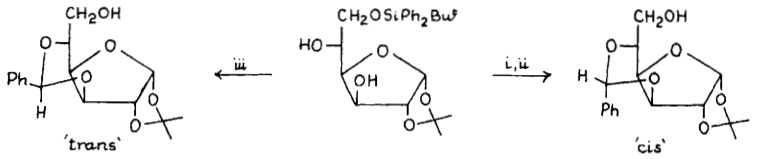
Isopropylidenation of lactose with 2,2-dimethoxypropane-tosic acid yielded 2,3:5,6:3',4'-tri-O-isopropylidene lactose dimethyl acetal and its 6'-O-(2-methoxy)isopropyl derivative, both useful in the synthesis of 2'-substituted lactose derivatives.[10] The products of the same reaction with raffinose have been analyzed: seven mono-, di-, and tri-acetals were identified with reactions occurring at 1',2-, 2,3-, 2",3"-, 3,4-, 3",4"-, and 4",6"- positions.[11]

The n.m.r. spectral data for isopropylidene groups is discussed in Chapter 21.

2 Benzylidene acetals

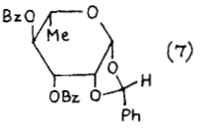
A reinvestigation of the main product from reaction of D-ribonolactone with benzaldehyde dimethyl acetal has shown that it is the 2,3-O-benzylidene derivative of the 1,4-lactone and not the 2,4-O-benzylidene analogue of the 1,5-lactone as previously suggested.[12] A

specific synthesis and stereo-chemical assignment of epimeric 3,5-O-benzylidene-1,2-O-isopropylidene-α-D-glucofuranoses has been reported (Scheme 1).[13] Both epimers of methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside have been prepared by treatment of the



Scheme 1

4,6-diol with α,α-dichlorotoluene in the presence of potassium butoxide and shown to have chair configurations in each case.[14] The 1,2-O-benzylidene-α-L-rhamnoside (7) has been synthesized by treatment of 2,3,4-tri-O-benzoyl-α,β-L-rhamnopyranosyl bromide with sodium borohydride in acetonitrile.[15]



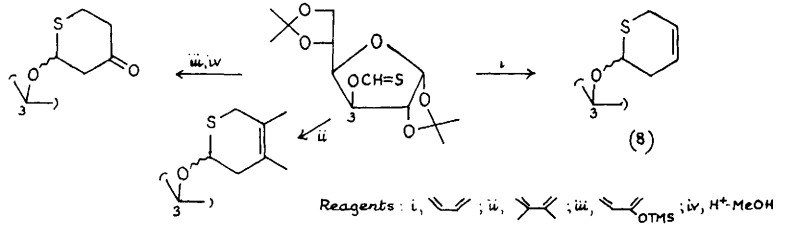
(7)

Application of vicinal $^{13}C-^{1}H$ J values to derivatives of 3,4-O-benzylidene-galactose, 2,3-O-benzylidene-mannose, and 2,3-O-benzylidene-gulose, each as separate R and S epimers at the benzylidene carbon, has provided data on the conformations adopted. Where data were also available from X-ray diffraction, the conformations were found to be the same in solution as in the solid state.[16]

3 Other acetals

An improved synthesis of 1,2-O-cyclohexylidene-myo-inositol in 45 - 50% yield utilized the reaction of 1,1-dimethoxycyclohexane with myo-inositol in DMSO catalyzed by Nafion-H, a perfluorinated strongly acidic ion exchange resin. Minor products were the 1,2:3,4-, 1,2:4,5-, and 1,2:5,6-diacetals.[17] The acidic reagent systems, phosphorus pentoxide-trimethylsilyl triflate and phosphorus pentoxide-boron trifluoride etherate, have proved effective for O-methoxymethylation of carbohydrate and nucleoside derivatives with dimethoxymethane; noteworthy is the compatibility of the reagents

with ester protecting groups which can migrate under alkaline conditions.[18] Cyclic oxythioacetals have been prepared by Diels-Alder reactions of sugar O-thioformates illustrated for a glucofuranose derivative in Scheme 2. Use of high pressure (2.5 kbar) led to a 5.2 ratio of the diastereoisomers of the thiene (8) rather than the 1:1

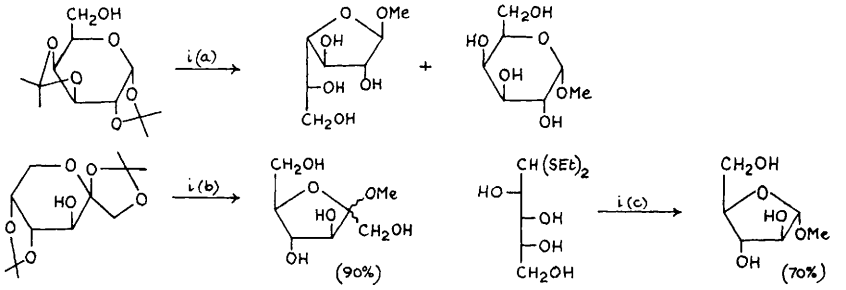


Scheme 2

ratio obtained in sealed tube condensation.[19]

4 Reactions of acetals

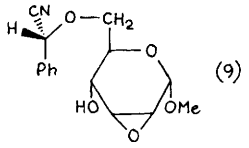
Treatment of carbohydrate acetals and dithioacetals with iodine in methanol gives acetal cleavage; where the acetal is attached at the anomeric centre, methyl glycosides usually result. Some examples are shown in Scheme 3.[20] Catalytic transfer hydrogenolysis of benzyl-



Scheme 3

idene acetals with palladium on charcoal and ammonium formate or hydrazine hydrate may be used to remove the acetals completely, or selectively for endo-isomers by using controlled conditions. The products are β-hydroxy benzyl ethers. Reaction with methyl 2-O-benzoyl-3,4-endo-O-benzylidene-β-L-arabinopyranoside yielded the 3-O-benzyl-4-hydroxy and the 4-O-benzyl-3-hydroxy derivatives in 3%

and 22% yield respectively. With methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside, methyl 3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside was produced.[21,22] The isomerization of 4,6-O-ethylidene--benzylidene-, and -(4-methoxy)benzylidene-1,2-O-carbonyl-α-D-galactopyranoses in the presence of Lewis acids has been studied. The products were the 3,4-acetals with retention of the 1,2-carbonyl groups.[23] The reagent system trimethylsilyl cyanide-boron trifluoride etherate reacts with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside to yield the α-cyanobenzyl ether (9). No epoxide



(9)

ring-opening occurred even with excess reagent.[24]

Reference to the reductive ring-opening of 2,3-O-acetals of 1,6-anhydro-β-D-mannopyranoses for the preparation of 2-azido-derivatives of 1,6-anhydro-mannose is made in Chapters 5 and 9.

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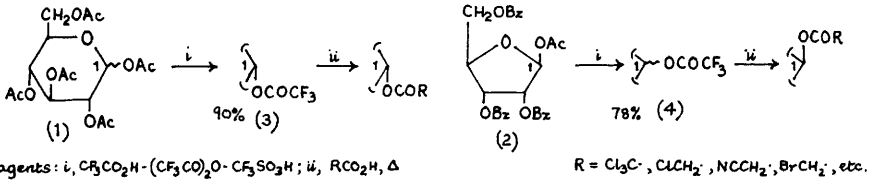
7
Esters

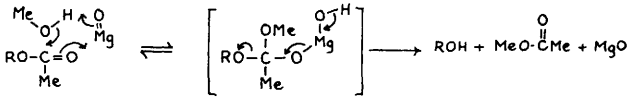
1. General methods

The anomeric acetoxy groups of the glucose or ribose peresters (1) and (2) can be substituted by trifluoroacetoxy groups to yield (3) and (4) respectively, which may then be readily replaced by a different acyloxy group on fusion with a carboxylic acid, as shown in Scheme 1. The predominant anomers were isolated by direct crystallization.[1] It has been found that magnesium oxide catalyzes non-



Scheme 1

selective and quantitative methanolysis of polyacylated sugars at room temperature. Many examples of the reaction, which is thought to proceed by the mechanism shown in Scheme 2, were tabulated, with reaction times varying from 25 min to 6 hours.[2] A facile procedure has been described for the regioselective 1-O-deacylation of fully



Scheme 2

acylated sugars which gives yields in the range 60 - 80%. A solution of 2 molar equivalents of sodium methoxide in THF with the acylated sugar was chilled in ice-water for 20 min, and then the reaction was quenched with acetic acid and the products isolated chromatographically.[3] Lipase has been used to effect selective cleavage of the primary acylate in methyl tetra-acylato-D-hexopyranosides. Pentanoyl esters were found to be the most convenient groups to use.[4] The

selective acylation of methyl 4,6-O-benzyl-α-D-mannopyranoside under various conditions with different reagents has been studied. Acetyl chloride in pyridine gave 64% 2-O-acetate, while acetic anhydride in pyridine gave 55% 3-O-acetate. Similarly tosylation could be selectively accomplished at either O-2 or O-3 by means of tosyl chloride in the presence of tetrabutylammonium sulphate and 5% sodium hydroxide in dichloromethane or tosyl chloride in pyridine respectively. Benzoylation on the other hand appeared always to yield predominantly the 2-O-benzoyl derivative.[5]

2. Carboxylic esters

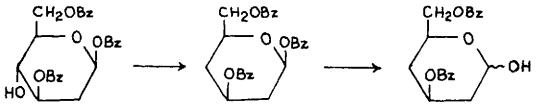
A convenient, high-yielding synthesis of 1,2,3,4,6-penta-O-acetyl-β-D-[1-^{2}H]glucopyranose has been described, in which D-glucono-1,5-lactone is acetylated with acetic anhydride-zinc chloride and reduced with sodium tetraborodeuteride in the presence of acetic anhydride in deuterium oxide. In the absence of acetic anhydride, the reduction yielded a mixture of anomers.[6] Replacement of O-benzyl groups by O-acetyl groups has been effected using acetic anhydride with iron(III) chloride. The differential rates observed allowed selective deprotection. Thus in D-glucopyranose derivatives the relative rates for replacement were 125:24:1 for O-6, O-3, and O-2 respectively.[7] All isomers of tetra-O-acetyl-D-glucopyranose and their corresponding monobenzyl and monotrityl ethers have been synthesized conventionally and their ^{1}H- and ^{13}C-n.m.r. spectra completely assigned.[8]

The structures of the hepta-O-acetylsucroses produced by deacetylation of octa-O-acetylsucrose on aluminium oxide impregnated with potassium carbonate have been determined. Four principal hepta-O-acetyl components were obtained in 34% total yield, all having a hydroxy group free in the fructose moiety (ratios of free hydroxy groups, 4' (43%), 1'(23%), 3' (19%), and 6' (15%)). Likewise two hexacetates (3',4'- and 1',3'-dihydroxy compounds) were isolated in 42% yield, others only being present in trace amounts.[9] The tetra-acetyl disaccharide 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl-(1-2)-4-O-acetyl-α-L-arabino-pyranose has been isolated as a steroidal glycoside from the plant *Trillium tschonoskii*.[10]

A comparison of bis(tributyltin)oxide, potassium cyanide, and potassium hydroxide as reagents for regioselective 1-O-deacetylation of fully acetylated sugars has been conducted. Potassium hydroxide

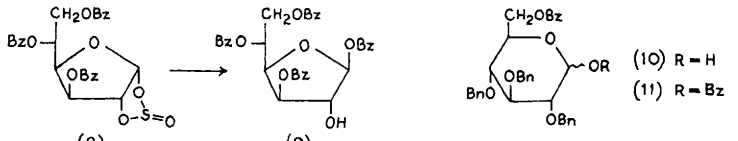
was much the fastest, but not always applicable due to its alkalinity.[11] Potassium cyanide has also been examined as a deacetylating agent when used in catalytic amounts in methanol. The conditions, though mild, produced yields approaching 100%.[12]

Selective benzoylation of 2-deoxy-D-arabino-hexose using benzoyl chloride in pyridine shows that the order of substitution is 6>3≈1>4. Thus 1 equivalent of the reagent gave 79% 6-benzoate; 2 equivalents, 40% 1,6- and 46% 3,6-di-benzoate; 3.2 equivalents gave 8% 1,6-dibenzoate, 13% 1,4,6-tribenzoate and 70% 1,3,6-tribenzoate (5). The tribenzoate (5), on treatment with thiocarbonyldi-imidazole as a deoxygenating reagent, yielded the 2,4-dideoxy-tribenzoate (6), which could be selectively 1-O-debenzoylated with ammonia in methanolic THF to give the dibenzoate (7).[13]



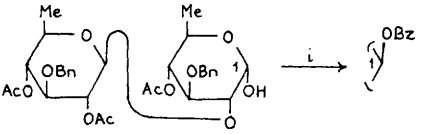
(5) (6) (7)

Cyclic sulphites have been reacted with sodium benzoate to yield the 1-O-benzoate with a trans-1,2-relationship to the C-2-hydroxy group, e.g., the sulphite (8) gave the β-glucosyl tetrabenzoate (9).[14] Glycosyl esters have been prepared by the Mitsunobu re-



(8) (9)

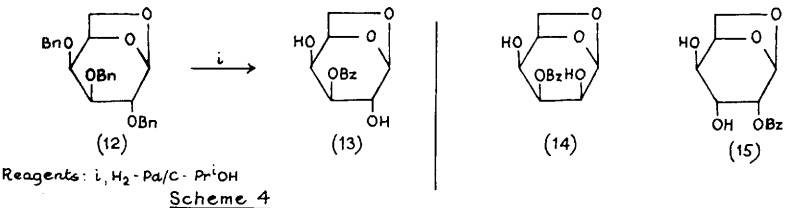
action; the product was produced by stereospecific inversion, and pure anomeric esters were obtained from anomerically pure sugars. Thus 2,3,4,6-tetra-O-benzyl-D-glucose (10) as a 4:1 α:β mixture gave the α,β-1-O-benzoate (11) in a 1:4 ratio. An example with a disaccharide derivative is shown in Scheme 3. The reaction, which



Reagents: i, Ph_3P-DIAD-BzOH-THF

Scheme 3

was also carried out with aliphatic acids, shows no participation from 2-O-acyl groups, and can be made selective at the anomeric centre in the presence of other free hydroxy groups.[15] An unusual trans benzoyl migration has been observed during allylation of 1,6-anhydro-2-azido-4-O-benzoyl-β-D-glucopyranose with allyl bromide-sodium hydride; the product consisted of a mixture of the expected 3-O-allyl derivative and a substantial amount of the 4-O-allyl-3-O-benzoyl derivative.[16] The benzyl groups in 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-hexopyranoses have been found to act as hydrogen donors in catalytic transfer hydrogenolysis, producing monobenzoyl ester derivatives. Thus the anhydro galactose tribenzyl ether (12) gave 1,6-anhydro-3-O-benzoyl-β-D-galactopyranose (13) in 70% yield (Scheme 4). The anhydromannose under the same conditions gave a 42% yield of the debenzylated 3-benzoate (14), whereas the corresponding anhydro-gulose yielded a 40% yield of the 2-benzoate (15). 1,6-Anhydro-2,3,4-tri-O-benzyl-β-D-glucopyranose gave no benzoylated products.[17]



Scheme 4

Selective dearoylation of peraroylated β-D-ribofuranosyl nucleosides has been carried out. When sodium methoxide in THF was used, the 2'- and 3'-hydroxy groups were unmasked, giving the 5'-O-acyl nucleoside. N-Acyl groups on the heterocyclic bases were unaffected. The reaction was successfully carried out with benzoyl, toluoyl and isobutyryl groups.[18] When potassium tert-butoxide in either THF or dichloromethane was used at low temperatures (-50 to -20°C), selective cleavage occurred at O-2' and yields were 65 - 80%.[19]

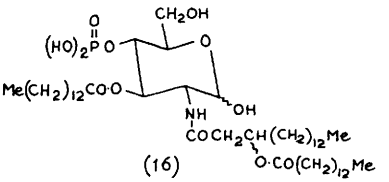
Lipase-mediated transesterification using 2-trichloroethyl butyrate and a free D-glucose produced 6-O-butyryl-D-glucose in moderate yield. The reaction with D-galactose and D-mannose also produced the 6-esters while D-fructose gave both the 1- and the 6-ester. Several other similar transesterifications were carried out.[20]

Esterification by means of 4-azidobutyryl chloride provides a useful temporary protecting group, and the resultant ester may be cleaved by hydrogen-palladium reduction to the 4-aminobutyrate, which, on heating in ethanol under reflux, gives 2-pyrrolidinone spontan-

eously, thus releasing the hydroxy group. The reduction occurs without affecting O-benzyl or an olefinic double bond, yet it is stable under conditions which remove an allyl group.[21]

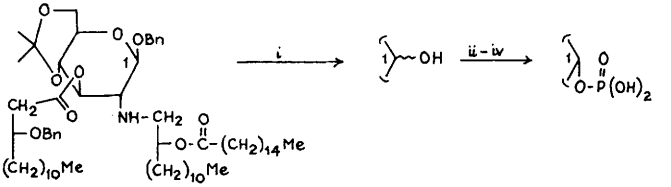
Reference to the preparation and properties of octanoyl esters of mannitol is made in Chapter 18. The synthesis of 3- and 5-monoesters and 3,5-diesters of D-xylose derived from C_{12}, C_{14}, and C_{16} fatty acids, required for studying surfactant properties, has been described.[22] Long-chain fatty acid esters of D-glucosamine derivatives have been synthesized from benzyl 2-amino-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside. 3-O-Acyl-2-acylamido-2-deoxy-D-glucoses and benzyl 2-acylamido-α-D-glucopyranosides of C_8, C_{12}, and C_{16} fatty acids were prepared.[23]

2-Deoxy-4-O-phosphono-3-O-tetradecanoyl-2-[(3R)- and (3S)-3-tetradecanoyloxytetradecanamido]-D-glucose (16), a diastereomeric pair of derivatives related to bacterial lipid A, have been synthesized conventionally.[24] Derivatives of lipid Y, a component of lipid A



(16)

from Salmonella minnesota, have been synthesized as shown in Scheme 5, the key step being a chemoselective debenzylation of the phosphate ester.[25] Bridged sugar esters used as antitumour and immunoadjuvant



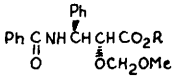
Reagents: i, 10% Pd/C-THF-EtOH; ii, BuLi; iii, $ClP(O)(OBn)_2$; iv, 10% Pd/C-THF

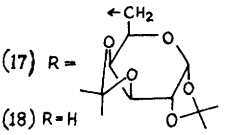
Scheme 5

agents are described in Chapter 9. The ester (17) has been prepared in a trial experiment to establish conditions for esterification of the hydroxy acid (18) which forms part of the complex diterpene taxol.[26]

The mesomorphic properties of α- and β-anomers of penta-O-decanoylglucopyranose have been confirmed by microscopy, liquid crystal

induced CD, and X-ray diffraction of non-oriented samples. A non-hexagonal columnar ordering was proposed.[27] Higher esters of



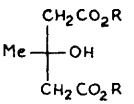


(17) R =

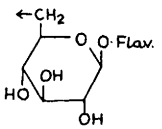
(18) R = H

sugars and inositols have been the subject of a discussion of the relationship of molecular structure to liquid crystal properties. Various higher esters of scyllo-inositol, cis-cyclohexane-1,3,5-triols and β-D-glucopyranose were used as model compounds.[28]

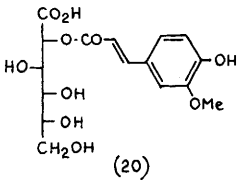
Sudachiin D, isolated from the green peel of Citrus sudachi, has the unusual structure (19) in which two flavone glycosides are ester linked by a 3-hydroxy-3-methyl glutaric acid moiety.[29]



(19) R =



The primary leaves of rye, Secale cereale, have yielded 2-(E)-O-feruloyl-D-gluconic acid (20) and a variety of positional isomers.[30] Seven bitter sucrose esters have been isolated from Lilium speciosum



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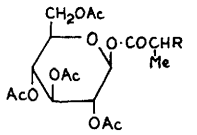


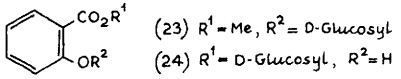
(21) R = 6-Methoxy-2-naphthyl

(22) R = Bu^{i}

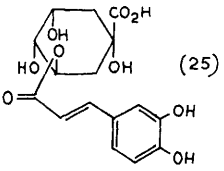
var. rubrum bulbs. Each was fernoloylated at the 3,6'-position, and in addition had up to three acetyl groups at various positions.[31]

The glycosyl esters (21) and (22) of 2-(6-methoxy-2-naphthyl)-propanoic acid (naproxen) and p-isobutylphenylpropanoic acid (ibuprofen) respectively have been prepared by a phase transfer method; the products were better antiinflammatory agents than the parent acids.[32] Glucosides of salicylic acid (23) and (24) have been synthesized by conventional methods.[33] The association of polyphenols, e.g., tri- to penta-O-galloyl-β-D-glucopyranose, or chlorogenic acid (25) or its sodium salt, with caffeine and with α- and β-cyclodextrins has been

probed and the binding of the galloyl esters or (20) shown to be considerably modified by the presence of saccharides such as the cyclo-



(23) R^1 = Me, R^2 = D-Glucosyl
(24) R^1 = D-Glucosyl, R^2 = H

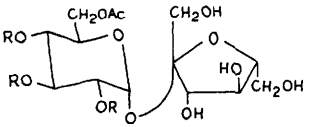


(25)

dextrins.[34] Pentagalloyl-glucose and related gallotannins have been shown to be potent inhibitors of glucan synthesis by glucosyl-transferase from a cariogenic bacterium, Streptococcus mutans, with 50% inhibition at 10^{-4}M. The enzyme is considered to be an appropriate target for dental caries prevention, and these compounds are more effective inhibitors than chlorhexidine.[35]

An improved synthesis of 6-O-mycoloyl- and 6-O-corynomycoloyl-α,α-trehalose, with observations on the permethylation analysis of trehalose glycolipids, has been described; potassium salts of the appropriate acid were used with 6-O-tosylate derivatives of trehalose to give the required products.[36] The same group has prepared 4,6-anhydro-α-D-galactopyranosyl-6'-O-mycoloyl- and -corynomycoloyl-α-D-galactopyranoside by a similar procedure.[37] The same displacement procedure has also been used to synthesize 6-O-mycoloyl-D-glucose, -2-acetamido-2-deoxy-D-glucose, and -D-galactose, as well as 5-O-mycoloyl-D-arabinose, besides 6-O-mycoloyl-α,α-trehalose; these compounds were examined for their lethal toxicity and adjuvant activity.[38] Zwitterionic anthocyanins, with malonic acid esters on their glucosidic residues, have been found to be widespread in the Compositae plant group.[39]

The (3S)-methylpentanoyl triester (26) of sucrose has been isolated from tobacco.[40] Determination of the position of the ester



(26) R = $MeCH_2\underset{Me}{C}HCH_2CO$→

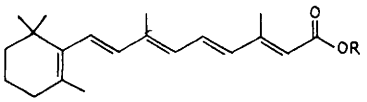
groups in (26) was achieved by means of 2D-n.m.r. spectroscopy to detect long-range coupling of the acyl group protons and the ring protons with the carbonyl carbon atoms of the ester.[41] Mono-oleoyl and -linoleoyl esters of sucrose have been synthesized in 80-

85% yields by esterification of the sugar with the corresponding fatty acid in DMF at 90 - 95° with potassium carbonate.[42] 3,4-Di-isobutyryl-6-O-capryl-sucrose has been identified as the major component of a complex contained in type B glandular trichomes on the leaves of the wild potato, Solanum berthaultii. The complex is indicated in the resistance of the plant to Phytophthora infestans infection.[43] Full details on the selective 1-O-acylation of lactose to give either α- or β-linked acyloxy moieties have been published (see Vol. 17, p.71); the work was extended to β-D-maltose and β-D-glucose using reactive acylating reagents prepared from acyl chlorides and mercaptothiazoline, mercaptobenzothiazole, p-nitrophenol, or 8-hydroxyquinoline.[44]

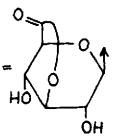
Regioselective phenylcarbamoylation of polyhydroxy compounds has been achieved using phenyl isocyanate-zinc naphthenate. Common aldohexo- and -pentopyranosides gave the 3-O-phenylcarbamates in fair to excellent yields, with the 2-ester being the minor product. In the absence of zinc naphthenate, the ester is formed at O-6. With N^6-benzyladenosine the product was the O-2'ester, while 3,4-O-isopropylidene-D-mannitol gave the 1,6-bisphenylcarbamate in high yield.[45]

Reference to peptido ester derivatives of sugars is made in Chapter 18.

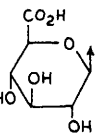
Retinoyl fluoride reacts with D-glucurono-6,3-lactone to yield the 1-O-acyl ester (27), which on acid hydrolysis and h.p.l.c. purification gave the free acid (28).[46] 18β-Glycyrrhet-3-yl and -30-yl β-D-glucopyranuronic acids have been prepared by Koenigs-Knorr synthesis.[47]



(27) R =



(28) R =

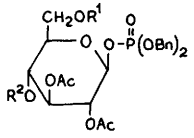


3. Phosphates and related esters

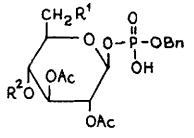
Xylitol 1-O-(dichlorophosphite)-2,3:4,5-bis-O-(chlorophosphite), L-arabinitol 1-O-(dichlorophosphite)-2,3:4,5-bis-O-(chlorophosphite), and ribitol 3-O-(dichlorophosphite)-1,2:4,5-bis-O-(chlorophosphite) have been prepared by reaction of pentitols with phosphorus trichloride.[48]

The secondary kinetic ^{18}O isotope effect on hydrolysis of D-glucose 6-phosphate labelled with ^{18}O in the non-linking phosphate positions has been determined. Using glucose and [1-^{13}C]glucose esters, the hydrolysis was stopped at half reaction and the unreacted ester was enzymically converted to ribulose 5-phosphate and carbon dioxide, the degree of labelling in which was determined. The isotope effect was found to be 1.0046 for each oxygen determined.[49] The kinetics of the oxidation of D-glucopyranose 6-phosphate and D-ribofuranose 5-phosphate to the corresponding aldonic acids by vanadium(V) in perchloric acid media have been studied and a mechanism proposed.[50]

D-Glucosyl dibenzylphosphates, (29) - (31), have been prepared by reaction of the corresponding α-glycosyl bromide with silver dibenzylphosphate and their reactions towards sodium azide investigated. Monodebenzylation occurred in each case and sulphonates at C-6 were displaced but 4-O-sulphonates were unreactive. Thus the 6-tosylate (29) gave the azide (32), the 4,6-dimesylate (30) gave the 6-azido-4-O-mesyl product (33), whereas the 4-O-mesylate (31) did not react.[51] With sodium iodide in butanone (29) gave the 6-iodide (34).



(29) R^1 = OTs, R^2 = Ac
(30) R^1 = R^2 = Ms
(31) R^1 = Bz, R^2 = Ms



(32) R^1 = N_3, R^2 = Ac
(33) R^1 = N_3, R^2 = Ms
(34) R^1 = I, R^2 = Ac

All four monodeoxyfluoro-α-D-glucopyranosyl phosphates have been prepared using the DAST procedure and their acid-catalyzed hydrolysis studied. Fluorine substitution was found to reduce the rate relative to the parent sugar phosphates.[52]

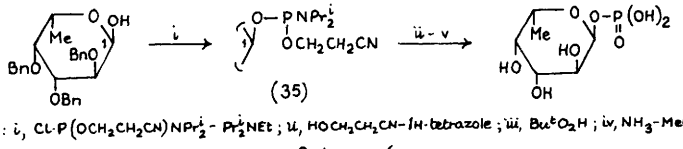
α-D-[U-^{14}C]Mannopyranosyl dolichyl pyrophosphate has been obtained conventionally from the corresponding mannopyranosyl phosphate.[53]

Total synthesis of optically active myo-inositol 1,4,5-triphosphate is described in Chapter 18.

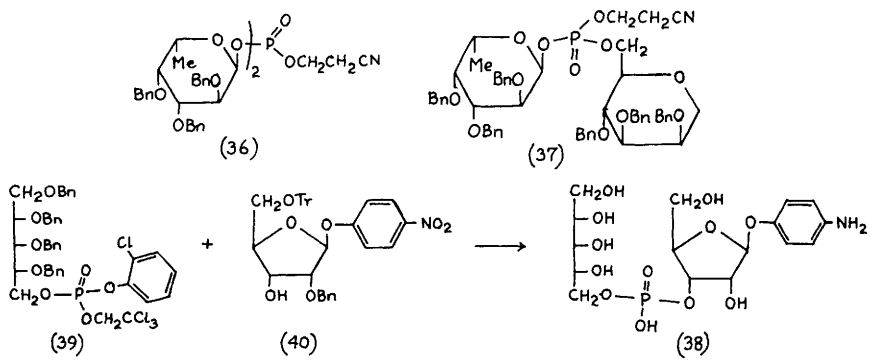
Direct synthesis of α-L-rhamnopyranosyl phosphate has been achieved as shown in Scheme 6. The intermediate (35) was also used to obtain the di-glycosyl phosphates (36) and (37).[54]

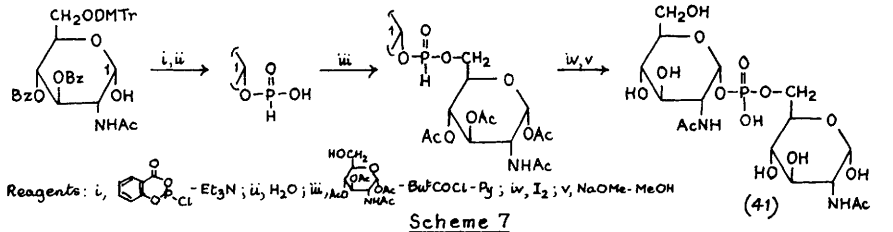
p-Aminophenyl β-D-ribofuranoside 3-(D-ribit-5-yl)phosphate (38) has been synthesized by coupling the tetrabenzyl ribitol O-chlorophenylphosphate (39) with the p-nitrophenyl glycoside (40) followed by deprotection and hydrogenation of the product.[55] The synthesis of bis(glucos-6-yl) phosphate, glucos-3-yl glucos-6-yl phosphate, and

glucos-2-yl glucos-6-yl phosphate has been achieved by a modified triester procedure. The products were confirmed by ^{1}H-, ^{13}C-, and ^{31}P-n.m.r. spectroscopy, which also indicated conformations around the phosphorus bridges.[56] The structure of agrocinopine, obtained from tobacco crown gall tumour cells, has been confirmed by ^{1}H- and ^{31}P-n.m.r. and 2D n.m.r. techniques, to be a phosphodiester of sucrose and L-arabinose linked *via* O-4 of fructose and O-2 of arabinose.[57] The repeating fragment of the cell wall of *Staphylococcus lactis*, 1-*O*-(*N*-acetylglucosamine) 6-*O*-(*N*-acetylglucosamine) phosphate (41), has been synthesized by the route shown in Scheme 7, which was better than the triester approach because of the participation of the group at C-2.[58]



Scheme 6

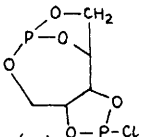




Scheme 7

The reaction product of ribitol and phosphorus trichloride in the presence of triethylamine has been re-examined and shown to be the tricyclic phosphite (42).[59] 1,2-*O*-Isopropylidene-D-glucuronic

acid 3,5,6-bicyclophosphite (43) has been synthesized from 1,2-O-isopropylidene-α-D-glucuronofuranose by treatment of its sodium salt with phosphorus trichloride in triethylamine. The bicyclophosphate (43) yielded the cyclophosphates (44) and (45) on reaction with ethanolic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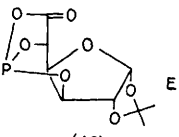
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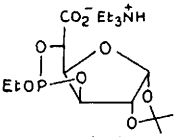
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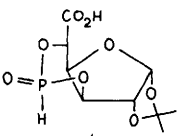
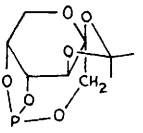

(45)

sodium ethoxide in the presence of triethylamine and aqueous THF respectively.[60] The novel bicyclophosphites (46) and (47) have been prepared from 2,3-O-isopropylidene-D-fructopyranose and methyl α-D-mannopyranoside respectively by treatment with $P(NEt_2)_3$ in pyridine, followed by heating to 110°C. The phosphapane ring was opened with hydrogen peroxide to yield the monocyclophosphates (48) and (49).[61]

Conformational studies on sugar phosphates are mentioned in Chapter 21.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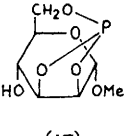
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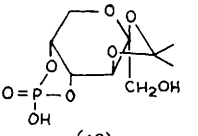
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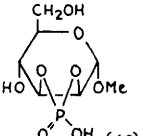
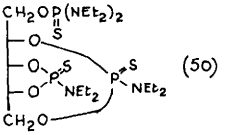

(49)

The pH dependence of the rate of hydrolysis of disodium adenosine triphosphate has been determined.[62] Other aspects of the synthesis and structure of nucleotides will be found in Chapter 20.

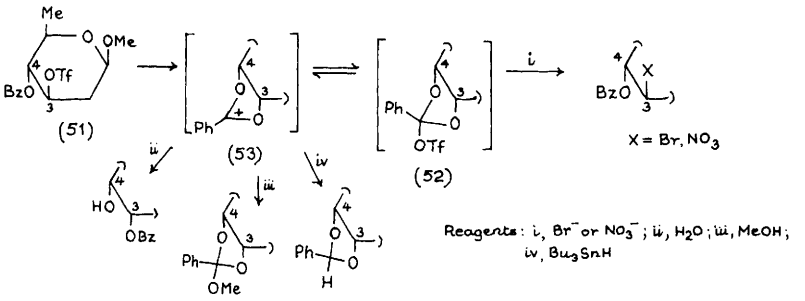
A bis(cycloaminothionophosphate) of ribitol (50) has been synthesized from ribitol, phosphorus trichloride, and sulphur in the presence of diethylamine.[63]


(50)

4. Sulphonate esters

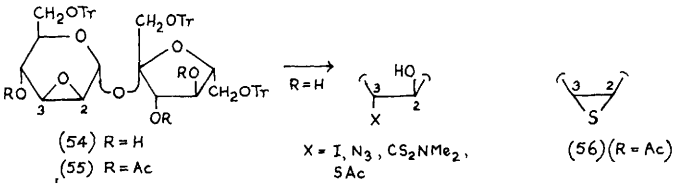
From a study of the partial tosylation of methyl α-D-mannopyranoside, the order of substitution was found to be 6>3>2>4. With two equi-

valents of tosyl chloride in pyridine the products were: 3,6-ditosylate, 35%; 6-monotosylate 35%; 4,6- and 2,6-ditosylate (not separated), 14%; 2,3,6-tritosylate, 3%; and 3,4,6-tritosylate, 1%. When three equivalents of tosyl chloride were used the yields of the same products were 40%, 25%, 15%, 5%, and 2% respectively.[64] The 3-triflate (51) undergoes the expected S_N2 reaction with bromide ion but, on extended reaction at room temperature, rearranges to yield the unstable orthoester (52), presumably *via* the benzoxonium ion (53). If other weak nucleophiles are present, then substitution occurs at the benzoxonium cation, while strong nucleophiles react at the C-3 with overall retention of configuration (Scheme 8).[65,66]



Scheme 8

The tosylation of cellobiose by tosyl chloride in pyridine and thermal analysis of the products using DTA and isothermal TGA has been carried out.[67] Selective tosylation of 6,1',6'-tri-*O*-trityl sucrose gave the 2-tosylate and not the 3-tosylate as previously claimed by I.Jeze (Chem. Zvesti, 1971, 25, 369). Base treatment of this gave 40% 2,3-manno-epoxide (54), which was opened with a variety of nucleophiles: in all cases the 3-nucleophilo-altro product resulted (Scheme 9). With ammonium thiocyanate, the acetylated epoxide (55) gave the 2,3-allo-epithio disaccharide (56).[68] Imidazolylsulphonyl derivatives of carbohydrates and their reactions are mentioned in Chapter 10.

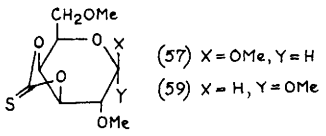


Scheme 9

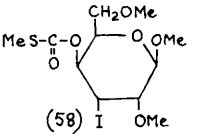
5. Other esters

The nature of ester formation between borate and D-mannitol, D-glucitol, D-fructose and D-glucose in aqueous solution at pH 6 - 12 has been elucidated using ^{11}B- and ^{13}C-n.m.r. spectroscopy.[69] In order to better understand the action of a gluconate-borate eluent for elution of anions from an anion-exchange resin, the structural features of such solutions have been investigated by potentiometric titrations and ^{13}C-n.m.r. spectroscopy.[70] Reference to borate esters as transport media in a model membrane will be found in Chapter 2.

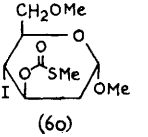
Selective protection of a primary hydroxy group can be effected with allyloxycarbonyl chloride in pyridine at -35°C: the product is the mixed allyl glycosyl carbonate. Where a vicinal hydroxy group is present, the product is the cyclic carbonate.[71] Methyl 2,6-di-O-methyl-3,4-O-thiocarbonyl-β-D-galactoside (57) gave rise to the 3-iodo-4-methylthio gulo-ester (58) on treatment with methyl iodide. When the α-anomer (59) was similarly treated the product was the 4-iodo-3-methylthioester glucoside (60). Similar results were obtained with the β-L-arabino-cyclothiocarbonate.[72] 1,2-Cyclic sulphites



(57) X = OMe, Y = H
(59) X = H, Y = OMe



(58)

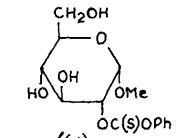


(60)

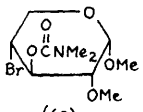
have been synthesized by treatment of reducing sugar derivatives having free hydroxy groups on C-1 and C-2 with thionyl chloride in pyridine.[73] Regioselective thioacylation of glycopyranosides has been achieved by means of the thioacyl chloride in the presence of dibutyltin oxide. Methyl α-D-glucopyranoside gave mainly the 2-phenylthionocarbonate (61) and some 6-ester with phenyl-thionocarbonyl chloride, whereas the β-anomer gave the 6-ester exclusively. The same reagent and methyl β-D-xylopyranoside gave the 4-ester exclusively, whereas the α-anomer gave a mixture of 2- and 4-esters. The products were useful for reduction to the corresponding deoxy sugars.[74] Dibutyltin oxide has also been used to achieve regioselective phenylcarbamoylation of ribonucleosides (see also Chapter 20).[75]

A one-pot synthesis of bromodeoxy carbamates has been achieved using Viehe's salt followed by treatment with lithium bromide. Thus

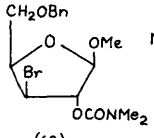
a 92% yield of the xylo-4-bromo-3-carbamate (62) was obtained from methyl 2-O-methyl-β-L-arabinopyranoside. The xylo (63) and manno (64) derivatives were similarly prepared.[76] Treatment of the 1,6-anhydro-sugar (65) with trichloroacetyl isocyanate followed by filtration through alumina gave the corresponding unsubstituted carbamate (66).[77]



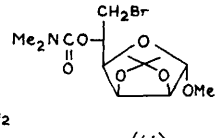
(61)



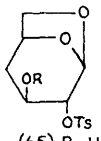
(62)



(63)

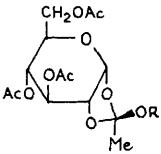


(64)



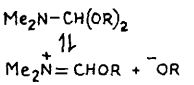
(65) R=H

(66) R=CONH2



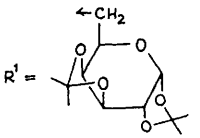
(67) R = Alkyl

(70) R = R¹



(68) R = Me, Et, etc.

(69) R = R¹



An efficient and stereoselective synthesis of 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-exo-alkyl ortho-acetates (67) has been achieved using DMF dialkyl acetals (68) and tetrabutyl ammonium bromide on acetobromoglucose. The DMF acetal from 1,2:3,4-di-O-isopropylidene α-D-galactopyranose (69) was also prepared and used to synthesize the mixed sugar orthoester (70).[78]

The synthesis of halogeno-sugars via an improved preparation of cyclic carbonates and sulphates will be found in Chapter 8 and the synthesis of glycosides using these intermediates in Chapter 2.

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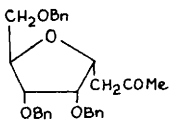
8
Halogeno-sugars

A review of reactions of carbohydrate acetals includes a section on conversion of acetals into halogen derivatives.[1] Reference to e.s.r. spectra of radicals produced by dehalogenation of sugars is made in Chapter 22.

1 Fluoro-sugars

The preparation and reactions of glycosyl fluorides have been reviewed.[2,3]

2,3,5-Tri-O-benzyl-D-ribofuranosyl fluoride has been synthesized by the reaction of 2,3,5-tri-O-benzyl-D-ribofuranose with an adduct of diethylamine and hexafluoropropene in dichloromethane. The reaction, conducted under nitrogen, was complete in four hours at room temperature and yielded 21.4% α-fluoride and 63.8% β-fluoride. The glycosyl fluorides are useful intermediates which can be reacted to produce O- or C-glycosides. Thus a mixture of the anomeric protected ribosyl fluorides reacted with the TMS derivative of vinyl alcohol with boron trifluoride etherate catalyst to yield 90 - 95% of the α-ribofuranosyl acetone (1); only traces of the β-anomer were present.

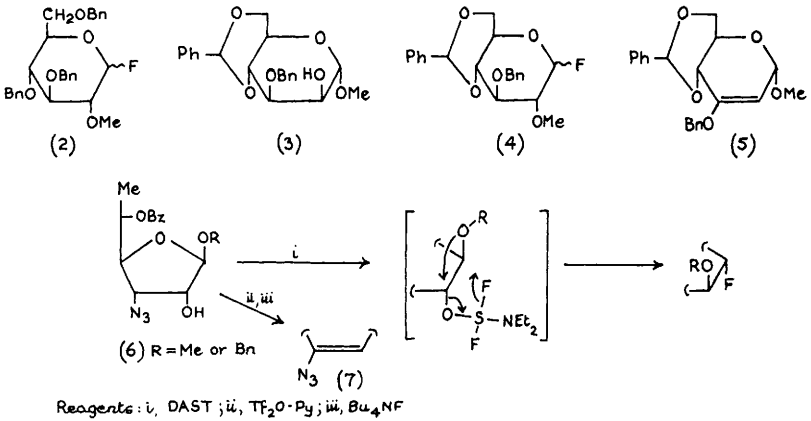


(1)

Hexabenzyl-β-D-ribofuranosyl-β-D-ribofuranoside was obtained by reaction of 2,3,5-tri-O-benzyl-D-ribofuranose, or its 1-trimethylsilyl derivative, with the corresponding β-glycosyl fluoride.[4] Per-O-benzylated α- and β-gluco-, β-galacto-, and β-xylo-pyranosyl fluorides have been prepared from the corresponding per-O-acetylated fluorides in 17 - 34% yield by phase-transfer catalyzed benzylation.[5]

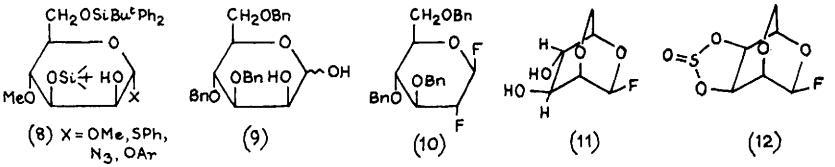
Attempts to prepare 2-fluorodeoxy derivatives from the free 2-hydroxy compounds using the DAST procedure have resulted in glycosyl

fluorides by a 1,2-migration. When methyl 3,4,6-tri-O-benzyl-α-D-mannopyranoside was used, the product was a 1:1 mixture of the 2-O-methyl α- and β-fluorides (2).[6] A similar result was obtained when methyl 4,6-O-benzylidene-α-D-mannoside (3) was treated with DAST, the products being the glucosyl fluorides (4). If pyridine was added to the reagent, the 2-ene (5) resulted.[7] A mechanism for the rearrangement was proposed for the furanosides (6) (Scheme 1). Attempts to prepare the 2-fluoride *via* the 2-triflate of (6) resulted in the 3-azido-2-enohexose (7).[8]



Scheme 1

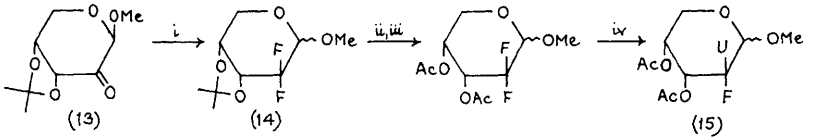
A study of the 1,2-migration in the silyl derivatives (8) has demonstrated that it occurs with thiophenyl glycosides and glycosyl azides as well as methyl and aryl glycosides; the glycosyl fluoride products were also converted to O-, S-, N-, and C-glycosides (see Chapter 2).[9] When DAST was employed on 3,4,6-tri-O-benzyl-α,β-D-mannopyranose (9), the 1,2-dideoxydifluoro-gluco-derivative (10) was obtained as a minor product together with the expected mannosyl fluoride.[6] Novel 2,6-anhydro-β-D-hexopyranosyl fluorides (11) and (12) have been prepared by treatment of 1,6-anhydro-α-D-gluco- and -galacto pyranoses. The migration of the anhydro bridge presumably



proceeds by an internal displacement of the intermediate 2-O-(di-

ethylaminodifluorothio) derivative.[10]

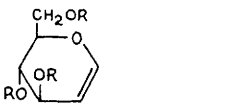
Application of the DAST procedure to the aldosulose derivative (13) gave the 2,2-difluoro-compound (14) as an anomeric mixture from which the separated anomers of the pseudonucleosides (15) could be prepared as shown in Scheme 2.[11] 1,3,4,6-Tetra-O-acetyl-β-D-manno-



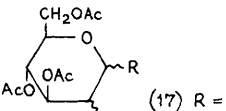
Reagents : i, DAST, ii, 95% HCO_2H ; iii, Ac_2O-Py ; iv, TMS·Uracil-BF_3

Scheme 2

pyranose, on treatment with DAST in diglyme at 100°, gave a 77% isolated yield of crystalline 1,3,4,6-tetra-O-acetyl-2-deoxy-2-fluoro-D-glucopyranose, which was readily deacetylated to the parent 2-fluoro-D-glucose.[13] A study of the factors affecting the ratio of 2-deoxy-2-fluoro-D-glucose and -mannose derivatives formed in the addition of gaseous acetyl hypofluorite to substituted glucal derivatives (16) in various solvents showed that the polarity of the solvent is more important than the size of substituents on the D-glucal. The amount of manno-isomer ranged from 4% in non-polar solvents up to 20% in the more polar media.[13] Similar results were



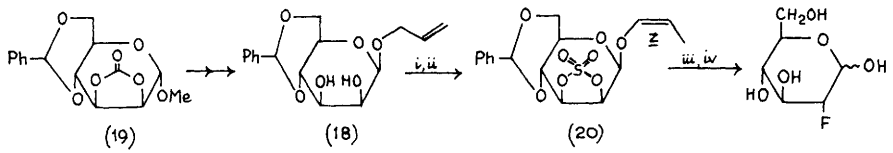
(16) R = H, Ac, Pr^iCO, Bz



(17) R = F(α-Glc, β-Man) or OH

reported for the syn-addition of fluorine and acetylhypofluorite to D-glucal and its triacetate, and the paper includes a rationale for the ^{19}F n.m.r. chemical shifts.[14] Fluorination of tri-O-acetyl-D-glucal in water gave a mixture of the fluoro-derivatives (17), which on treatment with hydrochloric acid gave 2-deoxy-2-fluoro-D-glucose and -mannose, separable by chromatography. The ^{18}F analogues were similarly prepared.[15] D-Glucal, D-galactal, and tri-O-acetyl-D-galactal have been stereoselectively fluorinated in water and water-organic solvent mixtures using fluorine or 18-fluorine in nitrogen or neon, yielding mainly the corresponding 2-deoxy-2-fluoro-D-glucose and -D-galactose derivatives respectively.[16] Strong acid conditions, e.g. 5M methylsulphonic acid at 110°, cause interconversion of

2-deoxy-2-fluoro-D-glucose and -D-mannose.[17] 2-Deoxy-2-fluoro-D-glucose has been synthesized from the allyl mannoside (18) as shown in Scheme 3. An improved synthesis of the 2,3-carbonate (19) was used to obtain (18).[18] A rapid synthesis of 2-deoxy-2-[^{18}F]fluoro-

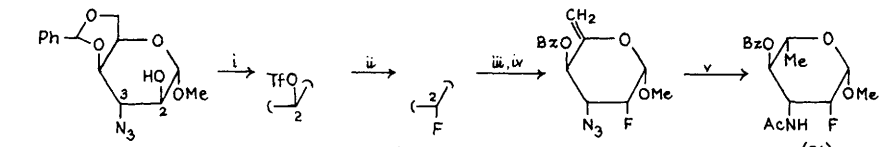


(19) (18) (20)

Reagents: i, KOBu^t-DMSO; ii $(Im)_2SO_2$-NaH; iii, Bu_4NF-MeCN; iv, H_3O^+

Scheme 3

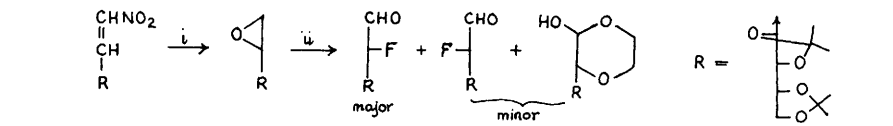
D-glucose using tetraethylammonium [^{18}F]fluoride with the cyclic sulphate (20) in yields up to 50% has been described by two other groups.[19,20] Methyl 2-acetamido-4-O-benzoyl-2,3-dideoxy-2-fluoro-β-L-rhamnoside (21) has been synthesized as shown in Scheme 4.[21] Conventional step-wise methods have been used in related preparations of 3-azido-2,3-dideoxy-2-fluoro- and 2-azido-2,3-dideoxy-3-fluoro sugars.[22]



Reagents: i, Tf_2O-Py; ii, Bu_4NF-DMF; iii, NBS; iv, AgF; v, H_2-Pd/C-Ac_2O (21)

Scheme 4

Reaction of 1,2-anhydro-3,4:5,6-di-O-isopropylidene-1-C-nitro-D-mannitol with potassium hydrogen difluoride in anhydrous ethylene glycol yielded 2-deoxy-2-fluoro-D-glucose; minor by-products arise by epimerization at C-2 of the initially formed fluoro-aldehyde, and by attack of solvent at C-2 of the intermediate nitro-epoxide. Part of the synthesis is shown in Scheme 5.[23]



major minor

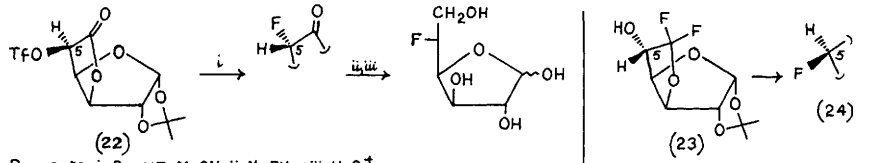
Reagents: i, H_2O_2-$NaHCO_3$; ii, KHF_2-$(CH_2OH)_2$

Scheme 5

3-Deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose has

been synthesized by caesium fluoride displacement of the corresponding allo-3-triflate and its crystal structure determined.[24] 3-Deoxy-3-[^{18}F]fluoro-D-glucose has been similarly prepared.[25]

Two papers describe the reaction of 6,3-lactone derivatives with fluorinating agents. In one, the 5-triflate (22) was subjected to fluoride displacement and the product converted to 5-deoxy-5-fluoro-D-glucofuranose as depicted in Scheme 6.[26] In the second, 1,2-*O*-

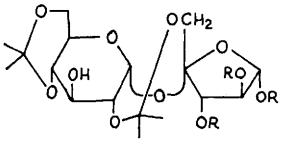


Scheme 6

isopropylidene-α-D-glucofurono-6,3-lactone was treated with DAST to yield the 6,6-difluoro anhydride (23) and a lesser amount of the inverted 5-monofluoride. 3,6-Anhydro-5-deoxy-5,6,6-trifluoro-1,2-*O*-isopropylidene-β-L-idofuranose (24) was prepared from (23) by triflate displacement methodology.[27]

Enzymic synthesis of several hexose derivatives from dihydroxypropanone and glyceraldehyde derivatives included a preparation of 6-deoxy-6-fluoro-sugars.[28] All four deoxyfluoro-α-D-glucopyranosyl phosphates have been synthesized and their acid-catalyzed hydrolysis studied. Fluorine substitution reduced the rate relative to the parent sugar phosphates.[29]

3-Deoxy-3-fluorosucrose has been synthesized by DAST treatment of the diacetal (25), followed by deprotection.[30] Reference to the use of 3-fluoro derivatives of a tri-galactose trisaccharide to investigate the binding site of an immunoglobulin is made in Chapter 4. Fluoro-sugar analogues of kanamycin A, daunomycinone, and adriamycinone are mentioned in Chapter 19.

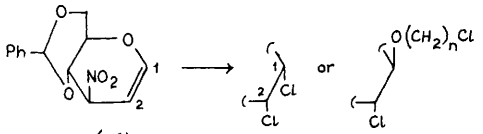


(25) R = SiBu^{t}Me$_2$

2 Chloro-, Bromo-, and Iodo-sugars

Crystalline tri-*O*-benzoyl-α-D-ribofuranosyl chloride and tri-*O*-

benzoyl-α-D-arabinofuranosyl bromide have been prepared by routine methods.[31] Glycosyl chlorides have been synthesized from 2,3-O-isopropylidene-5-O-tributylsilyl-ribofuranose by reaction with carbon tetrachloride: when tris(dimethylamino)phosphine was used at -78°, the α-chloride was produced exclusively, whereas triphenylphosphine at 67°C yielded the β-anomer.[32] Further examination of the reaction of chlorine with the nitroglucal derivative (26) (see Vol. 17, p.84) has demonstrated that the ratio of the glycosyl chloride (27) to the glycosides (28) can be varied by using different oxa- or dioxa-cycles as solvent and reactant. With dioxan, the product was exclusively the α-chloride (27), while use of tetrahydropyran, tetrahydrofuran, ethylene oxide or oxetan gave the glycosides (28) predominantly.[33] The addition of chlorine and bromine to di-O-acetyl-L-fucal and -L-rhamnal and their derivatives has been further investigated (see Vol. 19, p. 181). Non-polar solvents favour cis-chlorine adducts, and the C-6 substituent



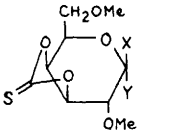
(26) (27) (28) n = 2-5

appeared to affect the anomeric carbocation stabilization produced in bromination.[34] 4-Chloro-4-deoxy-galacto-sucrose has been prepared by mesyl displacement at C-4 of sucrose.[35]

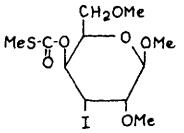
Titanium(IV) bromide reacts with acyl-protected glucose derivatives to yield glycosyl bromides. With N-acetylglucosamine derivatives, an N- to O-acyl rearrangement occurred.[36] Debenzylation accompanied reactions of O-benzyl-glucosyl esters. A rapid synthesis of 2-[^{82}Br]bromo-2-deoxy-D-mannose and -glucose from D-glucal by addition of 82-bromine has been described.[37] An alternative approach uses ^{82}BrCl with 3,4,6-tri-O-acetyl-D-glucal followed by deacetylation.[38] The use of bromo-derivatives formed by photobromination of 1,6-anhydrohexose derivatives is referred to in Chapter 5.

Treatment of the β-glycoside of the cyclic thionocarbonate (29) with methyl iodide gave the 3-iodo-gulo derivative (30), whereas the α-anomer (31) gave the 4-iodo-glucose derivative (32).[39] 6-Deoxy-6-iodo-L-ascorbic acid derivatives have been synthesized by the same method.[40]

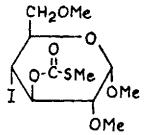
Reference to iodo derivatives of ascorbic acid is made in Chapter 16.



(29) X = OMe, Y = H
(31) X = H, Y = OMe



(30)



(32)

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9
Amino-sugars

1 Natural Products

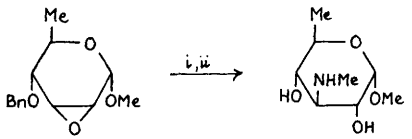
4-O-(2,6-Diamino-2,6-dideoxy-α-D-glucopyranosyl)-1-amino-1-deoxy-scyllo-inositol has been identified as a metabolite of Streptomyces ribosidificus SF-733 fermentation.[1] 5-Acetamido-3,5,7,9-tetradeoxy-7-formamido-L-glycero-L-manno-nonulosonic acid has been identified as a repeating unit in the lipopolysaccharide of Pseudomonas aeruginosa immunotype 6.[2] The occurrence of aminosugar containing antibiotics is reported in Chapter 19.

2 Synthesis

Syntheses covered in this section have been arranged according to the starting point for introduction of the amine functionality. The stereoisomers of 2,3,6-trideoxy-3-aminohexose (including daunosamine, acosamine, and ristosamine) have again been major synthetic targets, and syntheses of them and their 3-nitro-analogues have been reviewed (262 references).[3]

D-[U-^{14}C]Glucosamine has been prepared from labelled D-fructose in a two step, one pot reaction (i, NH_3-NH_4Cl-MeOH, 9 days, r.t.; ii, $HO_2C(CH_2)_3CO_2H$-$PhCO_2H$, 9 days, r.t.).[4]

3,6-Dideoxy-3-(methylamino)-D-hexopyranosides have been synthesized as standards for the identification of Rhizobium lipopolysaccharide units by g.c.-m.s. The D-gluco-isomer (1) was obtained by the abnormal trans-diequatorial ring opening of the D-allo-epoxide (2), synthesized in 6 steps from methyl α-D-glucopyranoside (Scheme 1). The C-2 and C-4 epimers of compound (1) were obtained

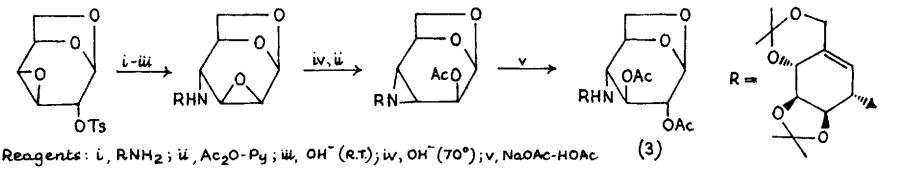


(2) (1)

Reagents: i, $MeNH_2$-EtOH; ii, H_2-Pd

Scheme 1

by oxidation-reduction procedures.[5] The 4-cyclitolamino-4-deoxy-mannose derivative (3), and thence its acetolysis product, which is considered an analogue of the α-glucosidase inhibitor acarviosin,

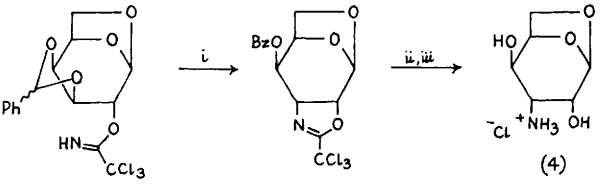


Reagents: i, RNH_2; ii, Ac_2O-Py; iii, OH^- (R.T); iv, OH^- (70°); v, NaOAc-HOAc (3)

Scheme 2

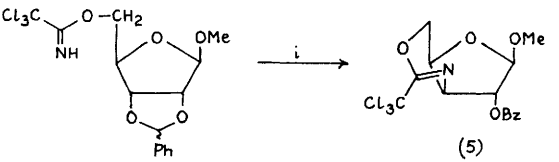
was synthesized via epoxide intermediates as shown in Scheme 2.[6] 6-Amino-6-deoxy-L-idopyranosides have been synthesized by opening 5,6-anhydro-L-idofuranose derivatives with azide.[7]

A novel variation on the Hanessian-type reaction of certain benzylidene acetals with N-bromosuccinimide involves neighbouring-group participation by a trichloroacetimidoyl group in the opening of an intermediate dioxolanylium ion. The reaction has been applied to the synthesis of the 3-amino-1,6-anhydro-3-deoxy-β-D-gulose salt (4) (Scheme 3),[8] the 3-amino-3-deoxy-D-xylose derivative (5) (Scheme 4), and a 3-amino-3,6-dideoxy-L-altropyranoside.[9]



Reagents: i, NBS; ii, OH^-; iii, H_3O^+ (4)

Scheme 3



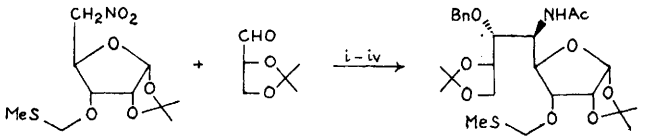
Reagent: i, NBS (5)

Scheme 4

Sulphonate displacement reactions have been used to introduce nitrogen functionality. 2-Amino-2-deoxy-D-arabinose has been synthesized in two related nine-step procedures from methyl 3,4-O-isopropylidene-D-arabinopyranoside, involving reaction of a 2-O-tosyl-D-riboside with either azide ion or hydrazine.[10] A variety of 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose derivatives, of potential as glucosamine monomers in oligosaccharide synthesis, have been obtained from the corresponding 1,6-anhydro-D-mannose 2-tri-

flates in a facile reaction with azide (LiN_3-DMF, 20°, 4 min).[11] 6'-Acetamido-6'-deoxy-derivatives of melibiose have been synthesized from methyl β-melibioside *via* displacement of a 6'-sulphonate with azide.[12] 1,2:3,4-Di-*O*-isopropylidene-6-*O*-triflyl-D-galacto-pyranose was used in the synthesis of 6-deoxy-6-(pyridinium aldoxime)-D-galactoses, potential antidotes against organophosphate poisoning (see also Chapter 10, Section 1).[13]

As a step towards the ezomycin nucleoside antibiotics which contain 5-amino-3,7-anhydro-5-deoxyoctulosonic acid units, the 5-amino-5-deoxyoctose derivative (6) was isolated chromatographically as the major of three isomers from the reaction sequence shown in Scheme 5.[14]

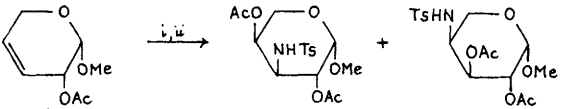


Reagents: i, KF-Bu_4NI; ii, H_2-Ni; iii, Ac_2O-MeOH; iv, BnBr-NaH (6)

Scheme 5

A variety of methods have been used for the preparation of 2-amino-2-deoxypentose derivatives of different configurations. Products with the D-*xylo*- and L-*arabino*-configurations were derived by azidonitration of D-xylal and L-arabinal esters, respectively. The D-*xylo*-product was converted into its D-*ribo*- and D-*lyxo*-isomers by C-3 oxidation-reduction, and formation and opening of a 3,4-epoxide, respectively. The L-*ribo*-isomer was obtained through reaction of a β-L-arabinopyranoside 2-sulphonate with azide ion.[15] 2-Acetamido-2-deoxy-5-thio-D-glucose has been synthesized from commercially available 5-thio-D-glucose, by azidonitration of 5-thio-D-glucal tetraacetate.[16]

Oxyamination of unsaturated sugars provides amino-sugars, but not always with good regioselectivity. The pent-3-enoside (7) gave a *ca*. 1:1 mixture of the 3- and 4-amino-sugars (8) and (9),



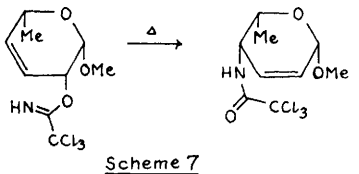
(7) (8) (9)

Reagents: i, Chloramine T-$AgNO_3$-OsO_4; ii, Ac_2O-Py

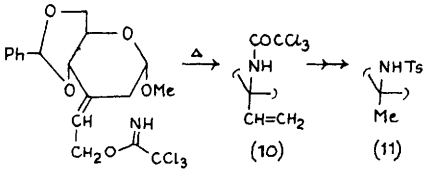
Scheme 6

respectively (Scheme 6). A related 4-*C*-methyl-pent-3-enoside could not be oxyaminated.[17] Oxyamination of an unsaturated trehalose derivative is covered in Chapter 3.

Allylic trichloroacetimidates undergo thermal allylic rearrangement to the corresponding trichloroacetamides (see also ref. 32), as exemplified for an endocyclic (Scheme 7) and an exocyclic alkene (Scheme 8). The tertiary amide (10) was converted in several steps

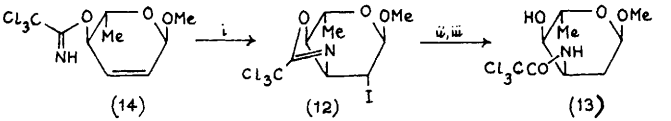


Scheme 7



Scheme 8

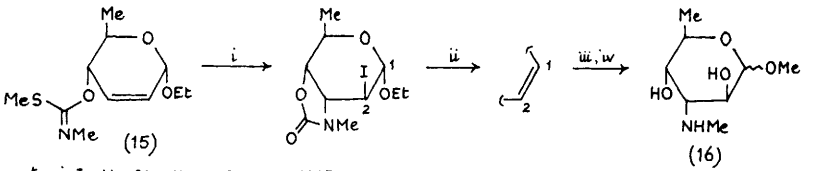
to the vancosamine derivative (11).[18] Alternatively, allylic trichloroacetimidates can be used to provide cis-hydroxyamino-sugars via iodocyclization, as shown for the synthesis of iodide (12), which was converted to the L-ristosaminide derivative (13) (Scheme



Reagents: i, Iodonium dicollidine perchlorate; ii, Bu_3SnH; iii, TsOH-Py-H_2O

Scheme 9

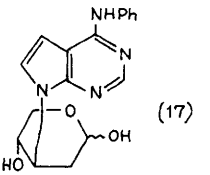
9). The corresponding L-daunosaminide derivative was obtained by applying the same sequence to the C-4 epimer of compound (14).[19] A related iodocyclization of the unsaturated carbonimidothioate (15) was used in the synthesis of (-) methyl ravidosaminide (16) (Scheme 10).[20]



Reagents: i, I_2-Na_2CO_3; ii, Zn-EtOH; iii, MCPBA-MeOH; iv, LAH

Scheme 10

The unusual nucleoside analogue (17) precipated from solution on prolonged reaction (7 days, 40°C) of 2-deoxy-D-erythro-pentose with

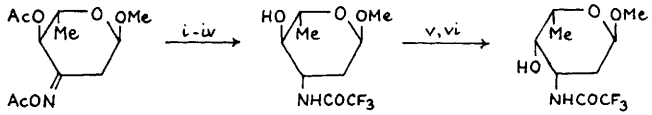


(17)

the corresponding free base in an aqueous solution of tributylammonium phosphates; the intermediacy of a carbohydrate enal was

postulated.[21]

Oximes can be reduced to amino-sugars with a variety of reagents. Diborane reduction of the acetylated oxime (18), derived from L-rhamnal, gave access to methyl N-trifluoroacetyl α-L-acosaminide

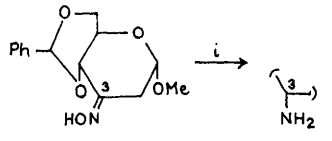


(18) (19) (20)

Reagents: i, BH_3-THF; ii, Resin(OH^-); iii, $(CF_3CO)_2O$; iv, MeOH; v, CrO_3-Py_2; vi, $LiBHBu^s_3$

Scheme 11

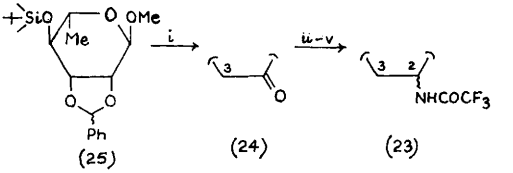
(19) and thence by an oxidation-reduction sequence to the L-daunosaminide (20) (Scheme 11); the synthesis of 1-thio-analogues was also described (c.f. Vol.14, p.72).[22] The Red-Al reduction of oxime (21) to the D-ribo-amine (22) (Scheme 12) was a key step in



(21) (22)

Reagent: i, $NaAlH_2(OCH_2CH_2OMe)_2$

Scheme 12

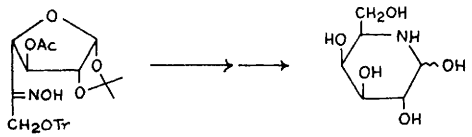


(25) (24) (23)

Reagents: i, BuLi; ii, $NH_2OH.HCl$; iii Ac_2O-Py; iv, B_2H_6-H_2O_2-OH^-; v, $(CF_3CO)_2O$

Scheme 13

an improved synthesis of N-trifluoroacetyl-L-daunosamine.[23] Regioisomers (23) of L-ristosamine and L-acosamine were obtained in a L-ribo:L-arabino ratio of 4:1 by diborane reduction of the acetylated oxime of ketone (24), derived by fragmentation of the benzylidene acetal (25) (Scheme 13).[24] 5-Amino-5-deoxy-D-galacto-pyranose (26) (or galacto-nojirimycin) has been synthesized in 12 steps from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose and converted to its 1-deoxy-analogue 1,5-dideoxy-1,5-imino-D-galactitol. These compounds were reported to inhibit α- and β-D-galactosidases.

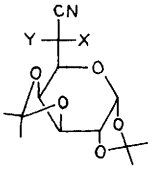


(27) (26)

Scheme 14

The synthesis was based on the catalytic reduction of the oxime (27), which yielded a mixture of C-5 epimers from which both compound (26) and its L-altro-analogue were obtained (Scheme 14).[25] Other anhydro-amino-alditols are covered in Chapter 18.

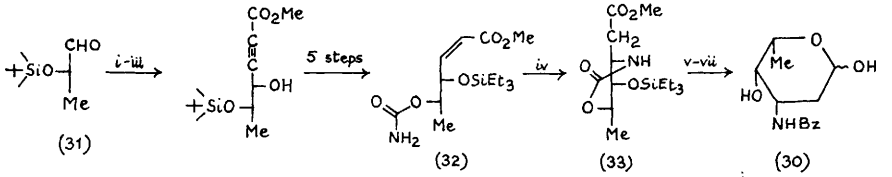
Various epimeric α-amino-nitrile mixtures, containing compounds (28) and (29) in 4-10:1 ratios and separable by chromatography or



(28) X = NR^1R^2, Y = H
(29) X = H, Y = NR^1R^2
R^1 = Me, Bn, PhCH(Me)-,
R^2 = H, Me, Bn

crystallization, have been obtained from the corresponding 1,6-dialdehydo-D-galacto-derivative under new mild conditions (aq. $NaHSO_3$, then R^1R^2NH-NaCN).[26]

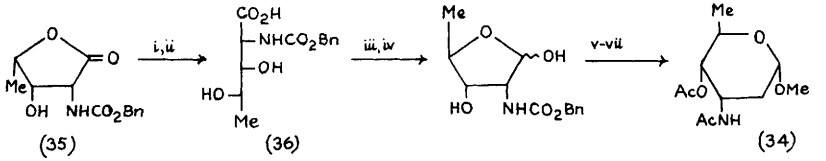
Several amino-sugar syntheses have used 3- and 4-carbon chiral starting materials. N-Benzoyl-L-daunosamine (30) has been constructed from the L-lactaldehyde ether (31) and methyl propiolate, the key step being intramolecular Michael addition of the (Z)-



Reagents: i, $HC{\equiv}CCO_2Me$-LDA; ii, CrO_3; iii, L-selectride; iv, Bu^tOK; v, OH^-; vi, BzCl; vii, Bu^i_2AlH

Scheme 15

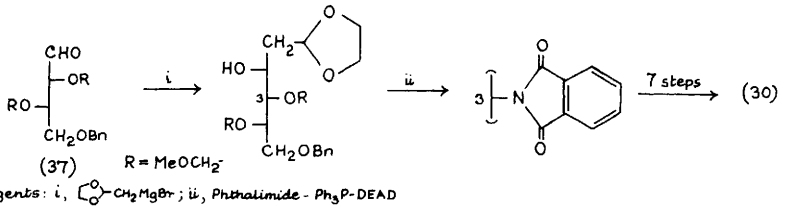
homoallylic carbamate (32), which displays dramatically improved 1,3-anti-diastereoselectivity of >100:1 in favour of compound (33), compared with that observed with its (E)-analogue of ∿5:1 (c.f. Vol.19, p.34) (Scheme 15).[27,28] The D-ristosamine derivative (34) has been synthesized from ethyl L-lactate via the L-lyxo-1,4-lactone (35) (see Vol.18, p.94) as shown in Scheme 16, the required



Reagents: i, KO_2-18-Crown-6; ii, HCl; iii, Ph_3P-DEAD; iv, Bu^i_2AlH; v, $Ph_3P{=}CHOMe$; vi, MeOH-HCl; vii, Ac_2O-Py

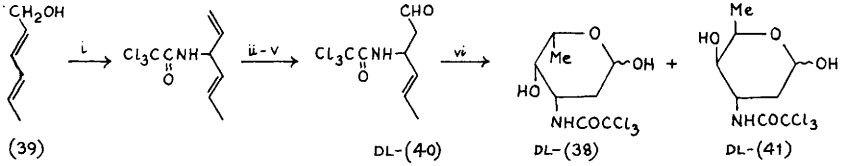
Scheme 16

inversion at C-4 being achieved by application of the Mitsunobu reaction to the acyclic dihydroxyacid (36).[29] An alternative synthesis of N-benzoyl-L-daunosamine (30) from the L-threose derivative (37), which is readily available from L-tartaric acid, involved chelation-controlled addition of a two carbon Grignard reagent, introduction of the amino-function at C-3 with inversion, C-6 deoxygenation, and deprotection (Scheme 17).[30]



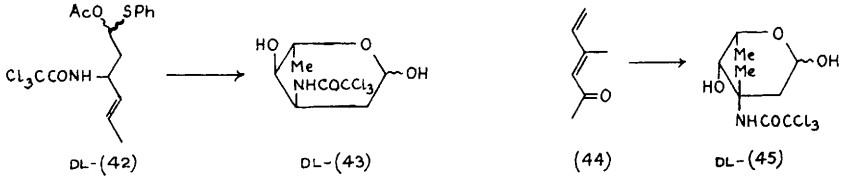
Scheme 17

The synthesis of daunosamine from a bicyclic furan-adduct (Vol.19 p.92) has been reported in full; on this occasion, chiral starting material obtained by asymmetric induction from a (-)-camphanic acid ester was used, and led to L-daunosamine.[31] A synthesis of the racemic daunosamine derivative (38) from 2,4-hexadien-1-ol (39) used



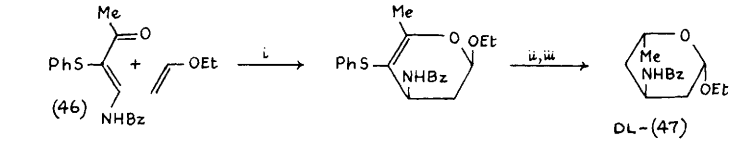
Scheme 18

an allylic rearrangement (the Overman reaction, c.f. ref.19) as the first step to introduce the required C-3 amino-functionality (Scheme 18). cis-Hydroxylation of the alkene (40), however, produced a mixture of the desired (38) and the xylo-isomer (41) in a 6:4 ratio. Alternative epoxidation of an intermediate (42) from the above route led to the racemic ristosamine derivative (43),



while related procedures applied to 4-methyl-3,5-hexadien-2-one (44) led to a mixture of the racemic vancosamine derivative (45) and its isomer epimeric at C-4 and -5.[32]

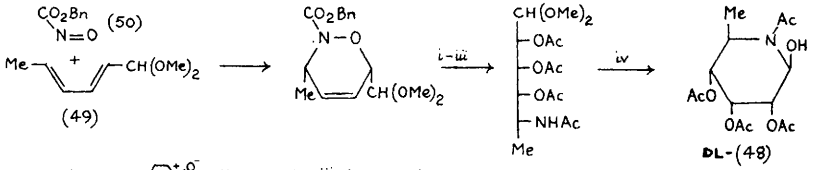
Racemic 3-amino-sugars have been synthesized through hetero-Diels-Alder reactions of enaminones. Thus the major adduct from enaminone (46) and ethyl vinyl ether was converted to the 4-deoxy-ristosaminide (47) (Scheme 19).[33] Racemic 5,6-dideoxy-5-amino-allose derivatives such as (48) have been constructed from the hetero-Diels-Alder adducts of diene (49) with acylnitroso



Reagents: i, PhMe-$C_6H_4(OH)_2$ (Δ); ii, $BF_3.OEt_2$; iii, Raney Ni

Scheme 19

derivatives such as (50) generated *in situ* by oxidation of the corresponding hydroxamic acids (Scheme 20).[34]



Reagents: i, OsO_4-  ; ii, H_2-cat.; iii, Ac_2O-Py; iv, HCO_2H-H_2O

Scheme 20

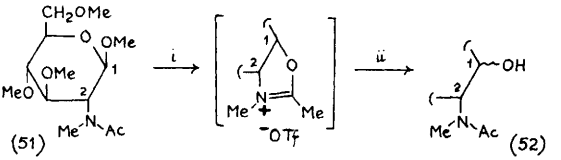
3 Reactions

Rates have been determined for the Schiff base condensation of 2-amino-2-deoxy-D-glucose with pyridoxal in physiological solution,[35] and with p-hydroxy- and p-methoxy-benzaldehyde in media of differing dielectric constant.[36] The ability of 2-amino-2-deoxy-D-glucose, and more particularly its 6-phosphate, to cause DNA strand scission by a mechanism considered to involve free radicals generated during autoxidation of aminosugars in aqueous solution has been studied.[37]

Infra-red spectra of the anion, cation, zwitterion and deuterated zwitterion forms of 1-deoxy-1-glycino-D-fructose, the glucose-glycine Amadori product, show the product to be predominantly in the β-pyranose form.[38] The synthesis, tautomeric equilibria in, and Fisher glycosidation of various 1-deoxy-1-[(2,2-diacylvinyl) amino]-D-fructoses have been reported as part of a study on the use of diacylvinyl as an amino protecting group.[39] The Maillard reaction of D-glucose with DL-phenylalanine in water and n-octanol has been studied.[40] The chemical and physical properties of sugar-amino acid derived melanoidins have been evaluated, and a polymer backbone derived from sugar moieties has been considered probable.[41]

As part of a study of the behaviour of 2-acetamido-2-deoxy-D-

glucopyranosyl residues during linkage analysis using the reductive cleavage method, the reactions of the permethylated derivative (51), its α-anomer, and related derivatives were examined. While the β-

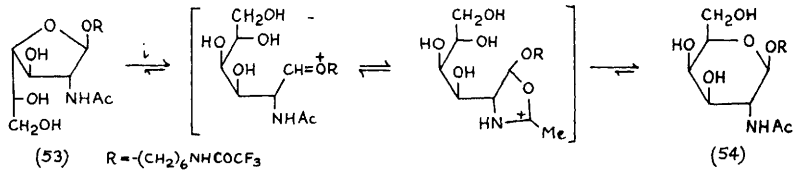


Reagents: i, Et_3SiH-Me_3SiOTf-CH_2Cl_2; ii, $NaHCO_3$

Scheme 21

anomer (51) yielded the free sugar (52), presumably via N-acetyl group participation as shown in Scheme 21, the corresponding α-glycoside was stable under the same conditions.[42]

The β-furanoside (53) is converted specifically (∿95%) to the β-

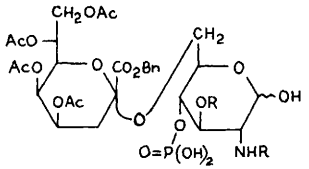


Reagents: i, Resin (H^+)-H_2O

Scheme 22

pyranoside (54) on exposure to strong acid resin in water; the intermediacy of an acyclic carbonium ion stabilized by the hydrophobic resin was postulated (Scheme 22). This observation permitted a more efficient synthesis of 6-aminohexyl 2-acetamido-2-deoxy-β-D-galactopyranoside from 2-acetamido-2-deoxy-D-galactose by using a 4:1 mixture of pyranosyl and furanosyl chlorides for Koenigs-Knorr glycosidation with a subsequent isomerization step.[43] Amino-sugar glycosides are also covered in Chapters 3 and 19.

The synthesis and immunological properties of MDP (N-acetyl-muramoyl-L-alanyl-D-isoglutamine) and bacterial lipid A analogues continue to attract considerable attention. A 'large scale' (20-50 mmol) preparation of stereochemically pure muramic acid derivatives, including α-amino-acid derivatives, has been achieved from benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside.[44] 1-S-, 6-O-Diacyl-1-thio-MDP analogues bearing one or two lipophilic acyl moieties have been reported,[45] and 2,3-diaminoglucosyl analogues of MDP are covered in Section 4. The KDO-glucosamine disaccharides (55) have been synthesized and shown to be lipid A analogues,[46,47] as have 2-(acylamino)-6-O-(2-aminoethyl)phosphono-2-deoxy-D-glucoses acylated with acetic or DL-3-



(55) R = C_{14}-O-C_{14} or C_{14}-O-C_{12} lipids

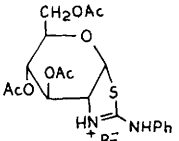
hydroxytetradecanoic acids,[48] and 1,5-anhydro-2-deoxy-4-O-phosphono-3-O-tetradecanoyl-2-[(3R)- and (3S)-3-tetradecanoyloxytetradecanamido]-D-glucitol.[49] By chemically coupling a lipophilic 1-deoxy-MDP analogue with an analogue for the non-reducing subunit of lipid A *via* a succinate bridging unit esterifying the 6-hydroxy groups in the two monosaccharide components, Hasegawa and co-workers have produced a range of efficient antitumor agents with strong immunoadjuvant properties.[50]

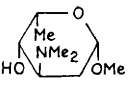
3-Alkylamino-3-deoxy-D-alloses and -D-glucoses have been synthesized and shown to have plant growth regulatory properties, the 3-laurylamino-derivatives being the most active for promoting growth at low concentration.[51] N-Alkylation of the 2-amino-2-deoxy-4,6-O-ethylidene-β-D-glucopyranoside moiety of the anticancer agent etoposide was achieved by reductive amination ($NaBH_3CN$) of various aldehydes, and α,β-unsaturated esters and nitriles. Of the 10 examples, the 2-dimethylamino-analogue displayed significantly enhanced activity.[52] The abnormal conformation adopted by methyl 3-deoxy-3-diallylamino-α-D-altropyranosides is discussed in Chapter 21. Byproduct formation in the Hakamori methylation of acetamido-alditols is covered in Chapters 18 and 24.

2-Acetamido-2-deoxy-D-glucopyranose peracetate has been converted into the corresponding oxazoline derivative by reaction with trimethylsilyl triflate, and the methodology successfully applied to the synthesis of a tetrasaccharide analogue.[53] Condensation of 2-deoxy-2-isothiocyanato-α-D-glucopyranose tetraacetate with a variety of amines gave the corresponding 2-(alkyl or -aryl-thioureido)-derivatives, which were cyclized to thiazoline derivatives such as (56) in high yield.[54] The e.i.-m.s. of 2-methylthio-glyco-oxazolines is covered in Chapter 22.

A one-pot high yielding conversion of primary and secondary carbohydrate azides into phthalimido derivatives has been effected using phthalic anhydride, a quaternary ammonium catalyst and triphenylphosphine[55] or better triethylphosphine,[56] the reaction proceeding *via* formation of phosphinimine (the Staudinger reaction).

Methyl 2,3,6-trideoxy-3-(dimethylamino)-β-L-*xylo*-hexopyranoside


(56)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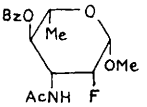
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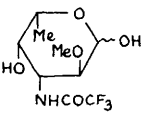
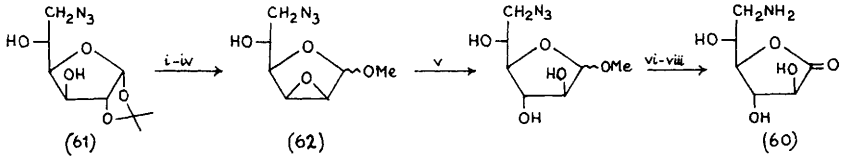

(59)

(57) has been synthesized in 6 steps from methyl 4,6-O-benzylidene-2,3-dideoxy-3-trifluoroacetamido-α-D-arabino-hexopyranoside,[57] while the 2-fluoro-acosamine analogue (58) has been obtained from a 3-azido-3-deoxy-D-idose derivative.[58] In both cases the required C-6 deoxygenation and C-5 inversion were achieved by the Hanessian reaction of a 4,6-O-benzylidene acetal with N-bromosuccinimide, elimination of the resulting 6-bromide, and hydrogenation of the 5,6-double bond. The 2-methoxy-daunosamine analogue (59) has been synthesized by hydrolysis of an appropriately substituted 2-O-methyl-β-L-galactofuranosyl fluoride, obtained unexpectedly on treatment of a methyl α-L-talofuranoside derivative with DAST (see Chapter 8).[59] Racemic methyl 3-amino-3,4-dideoxy-α-erythro-pentopyranoside (Vol.15, p.124) has been resolved by coupling of O-methyl-L-tyrosine or phenylalanine to the amino-group, and separation of the diastereo-isomers.[60]

6-Amino-6-deoxy-D-altronic acid along with its lactone (60) have

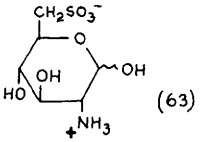

(61) (62) (60)

Reagents: i, BzCl-Py; ii, H⁺-MeOH; iii, MsCl-Py; iv, NaOMe-MeOH; v, NaOH; vi, H_3O^+; vii, Br_2; viii, H_2-cat.

Scheme 23

been synthesized from the 6-azido-6-deoxy-D-glucose derivative (61) (Scheme 23). In opening of the epoxides (62), the α-anomer gave exclusively the D-altro-isomer shown, whereas the β-anomer gave D-altro- and D-gluco-isomers in the ratio 5:4.[61]

2-Amino-2,6-dideoxy-D-glucopyranose-6-sulphonic acid (63) has


(63)

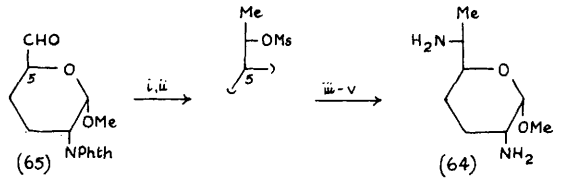
been synthesized from 2-amino-2-deoxy-6-thio-β-D-glucopyranose pentaacetate by oxidation (H_2O_2-HOAc) and acid hydrolysis and

shown not to be the 2-amino-2,6-dideoxyhexose-6-sulphonate present in a Halococcus sp. cell wall hydrolyzate.[62]

Branched-chain amino-sugars are covered in Chapter 14.

4 Di-, Tri-, and Tetra-amino-sugars

Purpurosamine B (64), isolated as its bis-N-(benzoyloxycarbonyl) derivative, has been synthesized from 2-amino-2-deoxy-D-glucose in



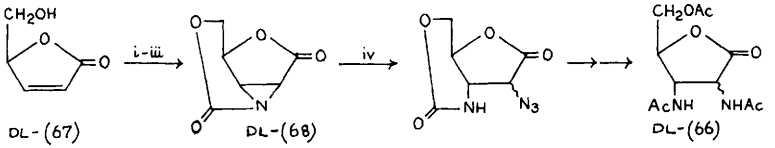
Reagents: i, MeMgBr; ii, MsCl-Py; iii, NaN_3; iv, H_2-Pd/C; v, N_2H_4

Scheme 24

14 steps, the key steps being chelation controlled chain-elongation from aldehyde (65) and introduction of the 6-amino-function by azide displacement with inversion of sulphonate (Scheme 24). A double C-6 inversion sequence provided 6-epi-purpurosamine B.[63] In the syntheses of N-(2-acetamido-2,3-dideoxy-D-glucopyranos-3-yl)-glycyl-L-alanyl-D-isoglutamines, MDP-analogues (c.f. Section 2, ref.44 and 45) which contain a 2,3-diaminoglucose unit, the required 3-amino function was introduced by reaction of benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-mesyl-α-D-allopyranoside with azide under improved conditions (NaN_3-Bu_4NHSO_4-DMF), and subsequently N-alkylated with ethyl bromoacetate.[64] Alkylation of related 2-acetamido-3-amino-glucoside derivatives with ethyl D- or L-2-bromo-propionate provided access to analogous (glycos-3-yl)-D- or L-alanyl dipeptides.[65] Di- to tetra-amino-disaccharides of the α,α-trehalose type, including 3-amino-3-deoxy-α-D-altropyranosyl 3-amino-3-deoxy-α-D-altropyranoside, and 2-amino-2-deoxy-3-amino-3-deoxy-, and 2,3-diamino-2,3-dideoxy-α-D-mannopyranosyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside, have been synthesized, the amino groups being introduced by standard methods.[66,67]

Racemic diamino-xylo- and lyxo-pentono-lactones (66) have been obtained from butenolide (67) via the tricyclic epimine (68) as shown in Scheme 25. The 2,3,5-triamino-analogues were also reported.[68] 3-Amino- and 2,3-diamino-D-xylono-1,4-lactone derivatives are reported in Chapter 24.

A platinum complex of a diamino-sugar is covered in Chapter 17.



Reagents: i, $COCl_2$; ii, NaN_3; iii, CH_2Cl_2 (125°); iv, NaN_3-HN_3

Scheme 25

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10
Miscellaneous Nitrogen Derivatives

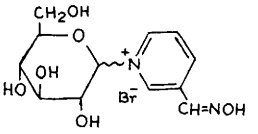
1 Glycosylamines

2-Acetamido -2-deoxy-β-D-glycopyranosylamines have been synthesized by reaction of the free sugars [i.e. GlcNAc, GalNAc, and β-GlcNAc (1 → 4)GlcNAc] with ammonium bicarbonate, and 1-N-acylated with amino-acid derivatives to give glycopeptide models.[1] N-Glycosyl derivatives of cyclopentylamine, 1,2,3,4-tetrahydro-1-naphthylamine and 5α-cholestanyl-3-β-amine have been synthesized and reduced ($NaBH_3CN$) to the corresponding 1-(substituted amino)-1-deoxy-alditols.[2] Seven 4-(β-D-gluco- and xylo-pyranosyl)aminopyrimidine derivatives have been characterized spectroscopically and their crystalline forms subjected to thermal analysis.[3] Reactions of L-arabinose, D-xylose, D-galactose and D-glucose with N-methylaniline and its p-methyl- and p-methoxy-derivatives in methanol have been studied in the presence and absence of acidic catalyst. Glycosylamines formed initially underwent rapid transformations including the Amadori rearrangement and subsequent methyl glycosidation.[4]

The acid-catalyzed hydrolysis of N-aryl-D-pentopyranosylamines has been re-examined, a bimolecular A-2 mechanism involving formation of a Schiff base intermediate being suggested. The lability of the C1-N bond increased with configuration in the order xylo<lyxo<ribo<arabino and with the base strength of the parent amine (i.e., for para-substituents on the N-phenyl-moiety, NO_2<Cl<H<Me).[5] Condensation of glycosylamines, e.g., β-D-gluco-pyranosylamine, with methyl 3-methoxy-2-nitroacrylate yielded methyl 3-(N-glycosylamino)-2-nitroacrylates.[6] Mass spectral studies of acylated glycosylamines are covered in Chapter 22.

Pyridinium aldoximes N-linked to C-1 or C-6 of hexoses or to a 3-carbon aglycone unit of a glycoside have been synthesized as potential antidotes of organophosphate poisoning; thus the N-glucosyl derivative (1) was obtained from acetobromoglucose.[7]

Reaction of D-xylose with tetracyanoethylene and ethanol in liquid hydrogen fluoride gave the bicyclic glycosylamine derivative



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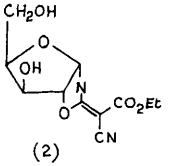

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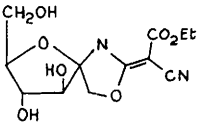
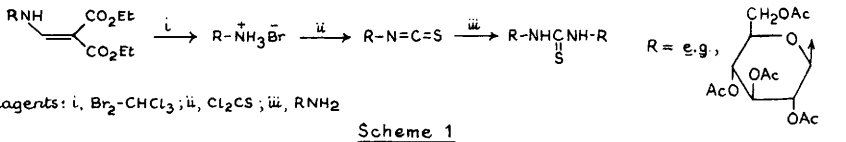


(3)

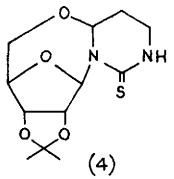
(2) in 92% yield. D-Ribose and D-lyxose similarly gave furanoid products in good yield, while D-arabinose and D-glucose gave mixtures containing a furanoid and a pyranoid product. D-Fructose gave the spiro-bicycle (3) in 39% yield along with two other isomers.[8]

A new synthesis of O-acylated glycosylamines and a transformation of the products into glycosyl isothiocyanates and thence N,N-di-glycosylthioureas have been reported (Scheme 1).[9] Other N-



Scheme 1

glycosyl-thiourea derivatives have been synthesized by condensation of various acetylated glycosyl isothiocyanates with 2-aminobenzothiazole derivatives,[10] with aminopropylsilica gel to form chiral h.p.l.c. phases capable of resolving enantiomers,[11] and with phenacylamine derivatives.[12] Cyclodehydration in the thiourea aglycone of the latter condensation products led to 5-aryl-2-(glycosylamino)thiazole derivatives. The tetracyclic N-ribosyl-thiourea derivative (4) was obtained in 80% yield from 2,3-O-isopropylidene-5-O-tosyl-D-ribofuranosylamine (by reaction with $OHCCH_2CH_2NCS$-Et_3N in $CHCl_3$) and yielded in part the anomerized product (5) on deprotection ($HOAc$-H_2O).[13]



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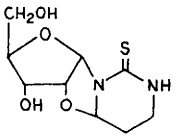
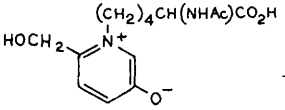
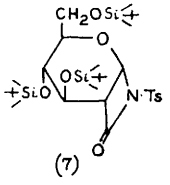


(5)



(6)



(7)

Several studies on the Maillard reaction have been reported, some being covered in Chapter 9, section 3. Glycoaldehyde and

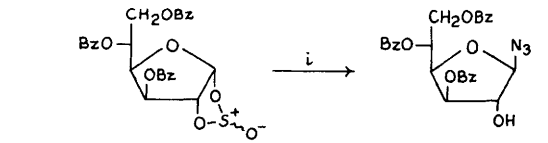
methyl glyoxal have been implicated as important sugar fragmentation products in the initial stages of the browning reaction of neutral and alkaline sugar-amino acid solutions. Bis(alkylamine) derivatives of methyl glyoxal have been detected from the reaction of glucose with alkylamines.[14,15] The formation and reactivity of 1-alkyl-3-oxypyridinium betaines, which arise from the reaction of pentoses, hexoses and disaccharides with primary amines or amino-acids, have been studied, e.g., the lactose - N^{α}-acetyl-lysine product (6).[16] Melanoidins formed from D-xylose and glycine have been characterized by solid state ^{1}H and ^{13}C-n.m.r. spectroscopy.[17] An i.r. study of sugar-aminoacid melanoidins and of a pseudo-melanoidin produced from sugar only has been reported.[18]

Bicyclic β-lactams, e.g. (7), have been obtained from [2+2]cyclo-additions of isocyanates to glucals.[19] (Further details of the reactions are given in Chapters 13 and 24.)

2 Azido-, Azi- and Diazo-sugars

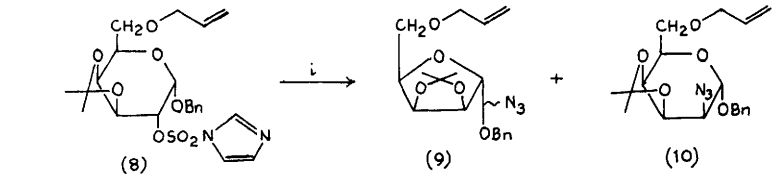
Azido-sugars are often used as intermediates in the synthesis of amino-sugars (see Chapter 9).

2,3,4-Tri-O-acetyl-α-D-ribopyranosyl azide has been obtained from reaction of the corresponding β-chloride or -bromide with sodium azide in HMPT; analogous displacement without neighbouring group participation to give a 1,2-*cis*-product was also observed in the reaction of the D-*xylo* and D-*lyxo*-chlorides.[20] 1,2-*trans*-Glycosyl azides with a free hydroxy group at C-2 have been obtained from 1,2-cyclic sulphites as exemplified in Scheme 2.[21]



Scheme 2

Displacement reactions of 2-(N-imidazolylsulphonate) esters of mannoside, galactoside, and lactoside derivatives with azide gave mainly ring contracted products along with some products of direct displacement. Thus the benzyl α-D-galactoside (8) gave the epimers (9) and the 2-azido-2-deoxy-D-taloside (10) in 40 and 17% yield, respectively (Scheme 3).[22] Direct displacement did occur, however,

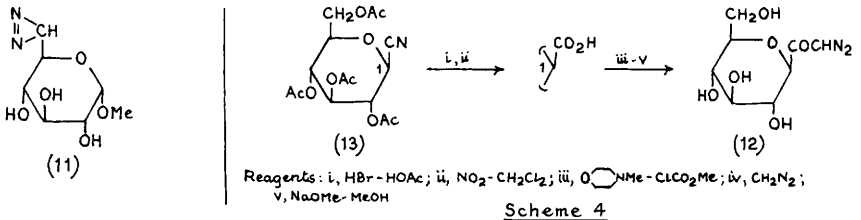


Reagents: i, Bu_4NN_3 - PhMe.

Scheme 3

in the reaction of 1,6-anhydromannose 2-triflate derivatives (see Chapter 9, ref. 11). 4-Azido-4-deoxy-D-galacto-sucrose has been synthesized from hepta-O-pivaloyl-sucrose having a free 4-hydroxy-group via sulphonate displacement.[23] 2-Azido-2,3-dideoxy-3-fluoro-D-allo-, gluco- and manno-pyranose and 3-azido-2,3-dideoxy-2-fluoro-D-altro-, gluco- and manno-pyranose derivatives, required for the synthesis of β-fluorinated α-aminoacids, have been synthesized by conventional means, the azido groups being introduced by either epoxide ring-opening or triflate displacement reactions.[24]

Methyl 6-azi-6-deoxy-D-glucopyranoside (11), suitable as a photoaffinity compound for labelling carbohydrate-binding proteins, has been synthesized from the corresponding 6-aldehydro-glucoside (i, NH_3; ii, NH_2OSO_3H; iii, I_2); the D-galactoside analogue and



Reagents: i, HBr - HOAc; ii, NO_2 - CH_2Cl_2; iii, O NMe - $ClCO_2Me$; iv, CH_2N_2; v, NaOMe - MeOH

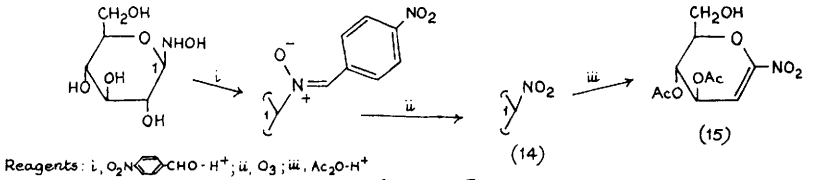
Scheme 4

the two free sugars have also been obtained.[25] Other compounds useful as affinity labelling reagents, the diazomethyl glucosyl ketone (12) and its β-D-galactopyranosyl analogue, have been synthesized from the corresponding peracetylated β-glycosyl cyanides, e.g., (13), as shown in Scheme 4.[26]

3 Nitro- and Nitroso-sugars and Glycosyl Nitrones

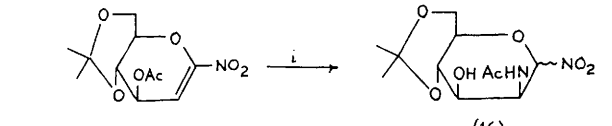
Syntheses of 3-nitro-2,3,6-trideoxy-hexoses have been covered in a review.[27]

1-Deoxy-1-nitro-derivatives of pentoses and hexoses, including β-D-glucopyranose [i.e., (14)], β-D-mannopyranose, 2-acetamido-2-deoxy-β-D-glucopyranose, β-D-galactofuranose, and β-D-ribofuranose, some partially protected, have been synthesized from the corresponding oximes as exemplified for the glucose derivative in Scheme 5.[28]



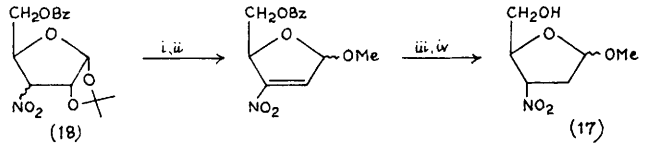
Scheme 5

The peracetylated 1-deoxy-1-nitro-sugars gave 1-C-nitroglycals either spontaneously or on base-catalyzed β-elimination, as shown for the 1-C-nitroglucal (15) in Scheme 5. Addition of ammonia or amines to some of these 1-C-nitroglycals gave 2-amino-2-deoxy-1-C-nitrohexose derivatives with an axial C-2 substituent, e.g., the 2-acetamido-2-deoxy-D-mannose derivative (16) (Scheme 6).[29]



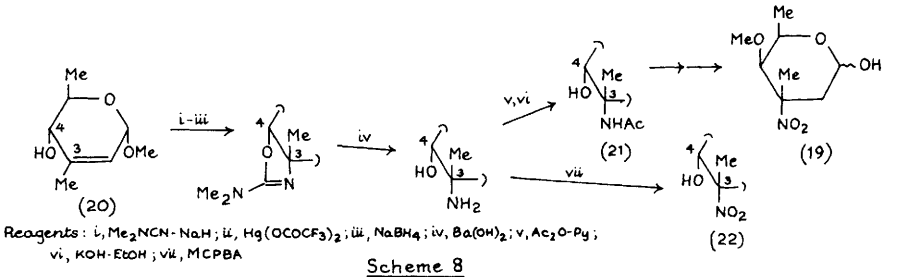
Scheme 6

The 2,3-dideoxy-3-nitro-sugar (17) has been synthesized from 1,2-O-isopropylidene-D-xylose via the known 3-nitropentose (18) (Scheme 7), a similar route from 1,2:5,6-di-O-isopropylidene-α-D-



Scheme 7

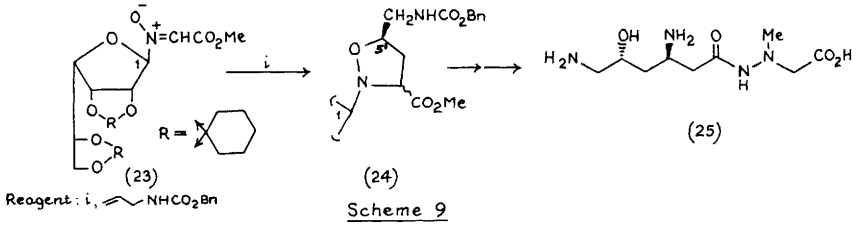
glucofuranose yielding the corresponding uronic acid.[30] A stereoselective route to D-rubranitrose (19) was demonstrated by conversion of alkene (20) to the branched-chain amino-sugar (21)(Scheme 8), since the conversion (21) → (19) has been reported before. The



Scheme 8

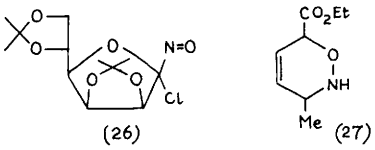
branched-chain nitro-sugar (22) was also synthesized.[31] Another synthesis of D-rubranitrose and the branched amino-nitro-sugar methyl α-D-tetronitroside is covered in Chapter 14.

A review has been published on the work of Vasella's group on asymmetric induction in 1,3-dipolar cycloadditions of, and the addition of phosphorus nucleophiles to, N-glycosyl-nitrones, with the purpose of providing a general synthesis of α-aminophosphonic acids.[32] The sugar nitrone (23), available from D-gulono-1,4-



Scheme 9

lactone, yielded a 2:3 mixture of cycloadducts (24) with high stereoselectivity at the 5'-centre, the aglyconic moiety of one of the isomers being used for the synthesis of (+)-negamycin (25) (Scheme 9).[33] Full details and an expanded scope have been published for the highly diastereoselective Diels-Alder reactions of the 1-C-nitroso-D-mannofuranosyl chloride (26) with various



dienes to prepare, after removal of the chiral auxiliary, dihydro-oxazines such as (27), which was obtained in 96% e.e., but with

undetermined absolute configuration (c.f. Vol.18, p.108).[34]

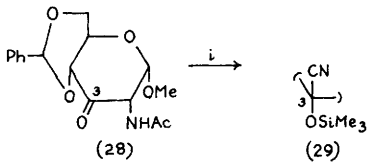
4 Nitriles, Isonitriles, Oximes and Hydroxylamines

1,2-O-(1-Cyanoethylidene)-α-D-galacto-, α-D-gluco-, and β-D-manno-pyranose triacetates are irreversibly and stereoselectively isomerized (by $BF_3.OEt_2$ in $MeNO_2$) to the corresponding peracetylated 1,2-trans-glycosyl cyanides, with only small proportions of the 1,2-cis-glycosyl cyanides being present. The glycosyl cyanides were not susceptible to anomerization under the reaction conditions. These observations led to a detailed examination of four routes for the improved synthesis of peracetylated aldohexopyranosyl cyanides: i) rearrangement of 1,2-O-(1-cyanoethylidene)-derivatives, ii) initial conversion of peracetylated glycosyl bromides into mixtures of 1,2-trans-glycosyl cyanides and their 1,2-O-(1-cyanoethylidene)isomers [$Hg(CN)_2$ in $MeNO_2$], with subsequent rearrangement [$BF_3.OEt_2$ in $MeNO_2$], iii) a 'one-pot' conversion of 1,2-cis- or 1,2-trans-aldohexopyranose peracetates (using Me_3SiCN-$BF_3.OEt_2$ in $MeNO_2$), and iv) a fusion reaction of peracetylated glycosyl bromides with mercury(II) cyanide (85°, 20 min). Route ii) was considered the method of choice for preparative syntheses of cyanides with the β-D-galacto, 6-deoxy-β-L-galacto, 2-deoxy-2-phthalimido-β-D-gluco, and α-D-manno configurations. Yields for the β-D-gluco analogue were relatively low for all methods, but the highest (39% and 12% for the 1,2-trans and 1,2-cis isomers respectively) were obtained using route iv).[35]

The aforementioned reagent system (i.e., Me_3SiCN-$BF_3.OEt_2$) was shown to convert certain glycosyl fluorides firstly into glycosyl isonitriles which then rearrange to glycosyl cyanides. While 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl fluoride gave exclusively the α-nitrile (85% yield), 2,3,5-tri-O-benzyl-β-D-ribofuranosyl fluoride gave a ∿1:1 mixture of anomeric nitriles.[36]

Reduction of five peracetylated 1,2-trans-aldopyranosyl isothiocyanates with tributyltin hydride at room temperature without a radical initiator gave the corresponding isonitriles in good yields (58-76%). Under forcing conditions (Bu_3SnH-PhMe-AIBN, reflux) the 1,5-anhydro-D-alditol peracetates were obtained in good yields. No isomerizations to the glycosyl nitriles were detected in these reactions.[37] The Me_3SiCN-$BF_3.OEt_2$ reagent can also be used to prepare non-anomeric cyano-sugars from derivatives

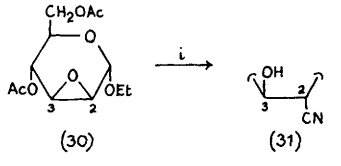
containing ketone, benzylidene acetal, or oxiran groups. The ketone (28) thus gave the protected cyanohydrin (29) (Scheme 10)



(28) (29)

Reagents: i, Me_3SiCN-BF_3-OEt_2-DMF

Scheme 10

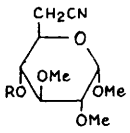


(30) (31)

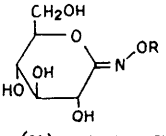
Reagents: i, Me_3SiCN-BF_3-OEt_2-$MeNO_2$

Scheme 11

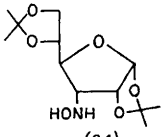
while the epoxide (30) gave the product (31) of "diequatorial" ring-opening (Scheme 11), participation by the 4-acetoxy group being suspected.[38] The preferential attack of this reagent on a 4,6-O-benzylidene moiety rather than an epoxide group is covered in Chapter 5. 6-Cyano-6-deoxy-D-glucose derivatives (32) have been prepared in good yield from the corresponding 6-bromides using tetrabutylammonium cyanide (prepared *in situ* from Bu_4NBF_4-NaCN-DMF-MeCN). Yields were low, however, in the case of the 4-O-benzoyl analogue, presumably due to intramolecular attack on the 6-cyanide by the O-4 anion. Attempted generation and alkylation of a C-6 carbanion from compound (32) even with LiN^iPr_2, NaH or BuLi as base was unexpectedly unsuccessful, only starting material being recovered.[39] The conversion of a 6-aldehydo-galactose derivative into a pair of α-aminonitriles is covered in Chapter 9.



(32) R = Bn or $CH_2O(CH_2)_2OMe$



(33) R = H, CONHPh, CONHMe



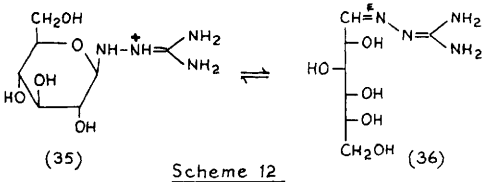
(34)

The inhibition of emulsin by the oxime derivatives (33) of D-glucono-1,5-lactone (*c.f.* Vol.19, p.115) has been reported.[40] A range of 3-deoxy-3-(hydroxyamino)furanose acetals, *e.g.*, (34), have been prepared by reduction ($NaBH_3CN$-MeOH-HCl, pH 2-3) of the corresponding 3-keto-oximes.[41]

5 Hydrazines, Hydrazones, Osazones, and Related Heterocycles

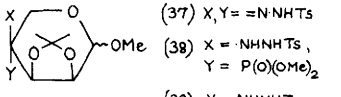
Aldose-aminoguanidine condensation products have been prepared and

their structures determined by ^{1}H-, ^{13}C-, and ^{15}N-n.m.r. spectroscopy. At pH 6 they exist as N-glycopyranosyl-amino-guanidines with a protonated, equatorial aglycone [e.g., as shown for the D-glucose-derived (35) in Scheme 12], while at pH 12 in DMSO they exist as the tautomeric acyclic E-carboximidamidehydrazones (e.g., 36).[42]



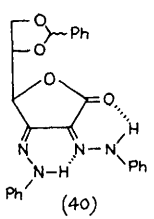
(35) (36)

Scheme 12

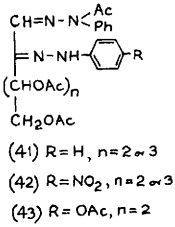


(37) X,Y = =N·NHTs
(38) X = ·NHNHTs, Y = P(O)(OMe)$_2$
(39) X = ·NHNHTs, Y = P(O)(OMe)Ph

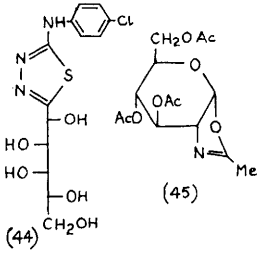
The L-erythro-pentopyranosid-4-ulose tosylhydrazone (37), prepared in four steps from D-lyxose, gave the phosphorus bound sugars (38) or (39) on treatment with dimethyl phosphonate or methyl phenyl phosphinate, respectively.[43] Benzylidenation of the phenylosazone of dehydro-L-ascorbic acid [to give the 5,6-acetal (40)] and of its C-5 epimer derived from dehydro-D-isoascorbic acid was shown to yield products with the 1,4-lactone ring intact.[44] A further study has been reported on the formation of 3,6-anhydrohexose phenyl-osazones on alkaline treatment of acetylated hexose phenylosazone derivatives.[45] The D-lyxo-hexose and L-erythro-pentose osazones (41) could be regioselectively nitrated ($NaNO_2$-HOAc or isopentyl nitrite) on the non-acetylated phenylhydrazone moiety to give compounds (42), or acetylated (Ac_2O-NaOAc) to give compound (43).[46]



(40)



(41) R = H, n = 2 ~ 3
(42) R = NO_2, n = 2 ~ 3
(43) R = OAc, n = 2



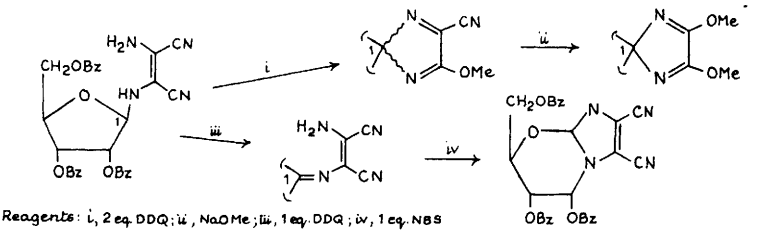
(44) (45) (46)

Ferric chloride oxidation of D-galactose 4-(p-chlorophenyl)thiosemicarbazone yielded the 1,3,4-thiadiazole derivative (44), the sugar chain on which could be reduced to a formyl group by periodate cleavage.[47]

6 Other Heterocyclic Derivatives

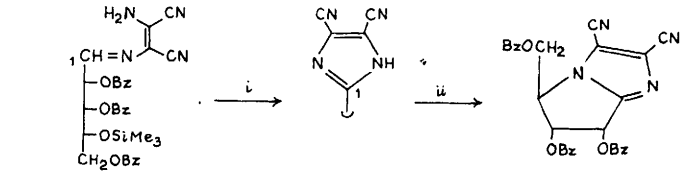
A new synthesis of oxazoline derivatives such as (45) by action of trimethylsilyl triflate on the corresponding peracetylated sugar has been successfully applied to an oligosaccharide.[48] Thiazoline derivatives, *e.g.*, (46), have been obtained from 2-deoxy-2-isothiocyanato-α-D-glucopyranose tetraacetate.[49]

Spiro- and bicyclo-nucleoside analogues have been obtained as shown in Schemes 13 and 14.[50]



Reagents: i, 2 eq. DDQ; ii, NaOMe; iii, 1 eq. DDQ; iv, 1 eq. NBS

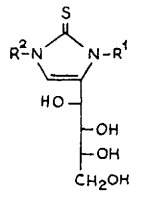
Scheme 13



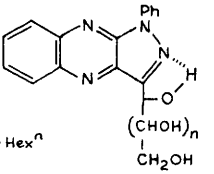
Reagents: i, NBS; ii, TsCl - 1,4-diazabicyclo[2.2.2]octane

Scheme 14

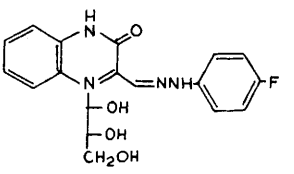
Various imidazole-2-thiones (47) have been obtained from the condensation of 1-alkylamino-1-deoxy-D-fructoses with methyl or phenyl isothiocyanate (*c.f.* Vol.19, p.113).[51]



(47) R^1 = Me or Ph; R^2 = Me, Pr^n, or Hex^n



(48)



(49)

The conformational changes induced by O-acetylation of the polyhydroxyalkylpyrazolo[3,4-b]quinoxalines (48) have been studied by ^{1}H-n.m.r. and c.d. spectroscopy; they are considered to be due to

disruption of the HO-1' and N-2 hydrogen bonding shown.[52,53] A 'one-pot' synthesis of compound (49) from the reaction of D-isoascorbic acid, o-phenylenediamine, and 4-fluorophenylhydrazine and its cyclization to an analogue of compound (48) have been described,[54] as have reactions of dehydroascorbic acid analogues with o-phenylenediamine.[55]

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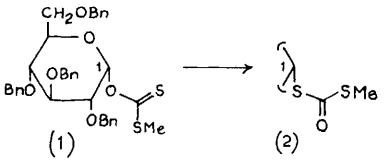
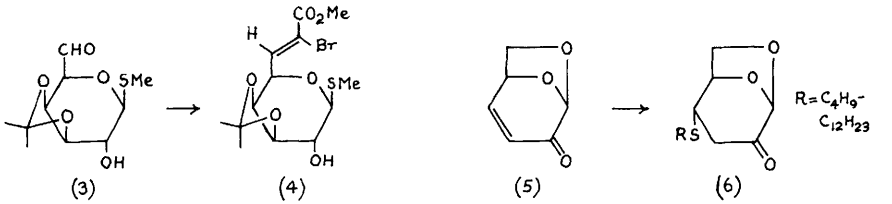
11
Thio-sugars

1-S-(S-Alkyldithiocarbonates) have been obtained by the thermal or Lewis acid rearrangement of perbenzylated glucosyl xanthates. Thus the S-methylxanthate (1) gave the thiocarbonate (2) on treatment with boron trifluoride-etherate at 65° in toluene. By-products of the



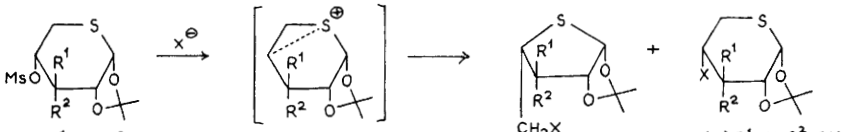
reaction were the alkyl 1-thio-α- and β-D-glucosides formed by competitive capture of the methylthiolate ion.[1] Acetobromogalactose has been converted into the methyl 1-thio-galactosides in a synthesis which involved the displacement of the glycosyl bromide using thiourea. The β-anomer was conventionally converted into the 6-aldehydo-derivative (3), which was used in a Wittig reaction to produce the chain-extended product (4), an intermediate in the synthesis of lincomycin analogues.[2]



Michael addition of thiols to levoglucosenone (5) in triethylamine gave the 4-alkylthio-3-deoxy-2-uloses (6) in yields greater than 80%.[3]

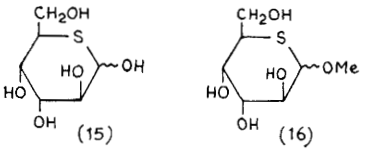
In an investigation of the participation of ring sulphur atoms in displacement reactions, the 1,2-O-isopropylidene-2,3-di-O-mesyl-5-thio-ribo- and -xylopyranoses (7) and (8) were treated with various nucleophiles. The products included 5-substituted-4-thiofuranoses (9) and (10) as well as the 4-substituted-5-thiopyranoses (11) and

(12) in varying ratios, showing the intermediacy of the sulphur atom in the displacement (Scheme 1).[4] 5-Thio-D-allose (13) and its

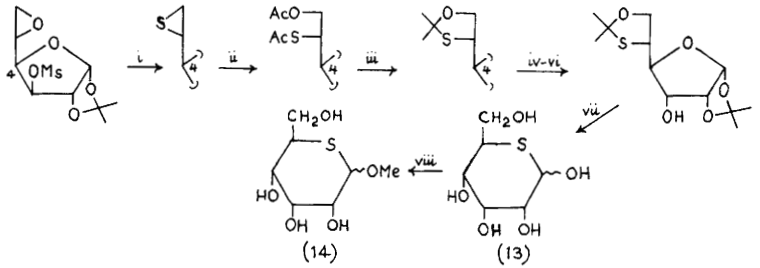


Scheme 1

methyl pyranosides (14) have been synthesized as shown in Scheme 2;[5] the corresponding D-altrose derivatives (15) and (16) were also prepared using a related procedure.[6] Azidonitration of 2,3,6-tri-O-



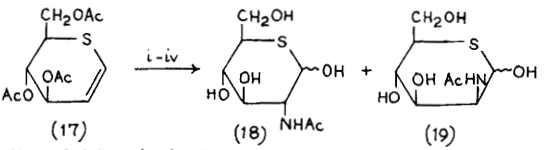
acetyl-5-thio-D-glucal (17) has been used to prepare 2-acetamido-2-



Reagents: i, $(NH_2)_2CS$-MeOH; ii, Ac_2O-NaOAc; iii, $Me_2C(OMe)_2$-MeOH-H^+; iv NaOMe; v, Ac_2O-DMSO vi, $NaBH_4$; vii, HOAc-H_2O; viii, MeOH-H^+

Scheme 2

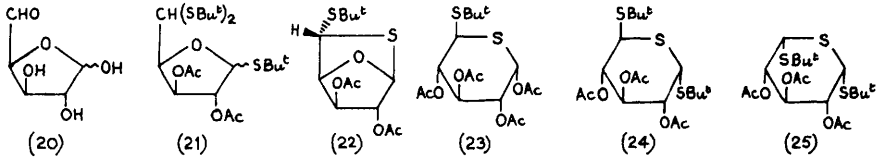
deoxy-5-thio-D-glucose (18) and -mannose (19) (Scheme 3).[7]



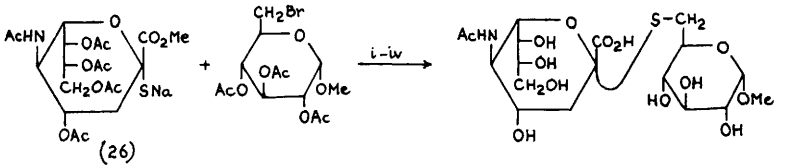
Reagents: i, NaN_3-Ce(IV)$NH_4(NO_3)$; ii, NaOAc-HOAc; iii, PtO_2-Ac_2O-MeOH-H_2; iv, MeONa-MeOH

Scheme 3

Treatment of xylo-pentodialdo-1,4-furanose (20) with 2-methylpropane-2-thiol followed by acetylation gave the products (21) to (24) in 6.1, 5.9, 20.1, 3.8, and 1.7% yields respectively.[8]



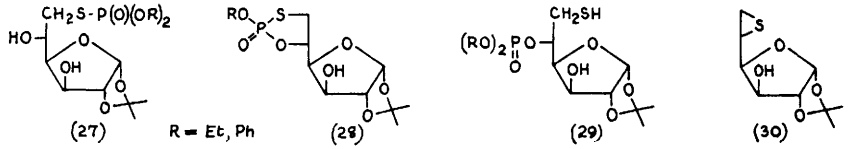
6-S-(5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonic acid)-6-thiohexopyranosides, i.e., (2→6)-linked disaccharides containing an α-linked 2-thio-N-acetylneuraminic acid, have been synthesized by the condensation of the sodium thiolate (26) with appropriate bromosugars in DMF followed by deprotection. For example, the 6-thioglucoside was prepared by the route depicted in Scheme 4.[9]



Reagents: i, DMF; ii, NaOMe-MeOH; iii, KOH-H_2O; iv, Resin-H^+

Scheme 4

A reinvestigation of the reaction of 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose with phosphorothioic acids, $(EtO)_2P(S)OH$ (see Vol. 14, p.57), has shown that the products are an equilibrium mixture of the esters (27) - (29). In the case of the diethylphosphorothioic acid, the cyclic ester (28) predominated if ethanol was continually azeotropically removed from the reaction mixture. More vigorous conditions gave the episulphide (30) irreversibly.[10]



Reference to novel sulphur-containing sugars as components of antitumour antibiotics is made in Chapter 19.

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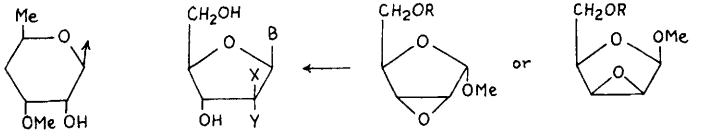
12
Deoxy-sugars

Another unusual sugar residue, the 4,6-dideoxy-3-O-methyl-D-ribo-hexosyl moiety (1), has been encountered in a cardenolide glycoside from the leaves of Anodendron affine.[1] A 2D ^{1}H-n.m.r. study of digitoxose has appeared.[2]

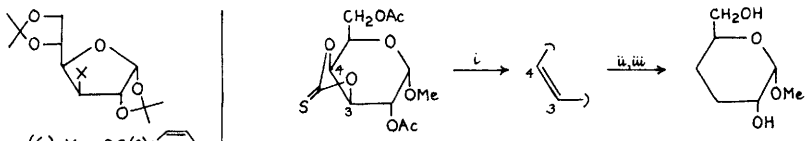


(1) (2) X=D, Y=H (3) X=H, Y=D (4) (5)

R = 4-methoxytrityl

Specifically deuterated 2'-deoxy-purine and -pyrimidine-nucleosides (2) and (3), required to simplify the ^{1}H-n.m.r. spectra and permit ^{2}H-n.m.r. spectroscopy of nucleosides in DNA molecules or segments, have been obtained through reduction ($LiAlD_4$) of epoxides (4) and (5), respectively; selective attack at C-2 vs. C-3 (ratio 9:1) was encouraged by the bulky O-5 protecting group. The required inversion at C-3' in the synthesis of (3) from (5) was achieved by mesylate displacement.[3]

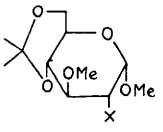
Further modifications and applications of Barton's radical deoxygenation procedure have been reported. The use of 1,1'-thiocarbonyldi-2,2'-pyridone has been promoted for derivatizing secondary hydroxy groups, since the biproduct in the subsequent reduction (with Bu_3SnH-AIBN) is the neutral and water soluble 2-pyridone. In this way diacetoneglucose was converted to the thiono ester (6) and thence the 3-deoxy-derivative (7) in 78% overall yield.[4] Prepara-



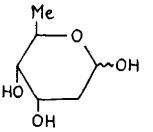
Scheme 1

tive procedures for the same conversion *via* radical reduction of the 3-xanthate ester in 70% overall yield have been detailed.[5] 3-Deoxy-sucrose has been synthesized similarly *via* a 3-xanthate derivative.[6] Deoxy-sugars have been synthesized by sequential regioselective thioacylation (Bu_2SnO then PhOCSCl), acetylation, and radical deoxygenation (Bu_3SnH). Methyl α-D-glucopyranoside gave mainly the 2-*O*-phenylthionocarbonate ester and thence a 2-deoxy-D-*arabino*-hexoside. Methyl β-D-xylopyranoside gave exclusively the 2-ester and thence the corresponding 2-deoxy sugar, while its α-anomer gave a mixture of 2- and 4-monoesters and thence 2- and 4-deoxy sugars. Pyranosides with *cis*-vicinal diols gave cyclic thionocarbonates. 3,4-Thionocarbonates were obtained from Me α-D-Gal-*p*, Me β-D-Gal-*p*, Me β-L-Ara, and Ph α-L-Ara, and on reduction these gave mixtures of 3- and 4-deoxy-compounds. Dideoxy-compounds could be obtained from these cyclic thionocarbonates *via* alkenes as exemplified in Scheme 1.[7]

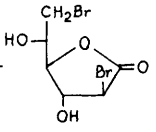
2-Deoxy-3-*O*-methyl-D-*arabino*-hexose has been synthesized in 5 steps from methyl α-D-glucopyranoside, the key step being photochemical deoxygenation (254 nm, HMPT-H_2O) of the 2-pivaloate (8) to 2-deoxy-sugar (9). Isopropylidene but not benzylidene acetals are stable to these deoxygenation conditions.[8]



(8) X = OCOBu^t
(9) X = H



(10)



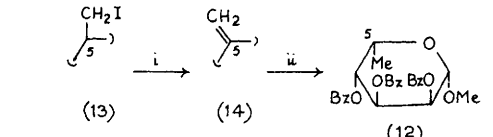
(11)

Deoxygenation can also be effected by reductive dehalogenation of halo-sugars derived by sulphonate displacement reactions. Such a strategy has been employed in conventional syntheses of 6- and 6'-deoxycellobiose from phenyl or methyl β-cellobioside *via* 6- or 6'-iodides,[9] 4-deoxy-sucrose *via* 4-chloro-4-deoxy-*galacto*-sucrose heptapivaloate,[10] and *N*-acetyl-4-deoxy-D-neuraminic acid *via* a 4-iodide.[11] Syntheses of the latter compound are further covered in Chapter 16. Halogen atoms can be introduced into sugar lactones on reaction with hydrogen bromide in acetic acid. 2,6-Dideoxy-D-*ribo*-hexose (10) was obtained by reduction (i, H_2-Pd/C-Et_3N; ii, disiamyl borane) of the 2,6-dibromide (11) obtained from D-allono-lactone. Application of the same route yielded 2,6-dideoxy-D-*xylo*- and *lyxo*-hexoses from D-gulono-1,4-lactone and D-talono-1,4-lactone,

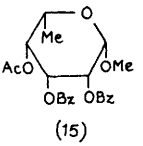
respectively.[12]

6,6'-Dideoxy-sucrose has been synthesized regiospecifically from sucrose by synthesis (2,2'-dipyridyldisulphide-Ph_3P) and reductive desulphurization (Raney Ni) of 6,6'-dideoxy-6,6'-bis(2-pyridylthio) sucrose.[13]

6-Deoxy-L-guloside (12), and thence the parent sugar, has been synthesized from the mannoside (13) (Scheme 2). The required C-5 inversion was achieved by formation and hydrogenation of the hex-5-



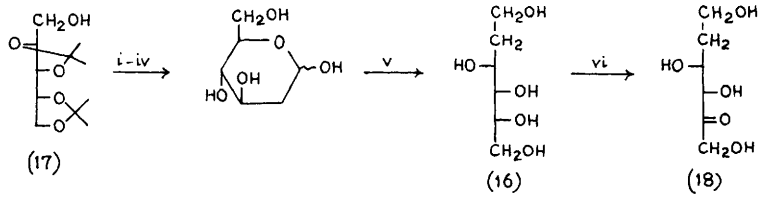
Scheme 2



enoside (14), an ~4:1 ratio of inversion to retention being attained, depending upon the catalyst. An analogous synthesis of 6-deoxy-L-taloside (15) from a methyl α-D-allopyranoside derivative was also achieved.[14]

3,6-Dideoxy- and 3,4,6-trideoxyhexopyranose and 3,6-dideoxyhexofuranose derivatives, obtained from L-rhamnono-1,5-lactone by sequential benzoylation with β-elimination, hydrogenation, and diborane reduction, have been studied by ^{13}C-n.m.r. spectroscopy.[15]

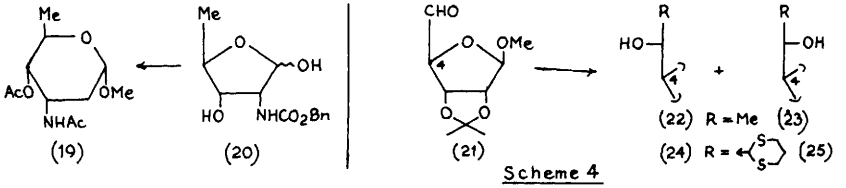
Deoxy-sugars can also be derived as a consequence of a one-carbon chain extension reaction. 2-Deoxy-D-*arabino*-hexitol (16) was obtained from the pentitol (17) through conversion into a Grignard reagent and formylation; oxidation to 5-deoxy-D-*threo*-hexulose (18) was effected using immobilized cells of *Gluconobacter oxydans* (Scheme 3).[16] The 3-acetamido-2,3,6-trideoxy-sugar



Scheme 3

(19), a derivative of D-ristosamine, was obtained in four steps from the pentose (20) *via* condensation with a Wittig reagent

$(Ph_3P{=}CHOMe)$.[17]



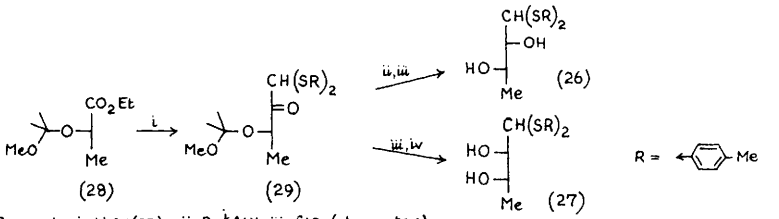
Scheme 4

Addition of methylmagnesium iodide to hepta-O-benzyl-6-aldehydo-sucrose-yielded a mixture of β-D-fructofuranosyl-7-deoxy-D- and L-glycero-α-D-gluco-heptopyranosides ('6-C-methylsucrose'). The analogous '6'-C-methylsucrose' was similarly obtained from a 6'-aldehydo-sucrose derivative.[18] The addition of organometallic reagents to methyl 2,3-O-isopropylidene β-D-ribo-pentodialdo-1,4-furanoside (21) has been examined (Scheme 4). Whereas methyllithium and methylmagnesium iodide gave the D-allo- and L-talo-isomers, (22) and (23), in a 2-3:1 ratio, respectively, 2-lithio-1,3-dithiane gave almost exclusively (97:3) the non-chelation product, D-alloside (24). Reductive desulphurization of (24) gave (22). The L-taloside (25) could be synthesized in modest yield by 5-sulphonate displacement with inversion by benzoate.[19]

Enzymatic condensations have been used in the synthesis of deoxy-sugars. The production of 1-deoxyketoses using cell free extracts of micro-organisms, this time Bacillus subtilis, to induce an acyloin-type condensation of an aldose with pyruvate, acetoin, or methylacetoin, has been further examined (c.f., Vol.18, p.123). Pyruvate dehydrogenase and acetoin dehydrogenase have been implicated from studies with mutant strains lacking these enzymes.[20] 5-Deoxy-D-fructose 1-phosphate was produced by aldolase-catalyzed aldol condensation between dihydroxyacetone phosphate (generated in situ from D-fructose 1,6-diphosphate via combined catalysis of the aldolase and triose phosphate isomerase) and 3-hydroxypropanal. This product, after hydrolytic removal of the 1-phosphate, was not converted to 5-deoxy-D-glucose with glucose isomerase since the equilibrium lies exclusively on the side of the ketose. 6-Deoxy-D-fructose was produced analogously using L-lactaldehyde as the aldehydic component; in this case glucose isomerase yielded a 1:4 mixture of 6-deoxy-D-fructose and 6-deoxy-D-glucose.[21,22] The synthesis of 3-deoxy-D-glucose by the same approach was claimed, but no details were presented.[22]

Deoxy-sugars have been elaborated from 3- and 4-carbon chiral materials. 4-Deoxy-L-threose and -erythrose dithioacetal deriva-

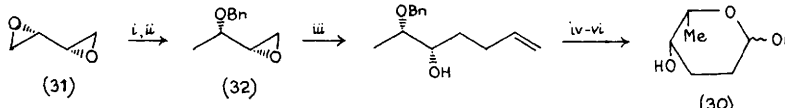
tives, (26) and (27) respectively, have been synthesized from the L-lactic acid derivative (28) (Scheme 5). The stereoselectivity



Reagents: i, $LiCH(SR)_2$; ii, Bu^i_2AlH; iii, SiO_2 (chromatog.), iv, $NaBH_4$

Scheme 5

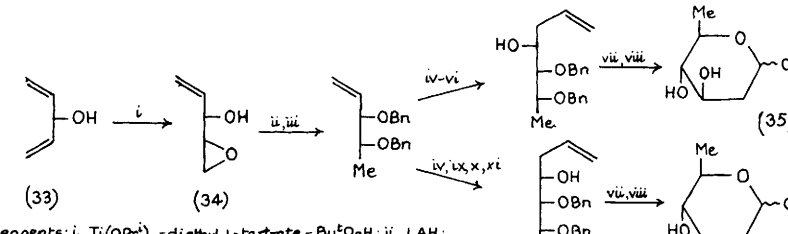
achieved in the reduction of the ketone intermediate (29) to (26) was reversed on prior removal of the 3-O-protecting group.[23] L-Rhodinose (30) has been synthesized from the diepoxide (31), available in six steps from D-tartaric acid (Scheme 6). The epoxide (32) was also converted to (+)-epimuscarine iodide in 3 steps.[24]



Reagents: i, $LiBHEt_3$; ii, BnBr-NaH-Bu_4NI; iii, MgCl-CuI; iv, Li-$NH_3(l)$; v, O_3, then Me_2S; vi, HCl

Scheme 6

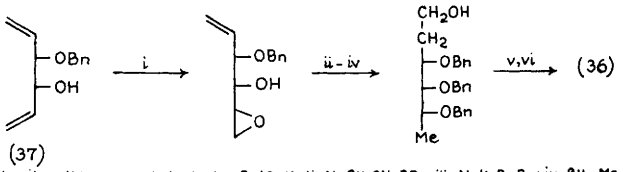
Tartrate esters also feature as the chiral reagents in the Sharpless asymmetric epoxidation, a reaction applied in the synthesis of deoxy-sugars. Two groups have epoxidized divinyl carbinol (33) and converted the resulting mono-epoxide (34) into the 2,6-dideoxy-sugars D-olivose (35), its 3-O-methyl ether (D-oleandrose) and 4-O-benzyl ether, and into D-digitoxose (36) and its 4-O-benzyl ethers (Scheme 7).[25,26] Epoxidation of the meso-



Reagents: i, $Ti(OPr^i)_4$-diethyl L-tartrate-Bu^tO_2H; ii, LAH; iii, BnBr-NaH; iv, OsO_4-O⌒N+O; v, $NaIO_4$; vi, $SiMe_3$-$TiCl_4$; vii, viii, Li-$NH_3(l)$; viii, O_3; ix, TsCl-Py; x, K_2CO_3; xi, CH_2=CHMgBr-CuI

Scheme 7

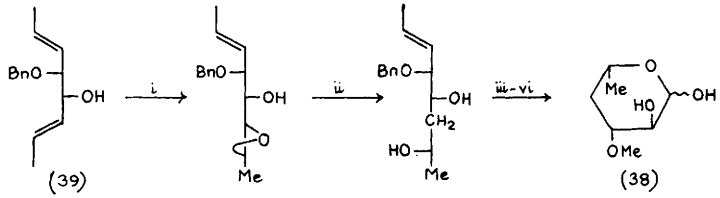
divinyl glycol monobenzyl ether (37), derived through reductive dimerization of acrolein, was used in the synthesis of D-digitoxose



Reagents: i, $Ti(OPr^i)_4$ - di-isopropyl L-tartrate - Bu^tO_2H; ii, $NaBH_3CN$-BF_3; iii, NaH-BnBr; iv, BH_3-Me_2S, then $NaOH$-H_2O_2; v, PDC; vi, H_2-Pd/C.

Scheme 8

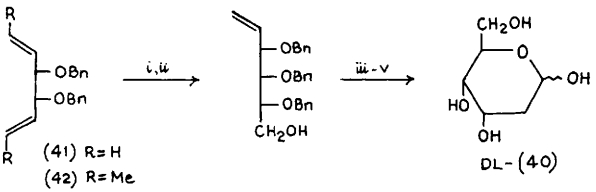
(Scheme 8).[27] L-Chalcose (38) was obtained by epoxidation of the racemic divinyl glycol derivative (39) with an L-tartrate reagent (Scheme 9), its D-enantiomer being obtained by use of the corresponding D-tartrate ester in the kinetic resolution.[28]



Reagents: i, $Ti(OPr^i)_4$ - diethyl L-tartrate - Bu^tO_2H; ii, Red-Al; iii, O_3, then Me_2S; iv, BnOH-HCl; v, MeI-NaH; vi, H_2-Pd/C

Scheme 9

Racemic 2-deoxy-*ribo*-hexose (40) has been obtained *via* vicinal hydroxylation of one double bond of the *meso*-divinyl glycol derivative (41) (Scheme 10), 6-deoxy-DL-talose being obtained in a related fashion from the starting material (42), derived from reductive dimerization of crotonaldehyde.[29]

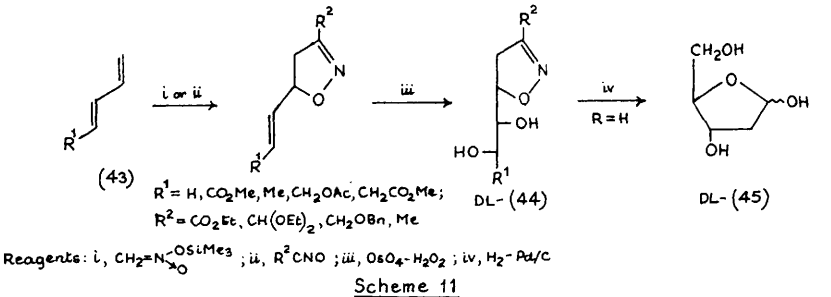


Reagents: i, OsO_4 -  ; ii, BnBr-NaH; iii, BH_3-Me_2S then $NaOH$-H_2O_2; iv, PCC; v, H_2-Pd/C

Scheme 10

A variety of racemic deoxy-aldoses and -ketoses, including oleose, digitoxose, 2-deoxygalactose, 3-deoxyfructose, and 1,3-dideoxyfructose, have been synthesized from dienes (43) (Scheme 11).

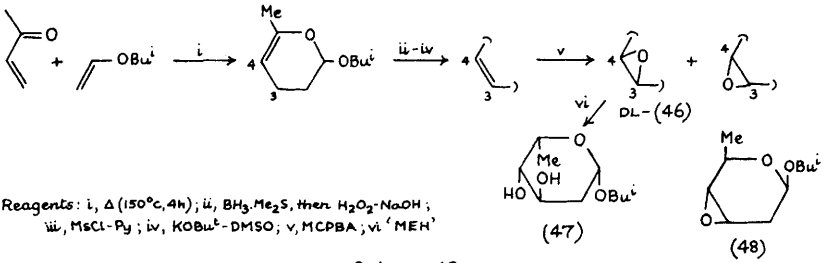
Regioselective dipolar cycloaddition of a silylnitronate or nitrile



Scheme 11

oxide to the terminal double bond, followed by stereospecific hydroxylation, yielded the 2-isoxazolines (44). Catalytic reduction of these gave the desired deoxy-sugars, as shown for 2-deoxyribose (45).[30]

Enantiomeric derivatives of boivinose (2,6-dideoxy-xylo-hexose) have been synthesized in 96±4% ee, using the selective enzymic hydrolysis of the L-epoxide in the racemic mixture (46) by microsomal



Scheme 12

epoxide hydrolase ('MEH') (Scheme 12). Enzymatic hydrolysis yielded the L-glycoside (47), while the unhydrolysed D-epoxide (48) gave the D-enantiomer of (47) on alkaline hydrolysis.[31]

An anhydrodideoxyalditol is covered in Chapter 24.

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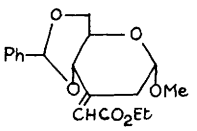
13
Unsaturated Derivatives

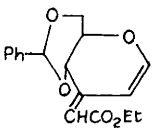
1 Glycals

Activated zinc/silver-graphite, used in tetrahydrofuran, efficiently converts acetal-protected and acetylated glycofuranosyl and glycopyranosyl halides into glycals - at least on the modest scales (2.2 mmol) reported. The method has particular potential value for preparing furanosyl glycal derivatives.[1]

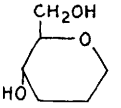
The exocyclic alkene (1) has been prepared from the corresponding ketone by Wittig and Peterson olefination. When excess of the lithium salt of ethyl trimethylsilylacetate was used, the conjugated glycal derivative (2) was produced; it can also be obtained from (1) by treatment with base, e.g., potassium tert-butoxide.[2]



(1)



(2)



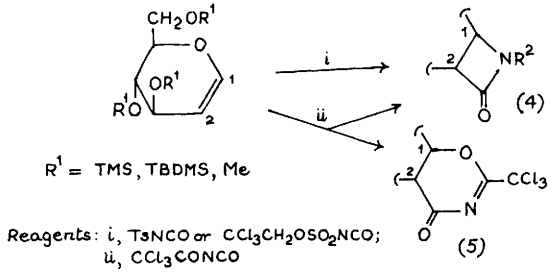
(3)

The chiral diol (3) can be made by hydrogenation of tri-O-acetyl-D-glucal or of its isomer 1,4,6-tri-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranose (both, it is suggested, by way of the 3-deoxyglycal intermediate) followed by deacetylation.[3]

The factors, especially the solvent polarity, that influence the syn-addition of fluorine and acetylhypofluorite to D-glucal and its triacetate have been studied. A 95:5 ratio of 2-deoxy-2-fluoro-D-glucose to -D-mannose was obtained following reaction of the hypofluorite in trichloromethyl fluoride with the triacetate. A rationale for the results and for the ^{19}F n.m.r. chemical shifts of the products was provided.[4] Further related study of the addition of chlorine and bromine to di-O-acetyl-L-fucal has shown that cis-related chlorine adducts are favoured in non-polar solvents and that substituents at C-6 appear to affect the stabilization of the anomeric carbocations in the case of the bromination reaction.[5]

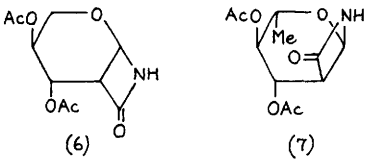
[2+2]Cycloaddition of some isocyanates to D-glucal derivatives

affords β-lactams (4) in high yields (Scheme 1). With trichloro-

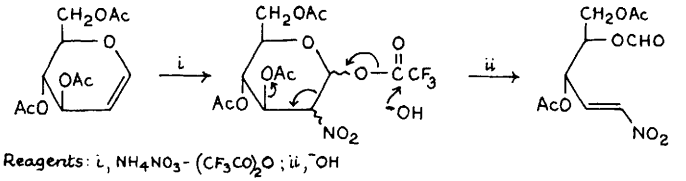


Scheme 1

acetyl isocyanate, however, some of the 6-membered adducts (5) are also formed, especially after long reaction times.[6] Similar studies using di-O-acetyl-xylal or rhamnal and trichloroacetyl isocyanate have led to compounds (6) and (7).[7]



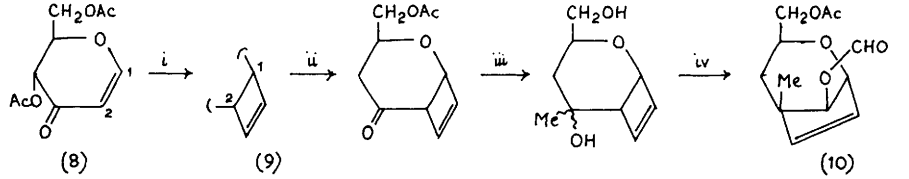
Treatment of tri-O-acetyl-D-glucal with trifluoroacetic anhydride and ammonium nitrate gives isomeric 2-deoxy-2-nitrato-glycosyl trifluoroacetates which, with base, undergo very efficient Grob fragmentation as indicated in Scheme 2. Glycal esters with 3,4-cis



Scheme 2

-related groups react with less efficiency, and glycals themselves and 3-O-methyl derivatives, both of which have poorer leaving groups at C-3, do not take part in this degradation.[8]

An improved method of oxidizing the allylic hydroxy group of D-

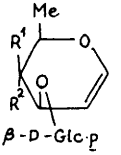


Scheme 3

glucal (PDC in ethyl acetate, acetic acid) gives the enone in about 50% yield.[9] The diacetate (8) of the product undergoes photochemical addition of acetylene, to give the cyclobutene (9) (also in 50% yield), which was converted as shown in Scheme 3 into compound (10), which represents the carbon skeleton of the B/C portion of the trichothecenes.[10]

Reference is made in Chapter 3 to the synthesis of C-glycosides from glycal derivatives by use of palladium adducts, and related work leading to 2,3-unsaturated C-nucleosides is reported in Chapter 20.

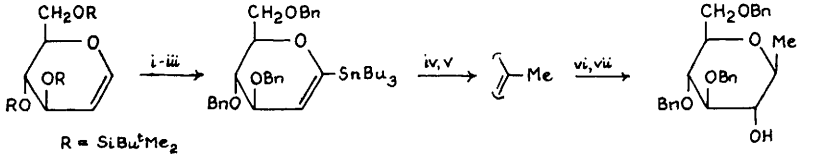
Somewhat unusually, glycal derivatives have been isolated from natural sources, compounds (11) and (12) (absolute configurations uncertain) having been found in Dianthus and Saponaria species, respectively.[11]



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

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

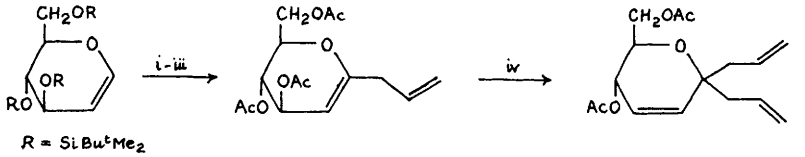
Interesting developments are taking place in the area of 1-substituted glycals. 1-Tributylstannyl derivatives have been used to prepare 1-alkylated compounds and hence C-glycosides (e.g.,



Reagents: i, KOBu^t-BuLi-Bu_3SnCl; ii, Bu_4NF; iii, BnBr-KH; iv, BuLi; v, MeI; vi, BH_3; vii, H_2O_2-OH^-

Scheme 4

Scheme 4; aldehydes lead to 1-hydroxyalkyl C-glycosides),[12] and methods have been found to effect direct alkylation and geminal C-1 bisalkylation with allylic rearrangement. Scheme 5 illustrates



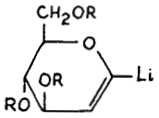
Reagents: i, BuLi-CuI-⌒Br; ii, Bu_4NF; iii, Ac_2O-Py; iv, $(⌒)_3Al$-$TiCl_4$

Scheme 5

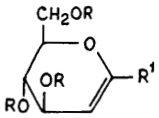
these processes for alkylation; other alkyl groups were also introduced.[13]

1-Lithiated glycals, e.g., (13), can be made by direct metalation

using butyllithium; treated with alkylation agents they afford 1-alkylated products, e.g., (14). Otherwise, lithiation and alkylation can be effected as shown in Scheme 6.[14]

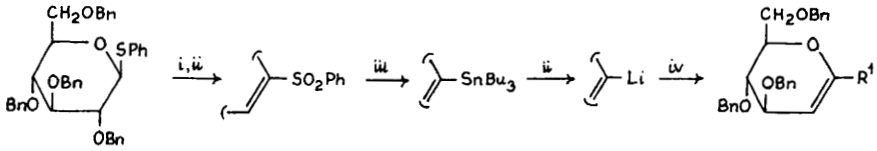


(13)



(14)

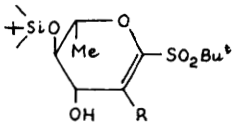
$R = SiBu^tMe_2$
$R^1 = Me, Allyl$



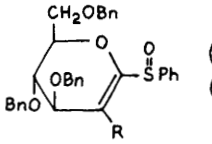
Reagents: i, MCPBA; ii, BuLi; iii, Bu_3SnH; iv, R^1X

Scheme 6

The vinyl sulphone (15), made from the corresponding 2,3-O-isopropylidene thioglycoside, did not give products of Michael addition but 2-alkylated products, e.g., (16), on sequential treatment with methyllithium and methyl iodide.[15]



(15) R = H
(16) R = Me



(17) R = H
(18) R = Li

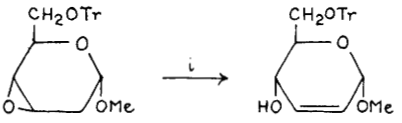
Lithiation of the phenylsulphinyl glycal (17) (obtained from the oxidized thioglycoside by treatment with LDA) occurred at C-2 to give compound (18) and afforded access to C-2-branched-chain compounds (see Chapter 14). 1-Nitroglycals are available from the corresponding saturated compounds under acidic or basic conditions and can be used to give 2-amino-2-deoxy-adducts (Chapter 10).

2 Other Unsaturated Derivatives

Fraser-Reid has reviewed his more recent developmental work using 2,3-unsaturated carbohydrate derivatives.[16]

Methyl magnesium N-cyclohexylisopropylamide, made from lithium cyclohexylisopropylamide and methylmagnesium bromide, acts as a very efficient base catalyst to effect the isomerization shown in Scheme 7.[17]

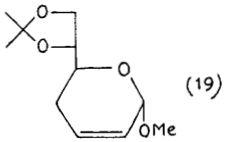
The effects of pressure, temperature and solvent on asymmetric induction in the [4+2]cycloaddition reaction of 2,3-O-isopropylidene



Reagent: i, $MeMgN(C_6H_{11})Pr^i$

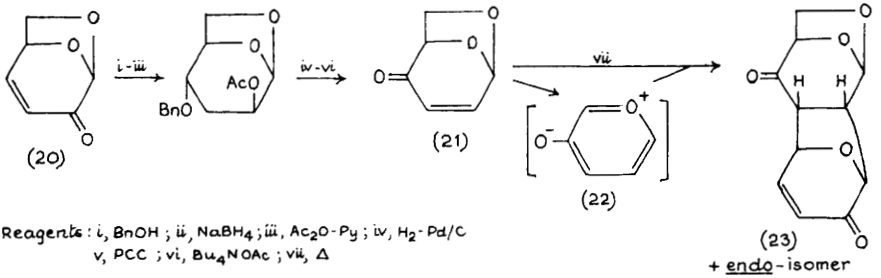
Scheme 7

-D-glyceraldehyde and 1-methoxybutadiene have been investigated. The four diastereomers were produced;[18] equilibration favours the product (19).[19]



(19)

"Levoglucosenone" (20) has been isomerized to "isolevoglucosenone" (21) as indicated in Scheme 8 and shown to degrade to an oxopyrylium species (22) with which it gives the adducts (23).[20] An

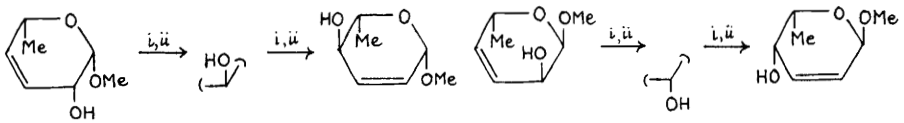


Reagents: i, BnOH; ii, $NaBH_4$; iii, Ac_2O-Py; iv, H_2-Pd/C
v, PCC; vi, Bu_4NOAc; vii, Δ

Scheme 8

addition reaction applied to a derivative of a 2,3-unsaturated aldono-γ-lactone has afforded access to the anthracene-based compound olivin (Chapter 24).

The interesting generalization has been proposed that, while 1,2-cis-related methyl 3,4,6-trideoxyhex-3-enopyranosides react with diethyl azodicarboxylate, triphenylphosphine and benzoic acid to give products of S_N2 displacement, the trans-related isomers react by the S_N2' path to give access to 2,3-unsaturated isomers (Scheme 9).[21]

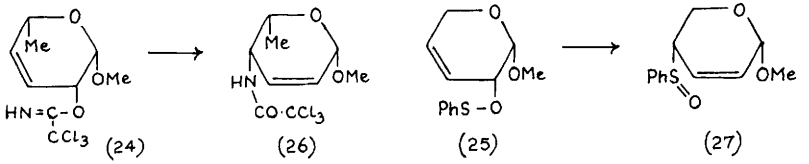


Reagents: i, DEAD-Ph_3P-$PhCO_2H$; ii, MeO^-

Scheme 9

Heating of the trichloroacetimidate (24)[21] and the sulphenate

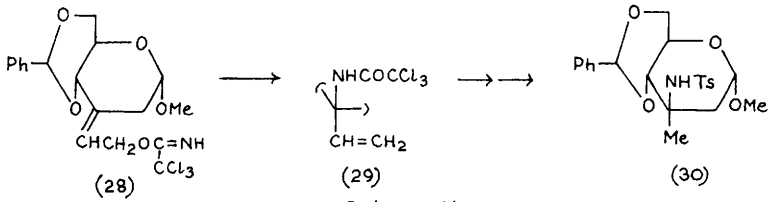
ester (25)[22] proceeded by sigmatropic rearrangements to give 2,3-unsaturated isomers (26) and (27), respectively (Scheme 10). In



(24) (26) (25) (27)

Scheme 10

parallel to the first of these, the exocyclic alkene (28) thermally rearranged to give the branched-chain aminosugar derivative (29) from which the vancosamine derivative (30) was obtained (Scheme 11).[21]

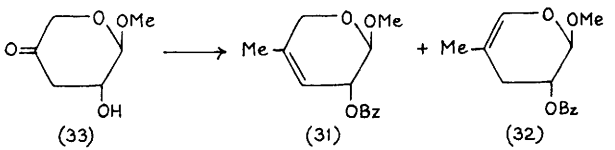


(28) (29) (30)

Scheme 11

Several 2,3-unsaturated compounds bearing substituents at C-3 are mentioned elsewhere (Chapters 8 and 14).

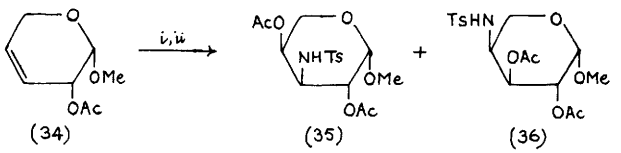
Other studies on 3,4-unsaturated compounds have included the synthesis of the branched-chain compound (31), which has been made with its isomer (32) from the ketone (33) as illustrated in Scheme 12. Compound (31) did not undergo oxyamination whereas the unbranched analogue (34) afforded the isomeric products (35) and (36)



(33) (31) (32)

Reagents: i, MeMgI ; ii, $SOCl_2$-Py ; iii, BzCl-Py

Scheme 12

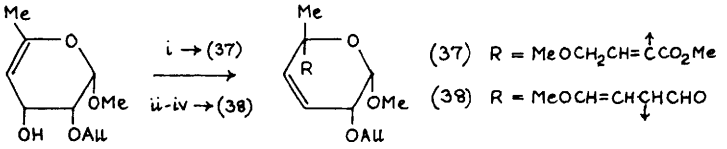


(34) (35) (36)

Reagents: i', Chloramine T, $AgNO_3$, OsO_4 ; ii, Ac_2O-Py

Scheme 13

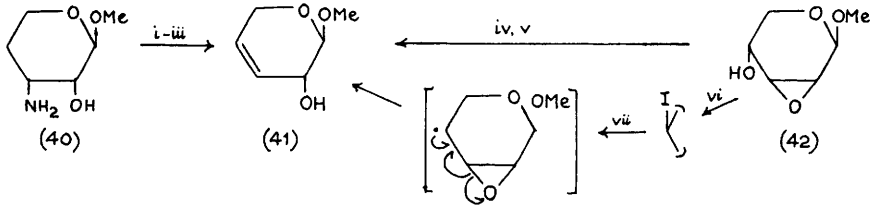
(Scheme 13).[22] The C-5 branched-chain compounds (37) and (38) were produced by Claisen rearrangement processes applied to the allylic alcohol (39) (Scheme 14).[23]



Reagents: i, MeO(F)C=C(SOPh)CH_2CH_2OMe-KH; ii, TsOCH=CHCHO-NaH; iii, MeOCH=PPh_3; iv, Et_2AlCl-Ph_3P

Scheme 14

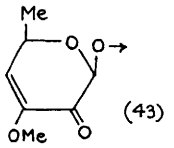
The resolution of methyl 3-amino-3,4-dideoxy-β-D- and -L-erythro-pentopyranosides, e.g., (40), was effected by coupling with O-methyl-L-tyrosine and separation of the stereoisomers, while the absolute stereochemistry was determined by conversion to the alkene (41), which was independently synthesized from the epoxide (42) in two ways (Scheme 15).[24]

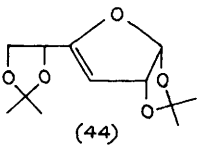


Reagents: i, HCHO-HCO_2H; ii, H_2O_2; iii, Δ; iv, TsCl; v, NaI-Zn; vi, $MeP(OPh)_3I$; vii, Bu_3SnH

Scheme 15

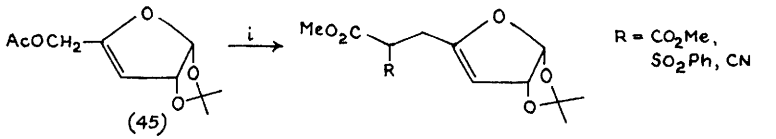
The unusual enolone unit (43) has been found as a component of a plant cardenolide.[25]



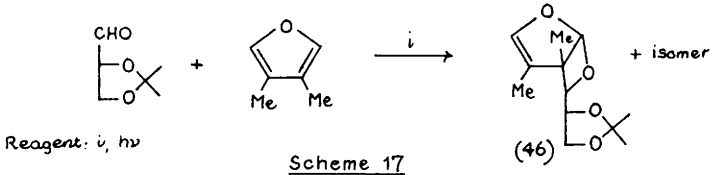


In the furanoid series an improved synthesis of the well known alkene (44) uses di-O-isopropylidene-α-D-glucofuranose 3-tosylate and treatment with potassium hydroxide.[26] The related compound (45) was used to obtain a set of compounds which were prepared as potential cyclopentane precursors (Scheme 16).[27]

Photochemical addition of 2,3-O-isopropylidene-D-glyceraldehyde to 2,3-dimethylfuran gives compound (46) and a stereoisomer (Scheme 17). The former was then employed in a synthesis of a



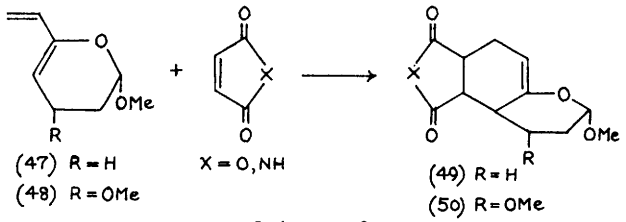
Scheme 16



Scheme 17

degradation product of asteltoxin, thereby establishing its absolute configuration.[28]

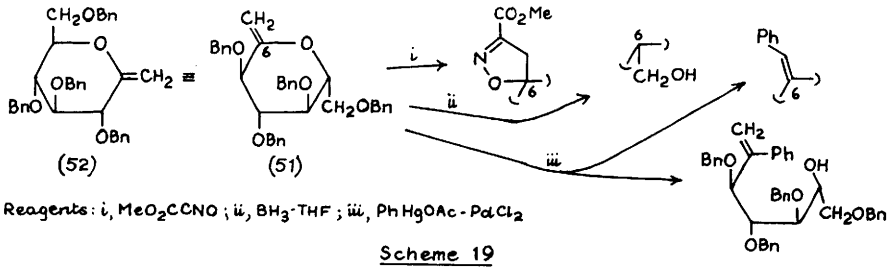
In the area of 4,5-unsaturated compounds the dienes (47) and (48) have been synthesized and treated with dienophiles to give the adducts (49) and (50) (Scheme 18).[29] An unexpected rearrangement



Scheme 18

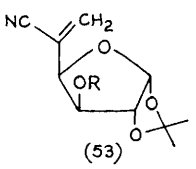
of a 4,5-unsaturated furanoid compound to a hexoseptan-4-ulose derivative is described in Chapter 15.

The 5,6-unsaturated compound (51), which is also the methylene derivative (52) prepared from the corresponding D-gluconolactone tetraether with Tebbe's reagent, underwent the reactions illustrated in Scheme 19.[29a] A set of furanoid compounds (53) have been found



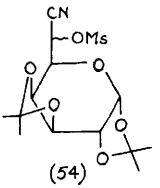
Scheme 19

to have cytotoxic and antiviral properties, whereas nucleoside analogues were inactive.[30]

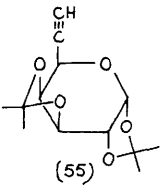


(53)

R = Me, Bu, $(CH_2)_3Ph$, $(CH_2)_7Me$

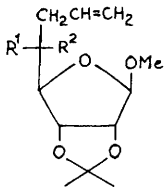


(54)

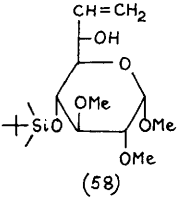


(55)

Treatment of the epimeric mesylates (54) with sodium azide in DMF caused eliminations to afford the acetylene (55),[31] and the epimeric 7-enes (56) and (57) were produced in high stereoselectivity from the C-5 aldehyde by use of allyltrimethylsilane in the presence of boron trifluoride and titanium tetrachloride



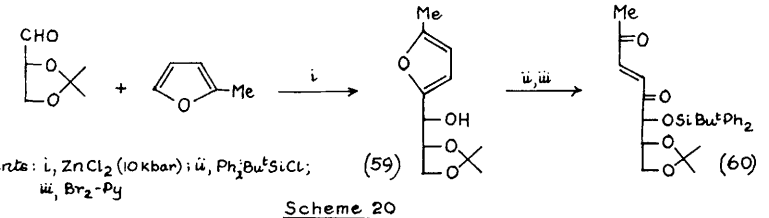
(56) R^1=OH, R^2=H
(57) R^1=H, R^2=OH



(58)

respectively. In contrast, the aldehyde derived from methyl 4-O-tert-butyldimethylsilyl-2,3-di-O-methyl-α-D-glucopyranoside afforded the D-glycero-D-gluco-adduct under both conditions. The pyranoid L-glycero-D-gluco epimer (58), on the other hand, could be obtained by way of the 2-trimethylsilylethylidene Wittig alkene.[32]

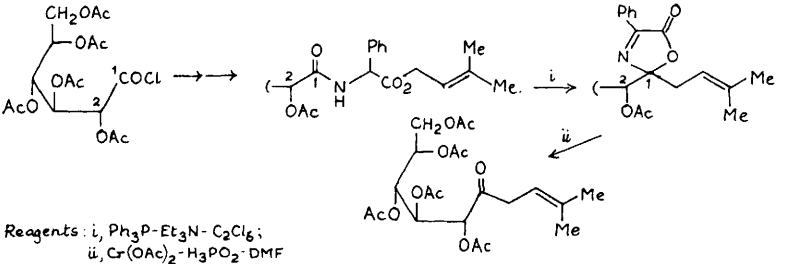
In the field of acyclic alkenes, compound (60) was obtained via the furan (59), which is the product of reaction of 2-methylfuran and 2,3-O-isopropylidene-D-glyceraldehyde (Scheme 20).[33]



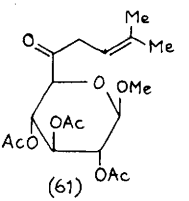
Scheme 20

Scheme 21 illustrates the rearrangement of a phenylglycine amide derivative of gluconic acid and its application to the preparation of an acyclic unsaturated sugar derivative. Likewise the 8-enose derivative (61) was obtained from the corresponding uronic acid chloride.[34] The same authors similarly produced hexadiene and derived Diels-Alder adducts from D-gluconic acid.[35]

The examples in Scheme 22 illustrate the participation of the

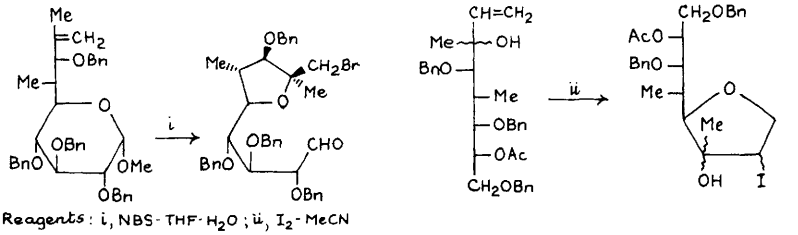


Scheme 21



(61)

ring oxygen and benzyl ether oxygen in electrophilic addition to alkenes.[36] See Chapter 17 for an example of a novel approach to ald-2-enitols.



Scheme 22

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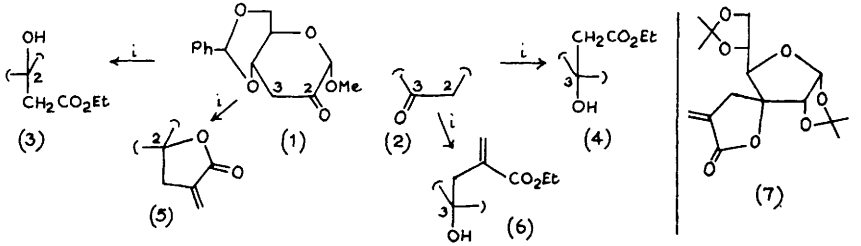
14
Branched-chain Sugars

1 Compounds with an R-C-O Branch

Weidmann's group has studied the application of Reformatsky-type reactions for preparing branched-chain sugars. The glycosulose derivatives (1) and (2) reacted with α-bromoacetic ester in presence of laminated zinc/silver graphite at low temperature to give the branched-chain sugars (3) and (4) respectively, with good stereoselectivity (Scheme 1);[1] the bromo-methylacrylate ester yielded



Reagents: i, Zn/Ag-graphite, $BrCH_2CO_2Et$ or $BrCH_2C(=CH_2)CO_2Et$, THF, -78°

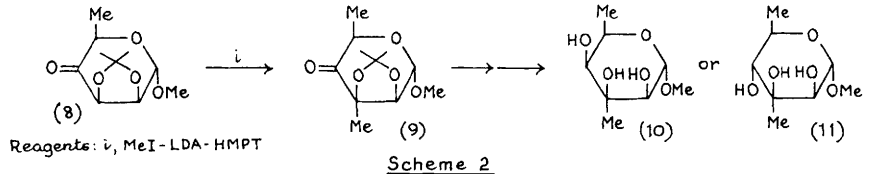
Scheme 1

either lactone (5) or hydroxy ester (6) from these glycosiduloses, and also the lactone (7) from di-O-isopropylidene-D-glucofuranose.[2] The branched-chain sugars (3) and (4) could also be obtained from the uloses by using an ethyl trimethylsilyl acetate - tetrabutylammonium fluoride reagent, the product tertiary alcohol group being silylated or not depending on whether the ammonium salt was anhydrous or hydrated (see also Scheme 12 below).[3,4]

A convenient synthesis of D-apiose from D-xylose using an aldol condensation of the aldehydo-sugar with formaldehyde has been described; the synthesis of the requisite di-O-isopropylidene derivative is mentioned in Chapter 6.[5] An aldol condensation of a pentulose with methyl propanoate giving an intermediate branched-chain hexonic acid derivative is described in Chapter 24.

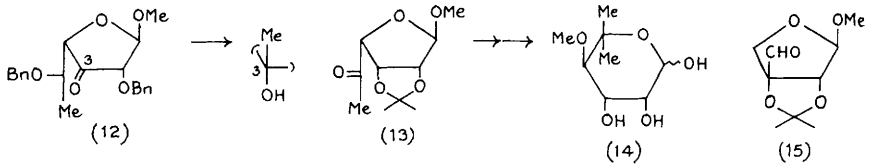
A synthesis of D-evalose (6-deoxy-3-C-methyl-D-mannose) utilized an enolate methylation reaction for the conversion of the 4-ulose (8) to the 3-C-methyl analogue (9); LAH reduction of (9) led to the talose derivative (10), whereas $NaBH_4$ reduction of the 2,3-di-O-acetyl analogue of (9) gave the required mannose derivative (11)

(Scheme 2). An analogous sequence on L-rhamnose provided a route to L-nogalose, the 2,3-di-O-methyl derivative of evalose.[6] Another synthesis of L-nogalose used a conventional Grignard addition to a



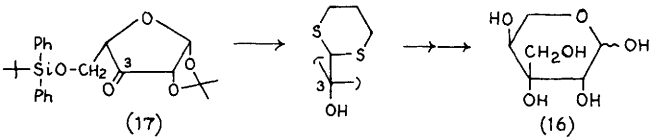
Scheme 2

3-ulose derivative of L-rhamnofuranose (12), giving high stereoselectivity for the required mannose isomer.[7] L-Rhamnose has also been used to prepare the 5-ulose (13), which by Grignard reaction gave a new route to noviose (14).[8]

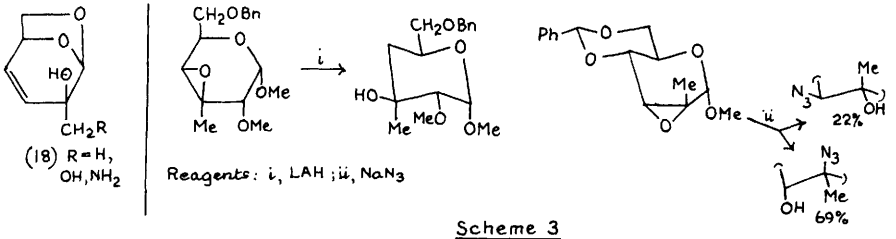


A practical procedure has been described for preparing the 3-C-formyl sugar (15) via methyl 2,3-O-isopropylidene-D-apiofuranoside using a modified Collins oxidation; (15) was required for a synthesis of tetrodotoxin.[9]

Reaction of the conventional 3-ulose prepared from di-O-isopropylidene-D-glucofuranose with nitromethane provided both the allo- and gluco- isomers of the corresponding 3-C-nitromethyl sugars, which were then converted by standard procedures to 3-C-hydroxymethyl pentoses with D-ribo, D-xylo, and D-lyxo configurations; the last of these proved to be enantiomeric with the monosaccharide isolated from Phase I Coxiella burnetii LPS, which was confirmed by a synthesis of the L-form (16) from L-arabinose using the 3-ulose (17) with lithio 1,3-dithiane to introduce the required L-lyxo branch chain.[10]

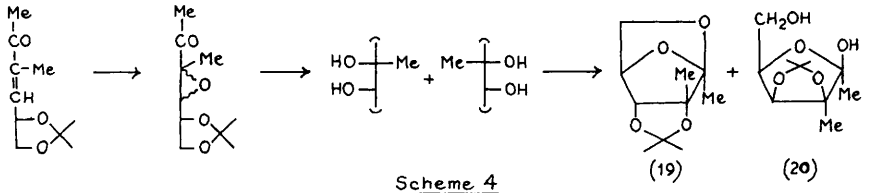


Standard procedures have been used on laevoglucosenone to produce a series of unsaturated branched-chain derivatives (18), which were also reduced to the corresponding 3,4-dideoxy analogues. The assigned configuration was established by X-ray crystal analysis (R=OH).[11]



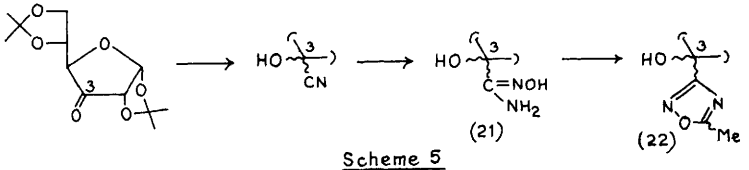
Scheme 3

A study of the epoxide ring opening of branched-chain sugar epoxides with hydride and azide nucleophiles revealed that a tendency towards anti-Furst-Plattner ring opening occurred where nucleophilic attack at the tertiary centre was required for Furst-Plattner opening, in some cases leading to the major product, as illustrated in Scheme 3.[12] 3,4-Anhydro-1-deoxy-3-C-methyl-D-hexulose derivatives have been prepared by epoxidation of the corresponding unsaturated sugar or its hexenitol analogue; hydrolysis of these oxirans gave 1-deoxy-3-C-methyl-D-psicose and -D-tagatose, which on acetonation yielded the derivatives (19) and (20) respectively (Scheme 4).[13]



Scheme 4

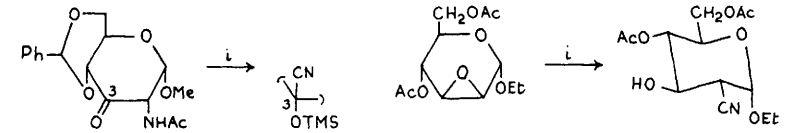
Stereoisomeric cyanhydrins formed from 1,2:5,6-di-O-isopropylidene-D-ribo-hexofuranos-3-ulose have been converted to corresponding α-hydroxyamidoximes (21) and oxadiazoles (22)(Scheme 5), the gluco isomer of (21) being characterized by X-ray analysis.[14]



Scheme 5

Cyanhydrin derivatives are also conveniently synthesized by treatment of uloses or oxirans with trimethylsilylcyanide - boron trifluoride etherate, illustrated in Scheme 6; the anti-Furst-Plattner reaction of the illustrated oxiran was attributed to 4-O-acetyl participation.[15]

The preferential reaction of benzylidene acetals in compounds also containing oxiran units is mentioned in Chapter 5. Other hydroxy branched-chain sugars are mentioned below as hydration products of unsaturated analogues.

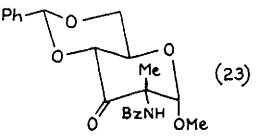


Reagents: $Me_3SiCN-BF_3.OEt_2$

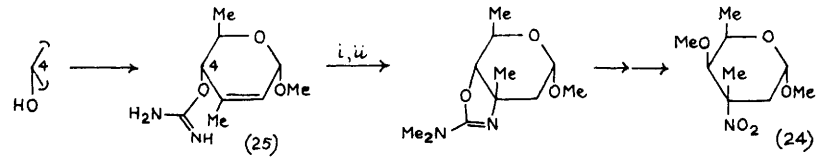
Scheme 6

2 Compounds with an R-C-N Branch

Enolate alkylation of glycosidulose derivatives of aminosugars provides methyl branched-chain sugars having the branch methyl group axially oriented, e.g., (23).[16] A stereoselective route to D-rubranitrose (24) is provided by the stereospecific rearrangement of the dimethylcyanamide derivative (25) obtained from the corresponding glycal (Scheme 7).[17] The same approach from diacetyl-L-rhamnal provides a synthesis of methyl α-L-decilonitroside (26) via the methylene branched-chain sugar (27)(Scheme 8).[18] D-Rubranitrose and the related 4-aminosugar, tetronitrose (28), have been prepared from D-galactose and D-glucose respectively by a sequence involving cyanomesylation of the intermediate glycopyranosid-3-uloses (29).[19]

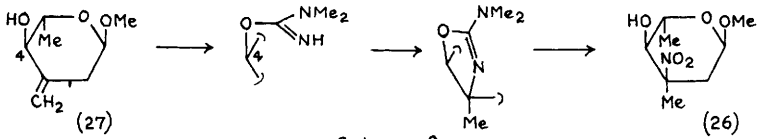


(23)

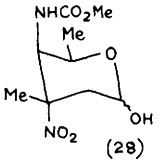


Reagents: i, $Hg(OCOCF_3)_2$; ii, $NaBH_4$

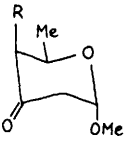
Scheme 7



Scheme 8



(28)

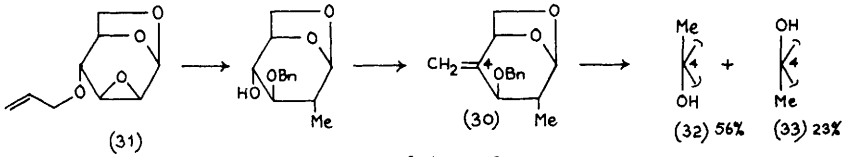


(29) R = OMe or $NHCO_2Me$

The synthesis of a vancosamine derivative by the rearrangement of a trichloroacetimidate of a branched-chain unsaturated sugar is mentioned in Chapter 13.

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

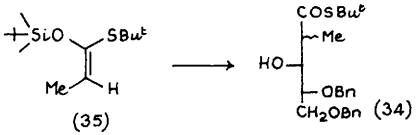
Laevoglucosan has been used as a source for the 2-C-methyl,4-C-methylene sugar (30) via the epoxide (31); epoxidation - reduction of (30) yielded a mixture of the hydrated analogues (32) and (33) (Scheme 9).[20]



(31) (30) (32) 56% (33) 23%

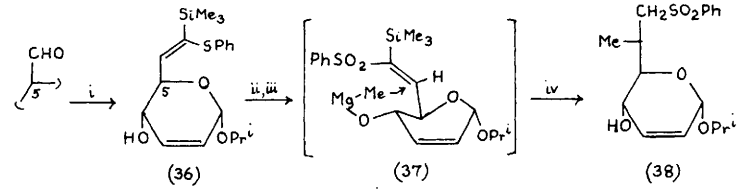
Scheme 9

The isomeric 2-deoxy-2-C-methyl-pentonic acids (34) have been prepared by Lewis acid-catalysed aldol condensation of the thioester silyl ketene acetal (35) with 2,3-di-O-benzyl-D-glyceraldehyde; either epimer can be obtained as the major product depending on the precise experimental procedure adopted.[21]



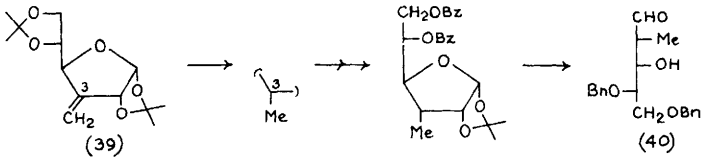
(35) (34)

The hetero-substituted alkene (36) obtained from a C-6 sugar aldehyde undergoes stereo-controlled methyl addition via the chelate (37) to give the 6-C-methyl sugar (38)(Scheme 10), which was then used in a synthesis of okadoic acid (see Chapter 24).[22] The 3-C-methylene sugar (39), derived from glucose, has been catalytically hydrogenated to the 3-C-methyl allo-analogue, which was then epimerized at C-5 and degraded to the 2-C-methyl-L-lyxose (40) and the corresponding lyxonic acid (both potential synthons in macrolide synthesis) by standard procedures.[23]

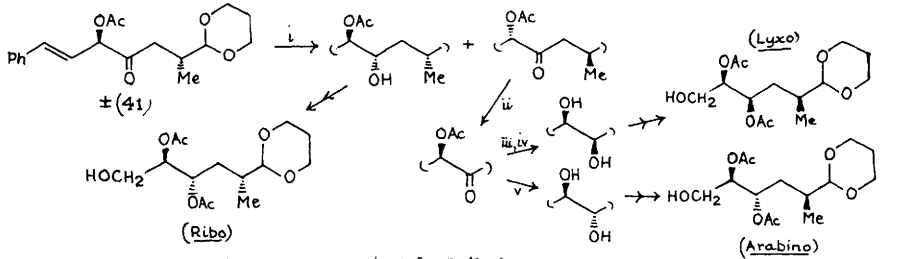


Reagents: i, $PhS(Me_3Si)_2C{\cdot}Li$; ii, MCPBA; iii, MeMgBr; iv, KF

Scheme 10



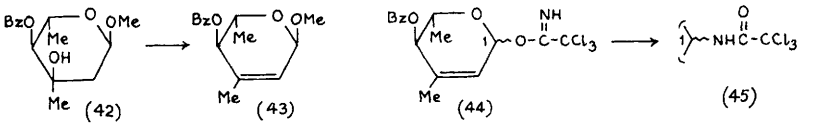
A synthesis of derivatives of three of the four possible 2,3-dideoxy-2-C-methyl-D-hexoses has been reported using Baker's yeast to achieve the stereospecific reduction of the racemic acetoxy ketone (41), the unreduced enantiomer being separately reduced stereospecifically after C-5 epimerization (Scheme 11).[24]



Reagents: i, Baker's yeast; ii, NEt_3; iii, $NaBH_4$; iv, OH^-; v $Zn(BH_4)_2$

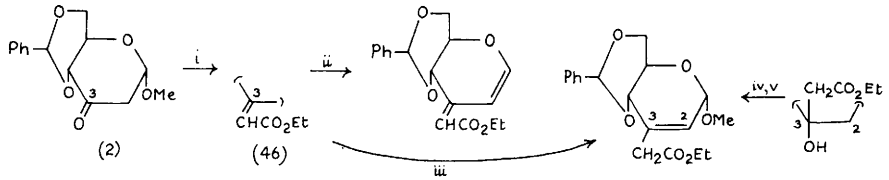
Scheme 11

Thiem's group has investigated the synthesis and thermal reactions of branched-chain unsaturated sugars. The mycaroside (42) undergoes elimination with thionyl chloride to give the unsaturated



analogue (43) as the major product; an attempt to rearrange the allylic trichloroacetamidate (44) by 3:3 sigmatropic shift in fact yielded the glycosylamine isomer (45).[25] Scheme 12 illustrates the synthesis and interconversions of unsaturated branched-chain sugars derived from the glycosidulose (2), the Wittig product (46) being

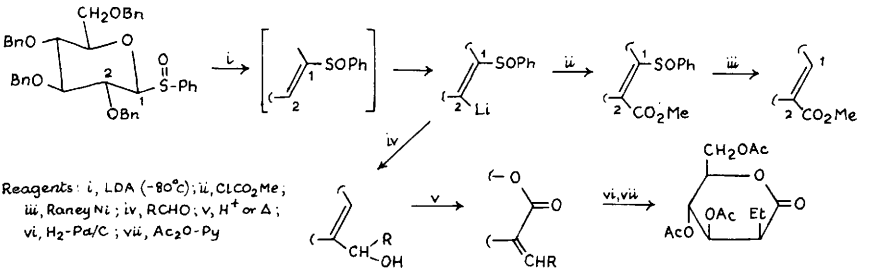
obtained in better yield using the lithium salt of ethyl trimethylsilyl acetate (Li-ETSA) than by Petersen olefination (see also Scheme 1 above).[3] The direct lithiation of glycosyl sulphoxides



Reagents: i, LiETSA; ii, excess i, or KOBu^t, or LDA; iii, Δ-Py; iv, Tf_2O-Py; v, $Bu_4NF.3H_2O$

Scheme 12

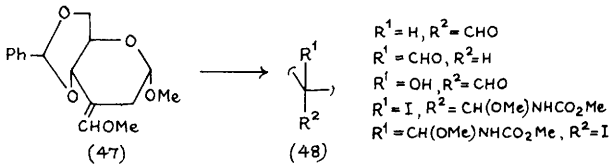
provides a route to 2-substituted glycals as illustrated in Scheme 13.[26] Related results with glycosyl sulphones are referred to in Chapter 13, and the formation of unsaturated branched-chain lactones

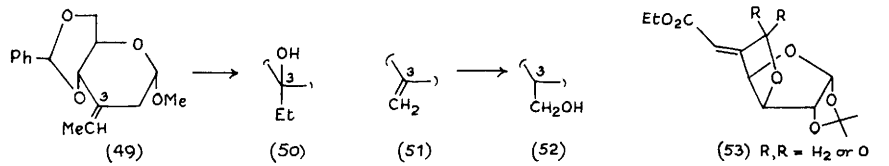


Reagents: i, LDA (-80°C); ii, $ClCO_2Me$; iii, Raney Ni; iv, RCHO; v, H^+ or Δ; vi, H_2-Pd/C; vii, Ac_2O-Py

Scheme 13

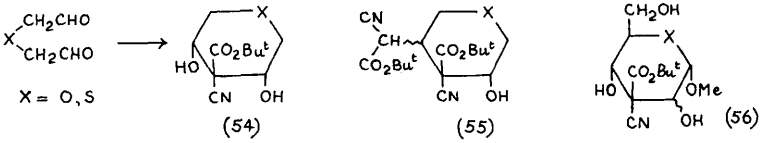
is mentioned in Chapter 24. Wittig olefination of the glcosidulose (2) gave the stereoisomeric branched-chain enol ethers (47), which were used to prepare a number of branched-chain analogues (48).[27] The standard glucofuranos-3-ulose derivative was similarly studied. Hydration of the ethylidene Wittig analogue of (47), i.e., (49), by the hydroboration-oxidation procedure unexpectedly gave the





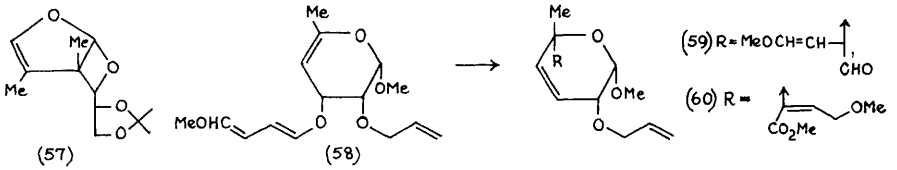
Markownikov product (50), whereas the methylene analogue (51) reacted normally to give (52).[28] The stereochemistry of the 5-C-ethoxycarbonylmethylene derivatives (53), including E/Z isomer ratios, has been investigated using n.m.r. and X-ray crystal analysis.[29]

Condensation of thiodiglycolaldehyde and diglycolaldehyde with t-butyl cyanoacetate gave corresponding anhydro-pentitol derivatives, e.g., (54), together with the 1:2 adducts, e.g., (55);

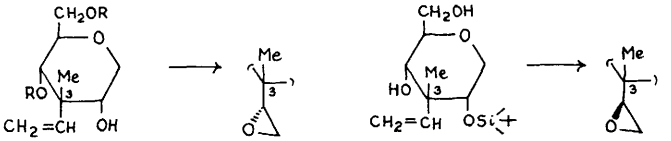


using α-(R)-hydroxymethyl-α'-(S)-methoxy-diglycolaldehyde, D-gluco and D-manno analogues (56) were obtained.[30] Δ^2- and Δ^3-unsaturated 3-cyano analogues have also been obtained.[31]

Photochemical addition of 2,3-O-isopropylidene-D-glyceraldehyde with 3,4-dimethyl-furan gave the oxetan (57), which was used to establish the absolute configuration of asteltoxin.[32] Claisen rearrangement of the unsaturated sugar (58) derived from glucose gave the branched-chain compound (59); a similar approach gave the analogue (60).[33]

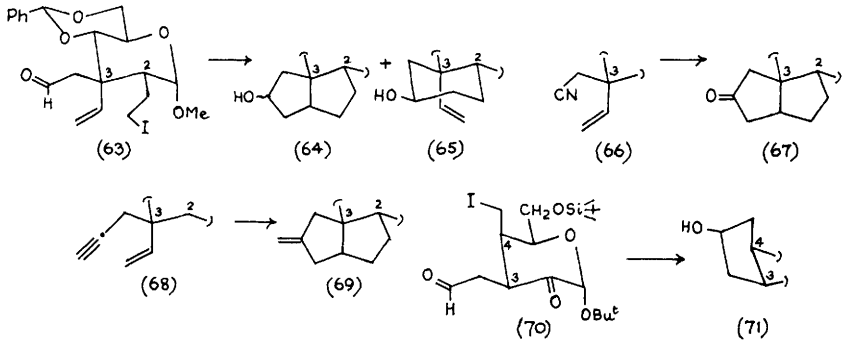


Fraser-Reid's group has investigated the chemistry of some geminally disubstituted branched-chain sugars. The vinyl derivative (61) undergoes stereospecific epoxidation with MCPBA, controlled by chelation with the C-2 hydroxy group; the analogue (62) conversely gives the epimeric oxiran by chelation with the C-4 hydroxy

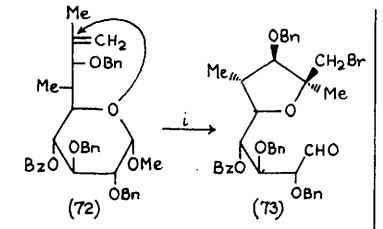


group.[34] The triply branched-chain compound (63) underwent tributylstannane-catalysed free-radical cyclization to give the products (64) and (65), while the cyano analogue (66) only gave

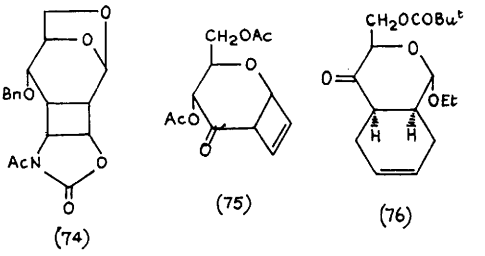
the bicyclopentane derivative (67), and (68) gave (69) in high yield; radical addition to the vinyl group is followed by addition to the other unsaturated group to generate the bicyclized products.[35] The direct radical addition to carbonyl which generates compound (65) also occurs with other doubly branched-chain sugars with vicinal iodo-alkyl and carbonyl branch chains, e.g., the conversion (70) → (71).[36] The participation of oxygens present in



ethers, esters, and pyranose rings in electrophilic reactions has been illustrated by examples including branched-chain sugar derivatives, e.g., (72)→(73)(Scheme 14).[37] Photochemically induced cycloadditions of the corresponding unsaturated derivatives have been reported, leading to the adducts (74)[38] and (75).[39] (See also Chapter 13, ref. 10.)



Scheme 14



A synthesis of a compactin fragment utilized the bicyclic adduct (76) obtained by aluminium trichloride-catalysed addition of butadiene to the corresponding glycosenone.[40]

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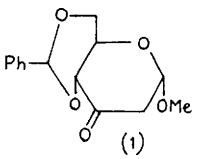
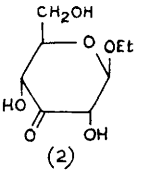
15
Aldosuloses, Dialdoses, and Diuloses

1 Aldosuloses

Nicotinium dichromate (made from nicotinic acid and chromium trioxide and used in benzene-pyridine) has been recommended as a new and inexpensive reagent for the efficient and large scale oxidation of the hydroxy groups in such compounds as 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose.[1] The particular aldosulose derivative (1), a key intermediate for the synthesis of L-daunosamine, has been prepared by use of pyridinium dichlorochromate,[2] and the ethyl glycoside (2) has been isolated from the roots of an Arctostapylos


(1)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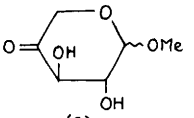
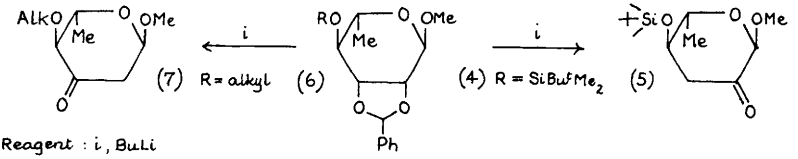

(3)

species following a long term extraction with ethanol, the glycosidation having occurred during the extraction procedure.[3] Oxidation of methyl α- and β-D-xylopyranoside with bromine water in the presence of borate gives mainly the 4-ulosides (3), but minor amounts of the 2- and 3-ketones are also formed.[4]

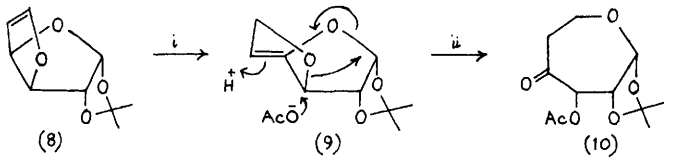
The interesting observation has been made that, whereas the silyl ether (4) gives the ketone (5) on treatment with butyllithium, corresponding compounds with carbon ether groups at C-4 (6) give the analogous 2-deoxy-3-keto products (7) (Scheme 1). Presumably



Scheme 1

these processes are initiated by proton abstraction from C-2 and C-3, respectively.[5]

The 4-ene (9), which is obtained by thermal or base-catalysed isomerization of the 5-ene (8), on treatment with acetic acid in

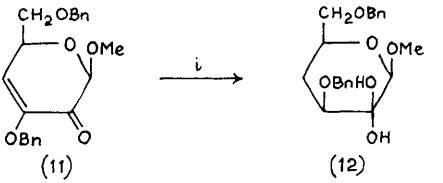


Reagents: i, Δ or OH^-; ii, AcOH

Scheme 2

dichloromethane, undergoes an unusual rearrangement to give the septanosulose derivative (10) as indicated in Scheme 2.[6]

Hydrogenation of the enolone derivative (11) affords the crystalline monohydrate (12) in 40% yield (Scheme 3), while reduction with zinc borohydride gives a complex set of products.[7]

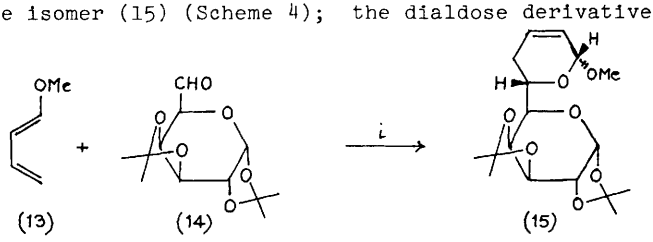


Reagents: i, H_2-Pd/C

Scheme 3

2 Dialdoses

The high pressure [4+2]cycloaddition of diene (13) to the dialdose derivative (14) in the presence of $Eu(fod)_3$ as catalyst gave largely the isomer (15) (Scheme 4); the dialdose derivatives (16)

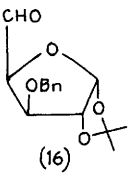


Reagents: i, $Eu(fod)_3$ - 11 Kbar

Scheme 4

and (17) reacted less selectively.[8]

Compound (17) undergoes interesting changes in stereoselectivity on reaction with different reagents. Whereas methyllithium and methylmagnesium iodide give the allo- and talo-adducts (18) and (19) in the ratio 2-3:1, 2-lithio-1,3-dithiane affords, almost exclusively, the alloxide (20).[9] Furthermore, with allyltri-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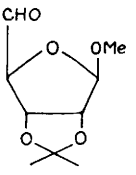
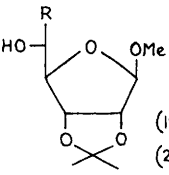
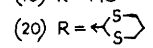
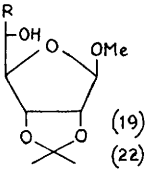
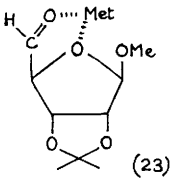

(17)


(18) R = Me
(20) R = 
(21) R = Allyl


(19) R = Me
(22) R = Allyl

methylsilane (17) gives the alloside (21) (20:1) when boron trifluoride is the catalyst, but the epimer (22) (20:1) when titanium tetrachloride is used. In the latter case metal complexing (23) is held responsible for the dramatic change in stereoselectivity. Similar selectivities were found with the aldehydes (14) and (16), but in the case of the D-gluco-compound (24) both catalysts led to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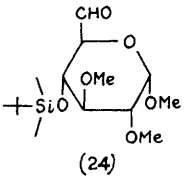
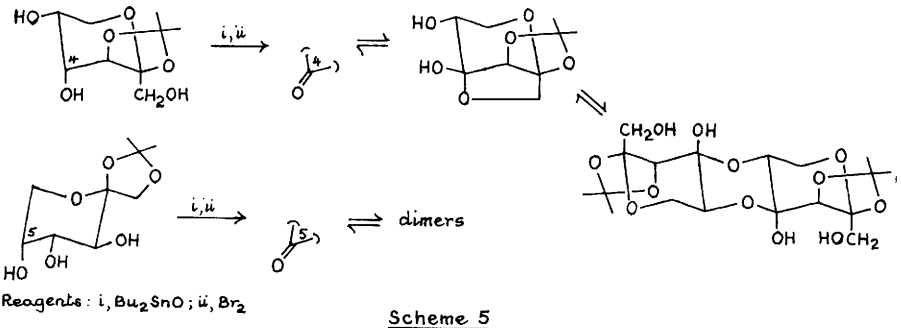

(24)

the D-glycero-D-gluco-adduct with high selectivity. Wittig products from these aldehydes are described in Chapter 13.[10]

3 Diuloses

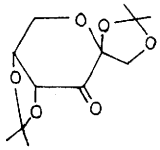
Selective oxidations have been used to prepare diulose derivatives as indicated in Scheme 5; the products equilibrate with dimeric forms.[11]



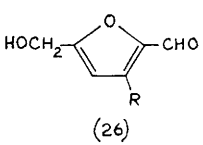
Scheme 5

The D-fructose-derived ketone (25) reacts with Grignard reagents mainly to give the D-ribo-adducts which, with acid, degrade to afford the furfural derivatives (26).[12]

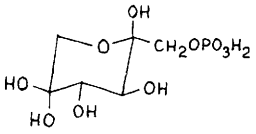
A ^{13}C and ^{31}P study of D-threo-hexo-2,5-diulose 1-phosphate and



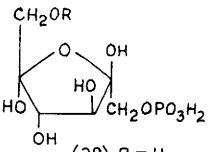
(25)



(26)



(27)



(28) R = H

(29) R = PO_3H_2

1,6-bisphosphate ("5-keto-D-fructose" esters) in water has shown that the former exists mainly in the β-pyranose form (27) with the remainder in the 2R,5R-furanose form (28). The bisphosphate exists as the 2R,5R (29) (ca. 80%) and the (2S,5R) isomers.[13]

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16
Sugar Acids and Lactones

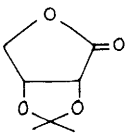
1 Aldonic Acids

One Chinese report has described a commercial process for the production of D-glucono-δ-lactone from calcium gluconate,[1] and another has reviewed this procedure and the properties and applications of the product.[2]

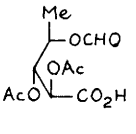
The oxidation of D-glucose on a platinized platinum electrode in acidified solution to D-glucono-δ-lactone has been described,[3] as has the oxidation of xylose and glucose catalysed by chromium and titanium porphyrin complexes anchored to a polyacrylamide support.[4]

The kinetics of the ruthenium(III) ion catalysed oxidation of polyhydric alcohols by N-bromosuccinimide to the corresponding aldonic acids in aqueous perchloric acid with mercury(II) acetate as "scavenger" have been studied.[5]

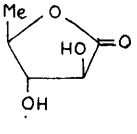
D-Erythrorbic acid has been oxidized, cyclized and acetonated to give the D-erythronolactone acetal (1),[6] and di-O-acetyl-D-rhamnal,



(1)

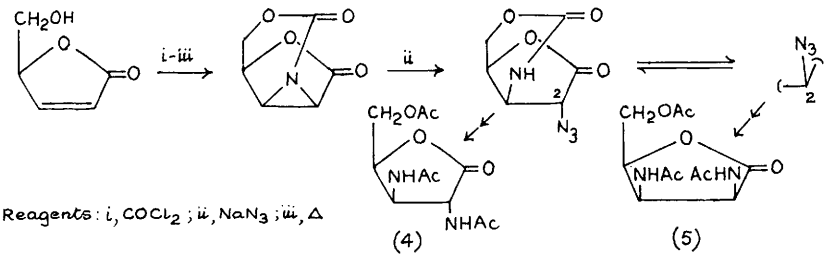


(2)



(3)

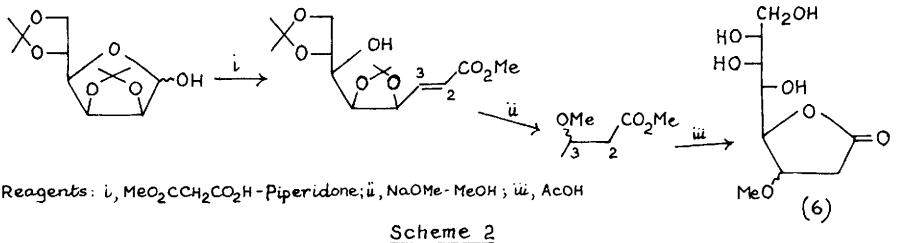
oxidized with ruthenium dioxide-sodium periodate, gave the formate (2) and hence, after base-catalysed hydrolysis, the lactone (3).[7] More complex compounds to have been made are the racemic amino-



(4) (5)

Scheme 1

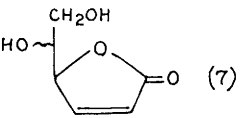
compounds (4) and (5) (Scheme 1)[8] and the 2-deoxyoctanoic acid lactones (6) (Scheme 2).[9]



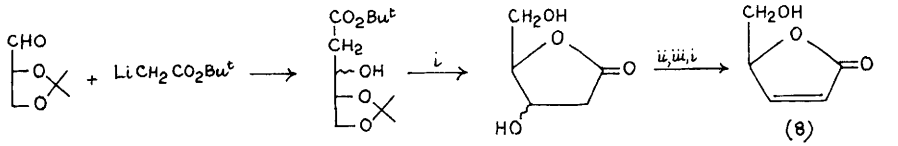
Reagents: i, $MeO_2CCH_2CO_2H$-Piperidone; ii, NaOMe-MeOH; iii, AcOH

Scheme 2

Several unsaturated aldonic acid derivatives have been reported. The enantiomeric 2,3-dideoxy analogues (7) of ascorbic acid have been prepared from 5,6-O-isopropylidene-L-gulono- and D-mannono-1,4-lactones by formation of their 2-(dimethylamino)-1,3-dioxolane



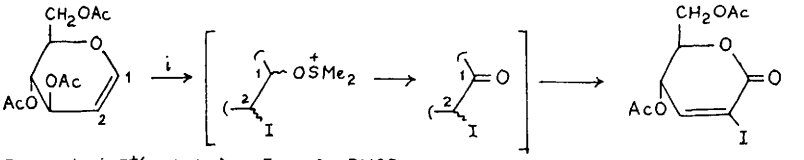
derivatives with DMF dimethylacetal, quaterization with methyl iodide, and thermal decomposition.[10] The pentose analogue (8) was prepared as indicated in Scheme 3.[11] Glycals can be converted into



Reagents: i, H^+; ii, Bu^tMe_2SiCl; iii, SO_2Cl-Py

Scheme 3

2-iodo-2,3-unsaturated aldonolactones (Scheme 4),[12] and the D-

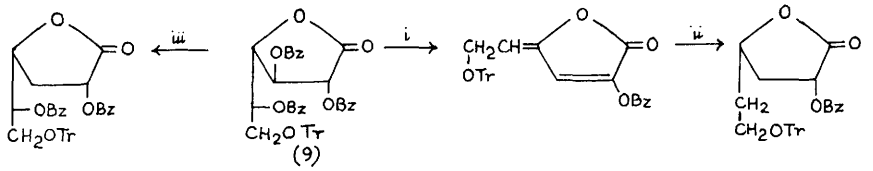


Reagents: i, $I^+(collidine)_2BF_4^-$, CH_2Cl_2-DMSO

Scheme 4

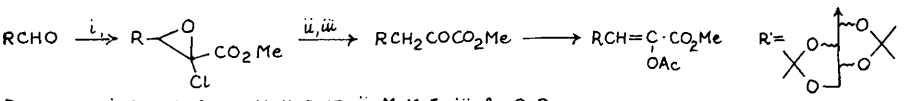
galactono-γ-lactone derivative (9) can be converted into 3- and 3,5-dideoxy compounds as shown in Scheme 5.[13] Enolized heptulosonic acid derivatives have been described, prepared from 2,4:3,5-di-O-isopropylidenepentoses as indicated in Scheme 6.[14] (See also ref. 27 below.)

Several reactions of aldonic acids have been reported. Aldono-



Reagents: i, Et_3N ; ii, H_2-cat.; iii, H_2-cat., OH^-

Scheme 5



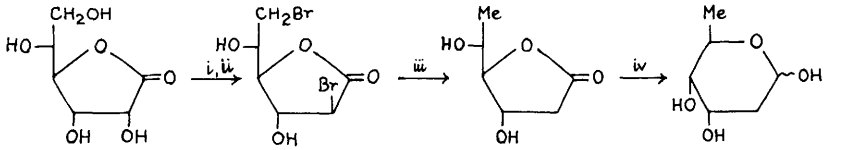
Reagents: i, Cl_2CHCO_2Me-NaH-DMF; ii, MeMgI ; iii, Ac_2O-Py

Scheme 6

lactones react with hydroxy radicals at C-2 preferentially but not specifically; the processes have been investigated by e.s.r. methods.[15]

The main product of reaction between D-ribono-γ-lactone and benzaldehyde dimethylacetal is the 2,3-acetal and not the 2,4-acetal of the δ-lactone as previously proposed.[16] Long chain aliphatic amines (C_6-C_{10}) have been condensed with D-gluconic acid lactone to give amphipathic products which form gels at low concentrations in aqueous solution. The morphology of the gels has been investigated by electron microscopy.[17]

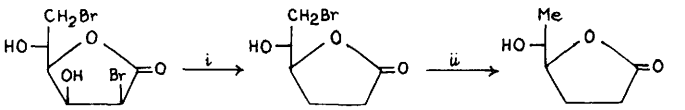
Pedersen and his colleagues have continued their studies on brominated aldonolactones which can be used for the preparation of 2,6-dideoxyhexoses (Scheme 7),[18] or 2,3-dideoxy or 2,3,6-trideoxy



Reagents: i, HBr-HOAc ; ii, MeOH ; iii, H_2-Pd/C ; iv, $(Pr^iCH_2CH_2)_2BH$

Scheme 7

compounds (Scheme 8).[19] The base-catalysed reactions of 6-bromo-

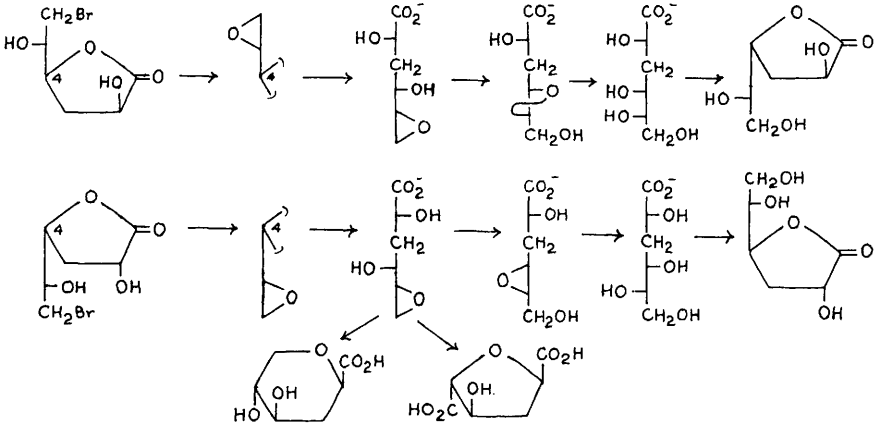


Reagents: i, H_2-Pd/C-EtOH ; ii, H_2-Pd/C-Et_3N

Scheme 8

3,6-dideoxyaldohexono-1,4-lactones afford products of complex

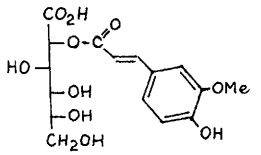
rearrangements (Scheme 9).[20] The lactone formed in the first



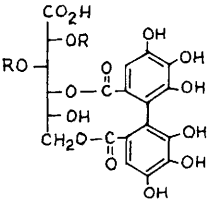
Scheme 9

example is the main product whereas the cyclic acids are the main compounds formed in the latter case.

The aldonic acid esters (10) and (11) have been isolated from



(10)



(11) R = Galloyl

plant sources. The former[21] was obtained, together with positional isomers, from the primary leaves of rye, and the latter,[22] from bark, is the first example of a hydrolysable tannin with a gluconic acid core.

2 Saccharinic Acids

The products formed by alkaline treatment of xylose-containing polysaccharides have been examined by ^{13}C n.m.r. spectroscopy. The main product from L-arabino-(4-O-methyl-D-glucurono)-D-xylan was 3-deoxy-2-C-hydroxymethyltetronic acid.[23]

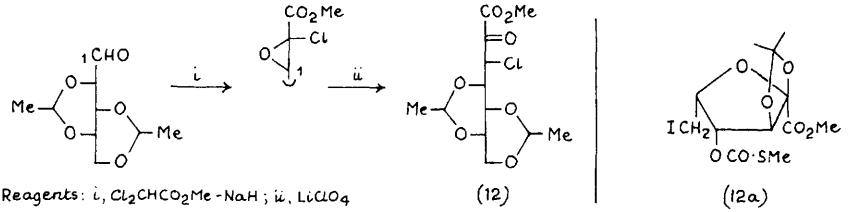
Reagent and carbohydrate concentration affect the nature of the products formed during the alkaline degradation of monosaccharides. Up to 50% of acids with more than six carbon atoms are produced with hydroxide concentration in the range 10^{-3}–10^{-2}M and sugar concentration above 10^{-2}M. Experiments with the presumed intermediates pyruvaldehyde, glyceraldehyde and dihydroxyacetone showed

that they react by aldol procedures to give acidic products with more than six carbon atoms. The effects of calcium and borate ions were investigated.[24]

Nitric acid oxidation of xyloisosaccharinic acid gives mainly 3-C-carboxy-2-deoxytetrono-γ-lactone and, to a lesser extent, the 2-C-carboxy-3-deoxy isomer.[25]

3 Ulosonic Acids

2-Ulosonic acids can be produced in high yield by oxidation of aldoses or aldonic acids in water with oxygen in the presence of lead salts.[26] The specific compound (12) can be prepared as shown in Scheme 10.[27]

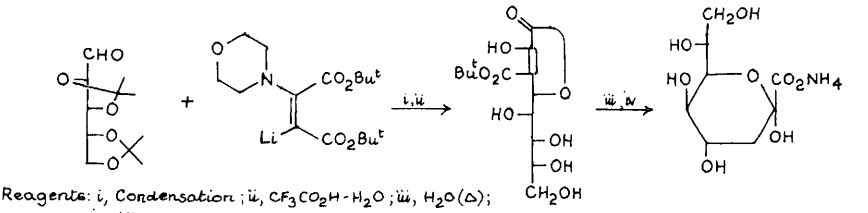


Reagents: i, Cl_2CHCO_2Me-NaH; ii, $LiClO_4$ (12) (12a)

Scheme 10

The kinetics of esterification of L-xylo-hex-2-ulosonic acid (2-keto-L-gulonic acid) with methanol in the presence of an acidic resin have been determined[28] and the fully substituted compound (12a) has been reported.[28a]

A four-step synthesis of 3-deoxy-D-gluco-oct-2-ulosonate ("D-gluco-KDO") is indicated in Scheme 11. The stereoselectivity of

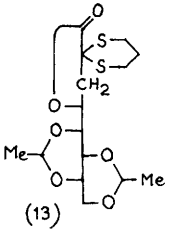


Reagents: i, Condensation; ii, CF_3CO_2H-H_2O; iii, H_2O(Δ); iv, NH_3

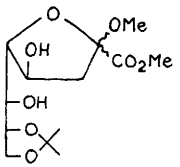
Scheme 11

the condensation step was 4:1 in favour of the D-gluco-product.[29] In related work the derivative (13) of 3-deoxy-L-gulo-oct-2-ulosonic acid was synthesized from 5,6-anhydro-1,3:2,4-di-O-ethylidene-D-glucitol and the anion of ethyl 1,3-dithiane-2-carboxylate.[30]

An improvement in the Cornforth procedure for making KDO (3-deoxy-D-manno-oct-2-ulosonic acid) has been reported together



(13)



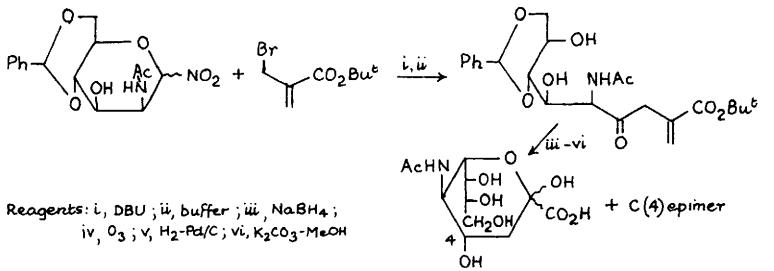
(14)

with syntheses of its methyl pyranosides and furanosides. For the β-pyranoside the acetylated α-glucosyl bromide was used with methanol and a mercury(II) salt; for the α-anomer the α-pyranosyl peracetate was methanolysed, and for the furanosides mild methanolysis of the furanosyl peracetates was employed. The products of this last reaction could be separated as the acetals (14) from which the glycosides were obtained by hydrolysis.[31]

Analogues of KDO have been made by condensation between pentoses or modified pentoses and oxalacetic acid. 5-Deoxy-D-arabinose gave 3,8-dideoxy-D-manno-oct-2-ulosonic acid (8-deoxy-KDO).[32]

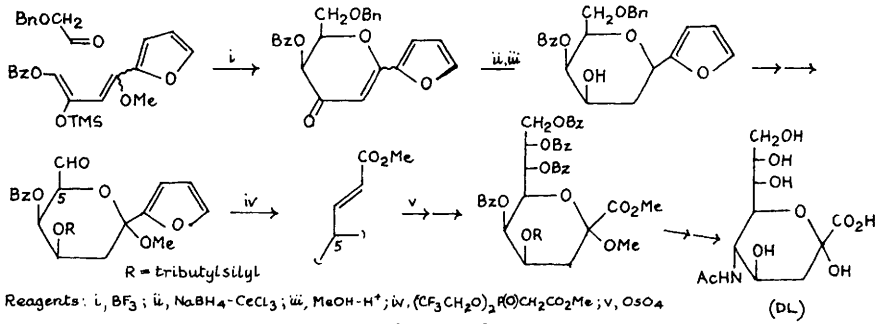
Various mono- and oligo-saccharide derivatives of KDO have been subjected to methylation, reduction and acetylation treatment to afford compounds suitable for mass spectrometric analysis. Rules for fragmentation of the 3-deoxyoctitol derivatives were developed.[33] The interconversion rates of the furanose and pyranose forms of KDO have been determined by n.m.r. methods.[34]

Schmidt has surveyed diastereoselective syntheses of KDO and 3-deoxy-D-glycero-D-gulo-non-2-ulosonic acid, a precursor of N-acetylneuraminic acid.[35] Two new syntheses of this compound are outlined in Schemes 12[36] and 13,[37] the latter giving the racemate in the first total synthesis.



Scheme 12

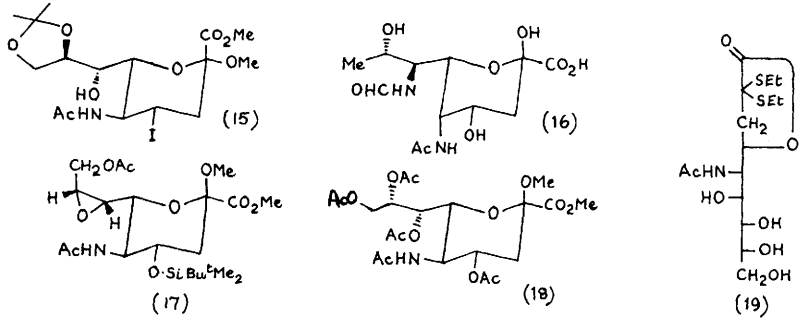
Two preparations of N-acetyl-4-deoxyneuraminic acid have been described, the first following the path outlined in Scheme 12 and



Scheme 13

using deoxygenation procedures based on a β-elimination step applied to the alcohols derived from the intermediate ketone.[38] The second used compound (15) which was obtained from the corresponding 4-mesylate.[39]

5-Acetamido-3,5,7,9-tetradeoxy-7-formamido-L-*glycero*-L-*manno*-nonulosonic acid (16) has been identified as part of the repeating

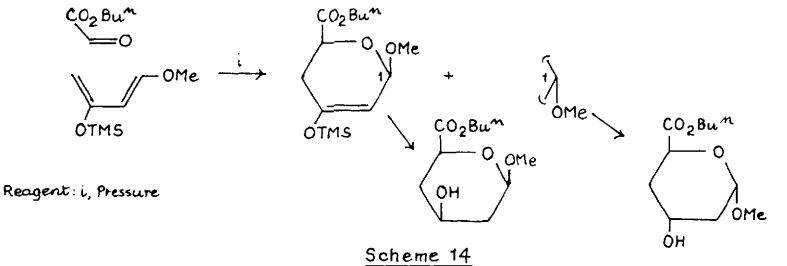


unit of the polysaccharide of *Pseudomonas aeruginosa* immunotype 6.[40]

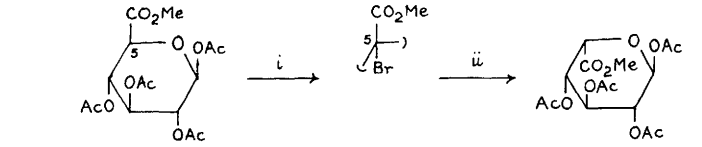
Acetolysis followed by acetylation of the epoxide (17) afforded the acetate (18) and its 7-epimer in the ratio 3:1,[41] and various derivatives of the N-acetylneuraminic acid derivative (19) have been reported.[42]

4 Uronic Acids

A preparation of racemic 2,4-dideoxyhexuronic acid derivatives is outlined in Scheme 14.[43] Reference is made to carbocyclic analogues of hexuronates in Chapter 18. A procedure for synthesizing L-iduronic acid derivatives by inversion at C-5 of D-glucuronic acid compounds is indicated in Scheme 15,[44] and the

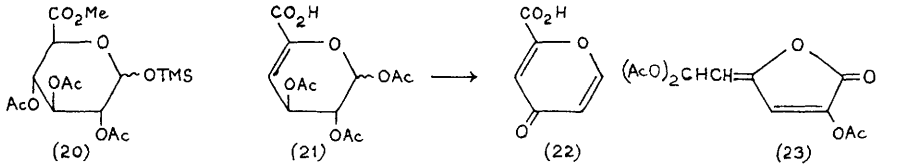


Scheme 14



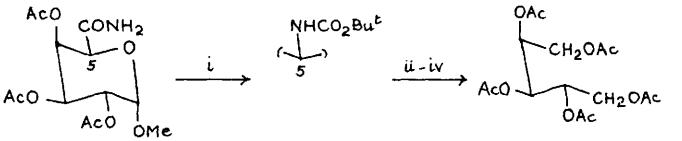
Scheme 15

anomers of compound (20) have been made from the 1-hydroxy analogue by direct silylation to give the β-anomer, which underwent anomerization on treatment with trimethylsilyl trifluoroacetate at -50°C.[45]



Base treatment of either anomer of 1,2,3,4-tetra-O-acetyl-D-glucuronic acid gave the 4,5-enes (21) and hence comanic acid (22) with the α-anomer reacting less readily.[46] Similar studies have been carried out by the same author on D-glucurono-6,3-lactone triacetate;[47] the latter compound has been reported to give the butenolide (23) under acetylating conditions.[48]

Acetylated hexosiduronamides with lead tetra-acetate in t-butanol give the 5-t-butyloxycarbonylaminopentoside analogues in high yield (Scheme 16), and the reaction can be used for the selective cleavage

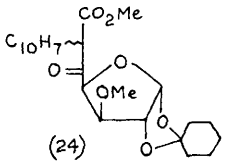


Scheme 16

of uronic acid-containing polymers, the uronic acid units affording the corresponding pentitols as indicated.[49]

The c.i.m.s. of a fully methylated D-mannuronic acid derivative is reported in Chapter 22, and some nucleoside uronic acid compounds are described in Chapter 20.

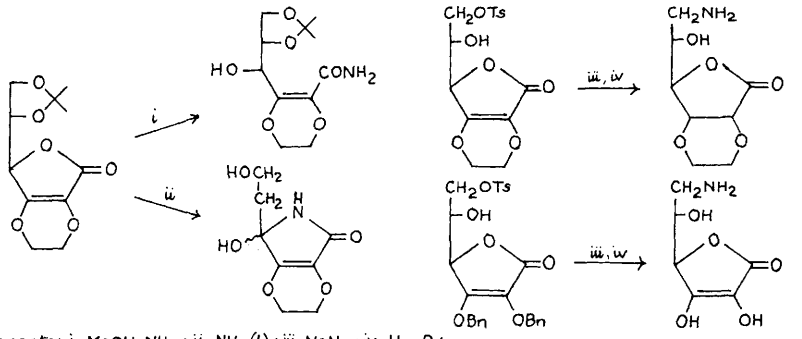
The analogues (24) of tropic acid have been made from the pentose dialdehyde derivative using the Grignard reagent derived from naphthalene acetic acid.[50]



(24)

5 Ascorbic Acids

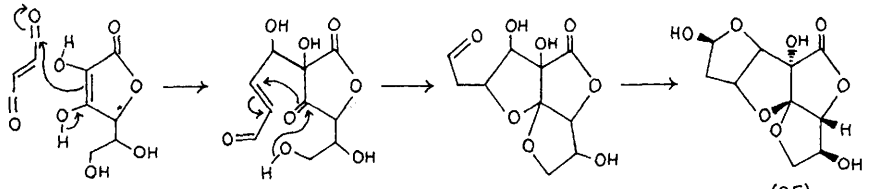
A range of derivatives of L-ascorbic acid have been produced as indicated in Scheme 17.[51] Reactions of 6-bromo-6-deoxy-L-ascorbic



Reagents: i, MeOH-NH_3; ii, NH_3(l); iii, NaN_3; iv, H_2-Pd

Scheme 17

acid derivatives have been noted[52] as have the syntheses of the 6-bromo-, 6-chloro- and 6-iodo-6-deoxy compounds.[28a] The reaction between ascorbic acid and electron deficient alkenes has been discussed; the product formed (Scheme 18) from ascorbic acid and

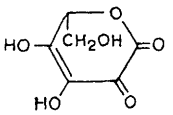


(25)

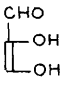
Scheme 18

fumaric dialdehyde has been shown to have structure (25) by X-ray diffraction analysis.[53]

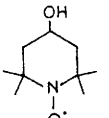
The X-ray structure of the tetra-acetate of dimeric dehydro-ascorbic acid is referred to in Chapter 23, and the hydrolysis products of the acid (2,3-diketo-L-gulonic acid; L-threo-hex-2,3-diulosonic acid) have been concluded to contain the δ-lactone (26).[54]



(26)



(27)



(28)

A theoretical study of the oxidation of triose reductone (27) has been completed, and the results compared with the oxidation of ascorbic acid.[55] Oxidation of the acid by nitroxide radical (28) has been examined kinetically by e.s.r. spectroscopy. An intermediate was observed and a 2-step, one-electron transfer process was proposed.[56] A further study of the oxidation of ascorbic acid by a histamine-containing polymer latex-Cu(II) complex has been reported.[57]

^{1}H And ^{13}C n.m.r. spectroscopy have been applied in a conformational analysis of L-ascorbic acid and D-arabino-ascorbic acid in acidic aqueous solution.[58] The absorption of these two acids from solution onto a mercury electrode showed a small differential effect.[59]

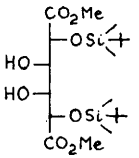
Elaeocarpusin is a plant product comprising equimolar amounts of the gallotannin geraniin and L-ascorbic acid, which has been synthesized by condensation of these two components.[60]

6 Aldaric Acids

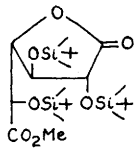
Aldoses and aldonic acids are oxidized in aqueous solution with oxygen over platinum-charcoal to give aldaric acids.[26] In related fashion hydrogen peroxide in the presence of iron salts oxidizes uronic to aldaric acids. The reaction is pH dependent and is inhibited by radical scavengers. An intermediate was a strong inhibitor of β-D-glucuronidase, and further enzymic experiments led to the conclusion that cytochrome P450 is likely to be responsible for glucaric acid production *in vivo*.[61]

The synthesis of 1,6-diamino-1,6-dideoxygalactitol from dimethyl galactarate by t-butyldimethylsilylation, ammonolysis and diborane

reduction of the diamide was complicated by the formation of the compounds (29) and (30) as reaction by-products.[62]



(29)



(30)

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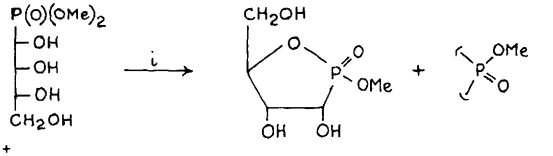
17
Inorganic Derivatives

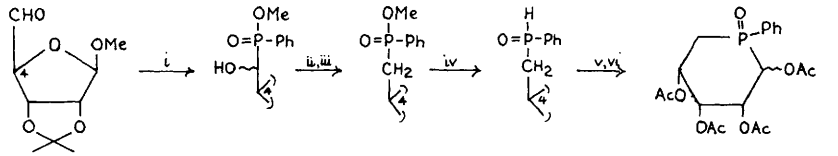
1 Carbon-bonded Phosphorus Derivatives

1,2-Oxaphospholane analogues of methyl D-ribo- and -arabino-furanoside having phosphorus at the anomeric centre have been produced as indicated in Scheme 1.[1] An amplification of this and previously reported related work (Vol.18, p.158) has also appeared.[2] A synthesis of tetra-O-acetyl-5-deoxy-5-C-[(R) and (S)-phenyl-phosphinyl]-α- and β-D-ribopyranose is outlined in Scheme 2.[3]



Reagent: i, H^+

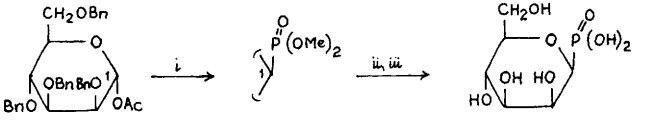
Scheme 1



Reagents: i, HP(O)(OMe)Ph - Et_3N ; ii, (Imidazolyl)$_2$CS ; iii, Bu_3SnH; iv, $NaAlH_2(OCH_2CH_2OMe)_2$; v, HCl-H_2O ; vi, Ac_2O-Py

Scheme 2

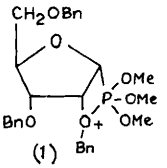
Sugar phosphonates continue to be of interest, the β-D-manno-pyranosyl compound having been produced as indicated in Scheme 3. Products - whether pyranoid or furanoid - of this type of reaction



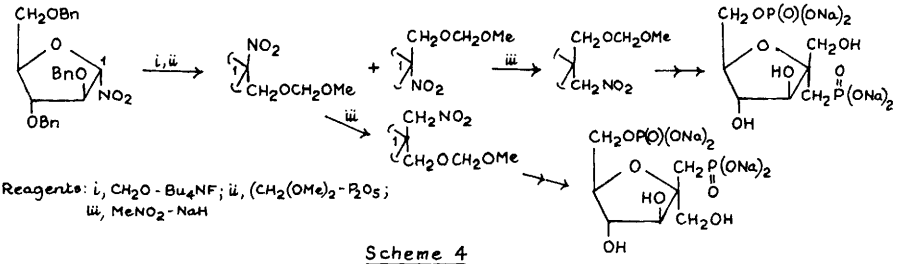
Reagents: i, $P(OMe)_3$; TMSOTf ; ii, TMSBr ; iii, H_2-Pd/C

Scheme 3

have the 1,2-cis-relationship, possibly, it is proposed, because of the intermediacy of species such as (1).[4] The isosteric mono-phosphonate analogues of α- and β-D-fructofuranose 2,6-diphosphate (Scheme 4) have been prepared for biochemical studies.[5]



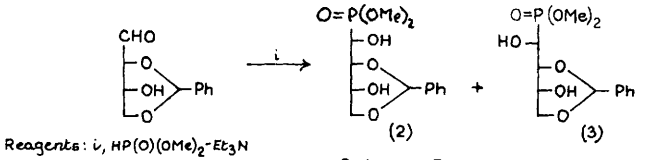
(1)



Reagents: i, CH_2O - Bu_4NF; ii, $(CH_2(OMe)_2$ - P_2O_5; iii, $MeNO_2$ - NaH

Scheme 4

In the acyclic series the D-ribo- and D-arabino-phosphonates (2) and (3) have been prepared as indicated in Scheme 5, and isomeric

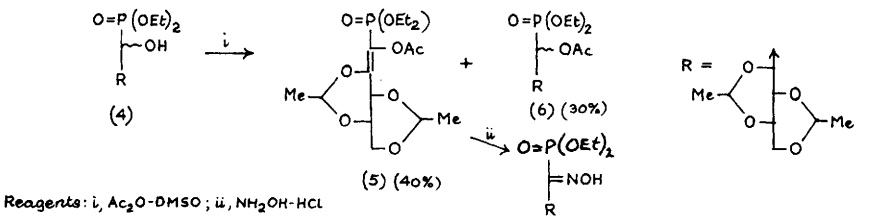


Reagents: i, $HP(O)(OMe)_2$-Et_3N

Scheme 5

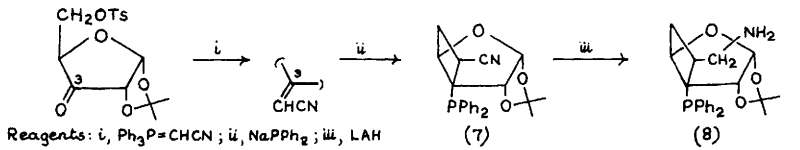
products were obtained from 2,4-O-ethylidene-D-threose.[6]

Oxidation of the related phosphonates (4) with acetic anhydride/DMSO gave a mixture of the enol acetate (5) and the products of direct acetylation (6). An oxime was obtainable from the former (Scheme 6).[7]



Reagents: i, Ac_2O-DMSO; ii, NH_2OH-HCl

Scheme 6



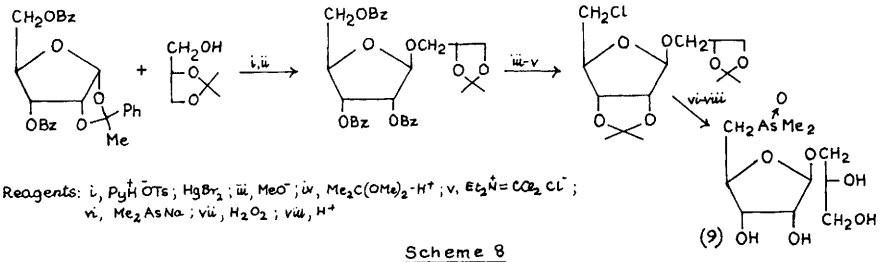
Reagents: i, $Ph_3P{=}CHCN$; ii, $NaPPh_2$; iii, LAH

Scheme 7

The phosphines (7) and (8), prepared as indicated in Scheme 7, have been used as ligands in the rhodium complex-catalysed asymmetric hydrogenation of prochiral alkenes with high enantiomeric inductions.[8] In related work 6-deoxy-6-diphenylphosphino-2,3,4-tri-O-methyl-α-D-glucopyranosyl 6-deoxy-6-diphenylphosphino-2,3,4-tri-O-methyl-α-D-glucopyranoside and the β,β-linked trehalose derivative analogue were prepared via the dimesylates and used as rhodium(I) ligands.[9] The α,α-compound complexed to rhodium(I) has given the highest selectivity so far reported for α-formylation in the hydroformylation of styrene.[10]

2 Other Carbon-bonded Derivatives

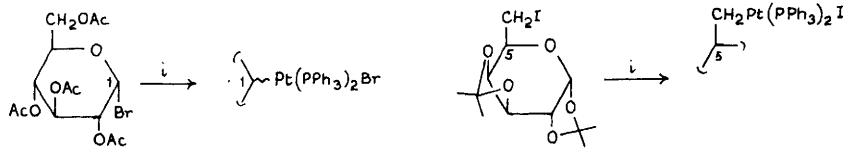
The arsenic-containing carbohydrate (9) of brown kelp has been synthesized as indicated in Scheme 8.[11]



Reagents: i, $PyH^+ \bar{O}Ts$; $HgBr_2$; iii, MeO^-; iv, $Me_2C(OMe)_2$-H^+; v, $Et_2\dot{N}{=}CO_2Cl^-$; vi, Me_2AsNa; vii, H_2O_2; viii, H^+

Scheme 8

Some C-platinum bonded compounds have been obtained as shown in Scheme 9; in the first illustration α,β-products were formed.[12]



Reagent: i, $(Ph_3P)_2Pt(C_2H_4)$

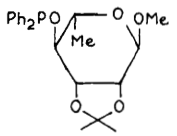
Scheme 9

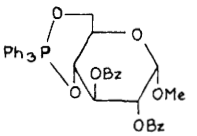
The synthesis of 2-amino-2,6-dideoxy-D-glucopyranose-6-sulphonic acid, an analogue of a bacterial cell wall component, has been prepared via an acetylated 6-deoxy-6-thio compound.[13]

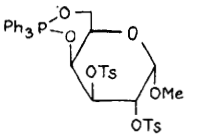
3 Oxygen-bonded Derivatives

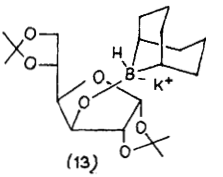
The diphenylphosphono compound (10) has been made from the corresponding alcohol by use of the corresponding chloride and used as a ligand in a rhodium complex for asymmetric hydrogenation of alkenes,[14] and the cyclic dioxytriphenylphosphoranes (11) and (12)

have been made using triphenylphosphine and di-isopropyl azodicarboxylate and the appropriate diols.[15]


(10)


(11)

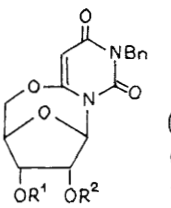

(12)


(13)

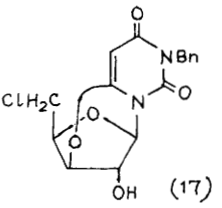
The complex (13) is effective for the asymmetric reduction of alkyl aryl ketones and hindered dialkyl ketones, acetophenone, for example, affording (R)-1-phenylethanol with 78% enantiomeric excess, and t-butyl phenyl ketone being reduced stereospecifically.[16] The same reagent reduced ethyl pyruvate with 98% selectivity to optically active ethyl lactate.[17]

The 4,6-ethylboronates of methyl α- and β-D-galactopyranoside have been prepared and used to obtain 2,3-diacetates of the glycosides.[18] Various disaccharides, sugar acids and polyols have been shown by potentiometric methods to give 1:1 and 1:2 complexes with borate anions, and the complexes formed between this anion and D-fructose have been examined by n.m.r. methods.[19] With excess of borate 2:1 complexes are favoured, the anomeric hydroxy group is always involved and the reaction shifts the equilibrium of sugar forms from pyranose to furanose.[20]

Partial esterification of the 2',3'-stannylene derivative of the 6,5'-anhydronucleoside (14) gave the 2- and 3-triflates (15) and (16) in the ratio 9:1. With lithium chloride in HMPA both gave the 6,3'-anhydride (17), indicating that a triflate migration had



	R^1	R^2
(14)	H	H
(15)	H	Tf
(16)	Tf	H


(17)

occurred in the case of the major ester.[21]

An extensive range of cationic complexes have been described. Studies of the interaction between D-ribose and D-arabinose with Ca^{2+} in aqueous solution have been carried out using electrochemical methods. Thermodynamic functions were determined and specific complexing was concluded to occur in the case of ribose.[22] Favourable enthalpy and unfavourable entropy of reaction are responsible for the weak association constants observed.[23]

A Raman spectroscopic study of the effects of cations on the anomeric equilibrium of D-glucopyranose in aqueous solution has shown that Ca^{2+} has a marked effect in shifting the equilibrium towards the α-anomer. Other cations have a lesser effect.[24] Complexes formed between D-fructose and Mg^{2+} have been shown to have the structure Mg(β-D-fructopyranose)$halide_2$ and to involve O-2, O-3 of one fructose moiety and O-4, O-5 of the other.[25]

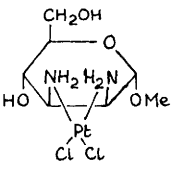
Solid, amorphous complexes formed between D-glucose, D-galactose, D-mannose and D-lactose and Fe^{3+} have been isolated, and the approximate structures have been proposed on the basis of Mössbauer, magnetic susceptibility and elemental analytical data.[26] D-Fructose and Fe^{3+} in acidic solution give a complex which accelerates the photochemical oxidation of the sugar.[27]

Zn^{2+}, Cd^{2+} and Hg^{2+} complexes with L-arabinose[28] and D-glucuronic acid[29] have been reported and structural data have been provided. The latter compound also gives complexes with ions such as Sr^{2+}, Ba^{2+}, Mg^{2+}, and D-galactaric acid and D-galacturonic acid and other acid carbohydrates react with ions like Pb^{2+} and Cu^{2+}.[31]

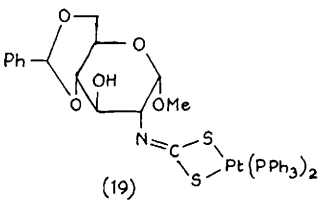
D-Glucose, 6-deoxy-D-glucose and L-rhamnose are rapidly epimerized at C-2 in the presence of nickel bis(N,N,N-trimethylethylenediamine)dichloride, the isomers with the C-2, C-3 cis-diol relationship giving Ni^{2+} complexes which can be isolated and hydrolysed to release the free sugars.[32]

4 Nitrogen-bonded Derivatives

The methyl 2,3-diamino-2,3-dideoxy-α-D-mannopyranoside complex (18) has been characterized crystallographically and shown to have antitumour activity.[33] Related complexes of 1,2-diamino-1,2-dideoxy-D-glucitol have been found to bind to DNA but not to show antileukemia activity.[34] N-Glycosides derived from free sugars and ethylene diamine give complexes with Co^{3+} which have been characterized.[35]



(18)



(19)

Reaction of $SnMe_2Cl_2$ and $SnPh_2Cl_2$ with adenine and some derivatives in methanol gave complexes with the structures

$SnMe_2Cl_2(adenine)_2$ and $SnPhCl_2(OH)(Adenine)_2$. Coordination is thought to involve N-7 of the bases.[36] Treatment of inosine and guanosine with palladium chloride in acid gave a set of complexes with variable nucleoside, palladium ratios.[37]

5 Sulphur-bonded Derivatives

Diglucosyl disulphide octa-acetate has afforded a platinum complex, and the dithiocarbamate derivative (19) has been synthesized from the methyl-2-amino-2-deoxy-α-D-glucopyranoside acetal by use of carbon disulphide followed by bis-triphenylphosphineplatinum dichloride.[12]

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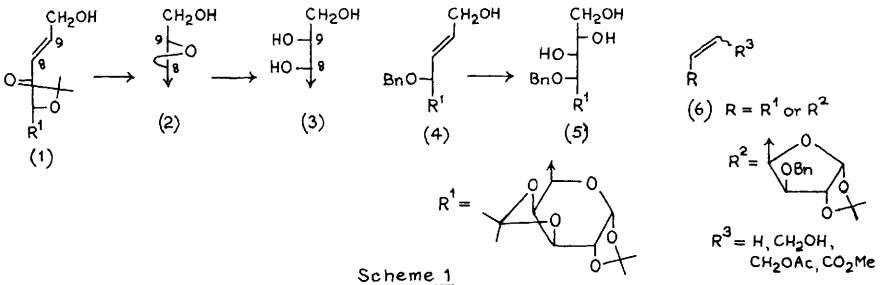
18
Alditols and Cyclitols

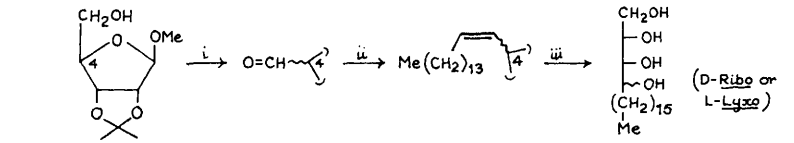
1 Alditols

1.1 Acyclic Alditols. - Brimacombe's group have published full details of their work on the stereoselective synthesis of higher sugars, some of which is covered in Chapter 2; other papers describe the Sharpless oxidation of the octose derivative (1) to give the oxiran (2), and hence the D-erythro isomer (3),[1] osmylation of the benzylated analogue (4) giving primarily the diol (5), leading conventionally to L-lyxo-L-altro-nonitol, a new nonitol,[2] and osmylation of other alkene sugars (6) to give heptose and heptitol derivatives (Scheme 1).[3]



Scheme 1

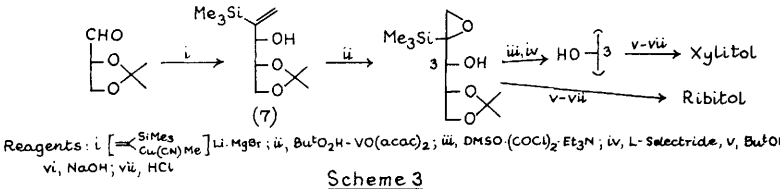
The Wittig reaction with dialdose derivatives has also been employed to synthesize polyols of long-chain hydrocarbons, as illustrated in Scheme 2; lyxose and xylose derivatives were similarly used to prepare stereoisomers which are relatives of naturally occurring plant products.[4]



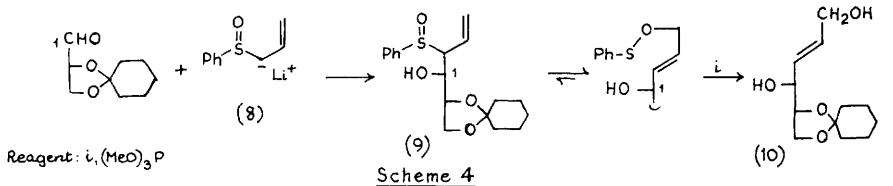
Scheme 2

Another strategy has used D-glyceraldehyde with unsaturated organometallic reagents. A silylated cuprate reagent gave predominantly (95:5) the erythro adduct (7), which could be converted either into ribitol or xylitol as indicated in Scheme 3.[5]

Alternatively, the allyl sulphinyl anion (8) gave the threo adduct (9), which underwent sulphoxide - sulphinate ester rearrangement, leading to the hex-2-enitol derivative (10)(Scheme 4); the threo isomer predominated by non-chelation control, which has previously been difficult to achieve.[6]

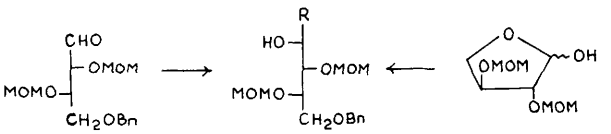


Scheme 3



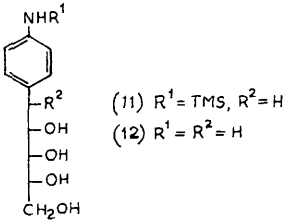
Scheme 4

Addition of Grignard reagents to threose derivatives, in either cyclic or acyclic form, gave mainly the corresponding xylitol product (Scheme 5). Oxidation of these tetritol derivatives at C-1 followed by zinc borohydride reduction gave mainly lyxitol, whereas L-Selectride favoured the xylitol products; these stereoselectivities were discussed.[7]



Scheme 5

Reaction of 2,3:4,5-di-O-isopropylidene-D-ribose with a lithiated aniline derivative gave the pentitol (11) and hence, after LAH reduction and hydrolysis, the deoxypentitol (12), which was shown identical to the degradation product from methanopterin, thus establishing the stereochemistry of the polyol in this compound.[8]



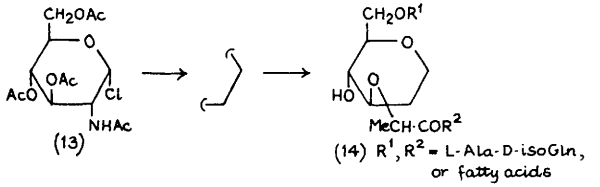
(11) R^1 = TMS, R^2 = H
(12) R^1 = R^2 = H

Epimerization can occur during the Wittig reaction of 2,3,5-tri-O-benzyl-D-ribose with methylene-triphenylphosphorane, giving both ribitol and arabinitol derivatives, probably via the aldose enolate.[9]

Improved conditions for the semi-continuous hydrogenation of glucose solutions to sorbitol have been described, using a nickel-aluminium-titanium catalyst.[10]

The conversion of 2-deoxy-ribose to 1,2-dideoxy-D-threo-pentitol derivatives is mentioned in chapter 24, a synthesis of 2-deoxy-D-arabino-hexitol is referred to in Chapter 12, and the formation of L-arabinitol pentaacetate from glycosiduronamides is covered in Chapter 16. Intramolecular C-glycosidation of benzylated ribofuranoses, giving alditol derivatives, is referred to in Chapter 3.

1.2 Anhydro Alditols. - A standard procedure has been used to convert the glucosamine derivative (13) to its 1,2-dideoxy analogue, and then to prepare the glycoprotein 1-deoxy-MDP and some other lipophilic analogues (14) in a study of their immunoadjuvant activity.[11]



R^3HgEt (15) R^3_2Hg (16)

R^3 = β-D-Gal-p-CH_2S→

Related 1-acyl derivatives of glucosamine are covered in Chapter 7.

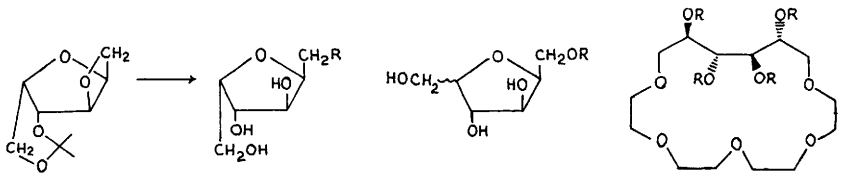
Reaction of di-O-isopropylidene-aldehydo-D- or -L-arabinose and -L-xylose derivatives with a methylene sulphoxonium ylide gave the corresponding anhydro-hexitols in 50% yield.[12]

Deamination of N-deacetylated glycosamino-glycans followed by sodium borodeuteride reduction led to pseudo-disaccharides of 2,5-anhydro-D-mannitol or -D-talitol (from D-glucosamine and D-galactosamine residues respectively) with attached glucuronic acid, iduronic acid, or galactose units, including sulphate groups.[13]

Mercury derivatives (15) and (16) have been prepared from D-galactopyranosylmethanethiol, and their interaction with a β-D-galactosidase studied.[14]

A new set of carbohydrate-based thermotropic liquid crystals (17) have been prepared via reaction of the oxetan (18)(derived from glucose) with lithium acetylide reagents followed by catalytic hydrogenation.[15] A related series of 2,5-anhydro-hexitol derivatives (19) have been prepared by a similar route, reacting the oxetan with long-chain alcohols in presence of trifluoroacetic

acid.[16]



(18) (17) R = C_4–C_{18} alkyl (19) (20)

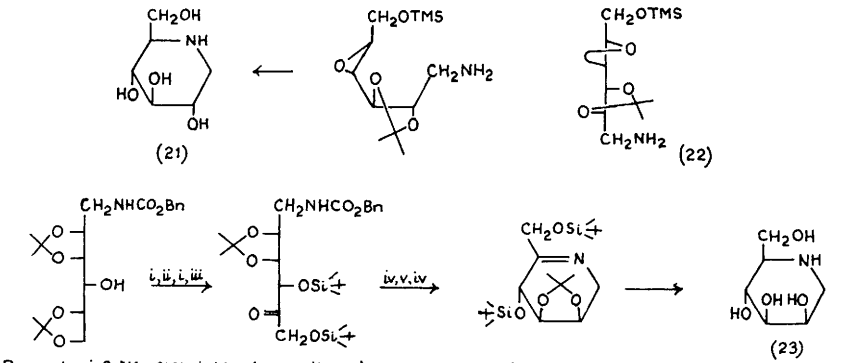
The chemistry of isosorbide has been briefly reviewed, and the mixture of anhydro compounds produced by acid-catalysed dehydration of sorbitol has been analysed.[17] The platinum-catalysed oxidation of isosorbide has been studied; the influence of major parameters was assessed and a reaction scheme discussed.[18]

Crown ether derivatives (20) have been prepared from 2,3,4,5-tetra-O-benzyl-D-mannitol with tetraethylene glycol ditosylate.[19]

The surfactant properties of 1-, 2-, and 3-O-octanoyl-D-mannitols have been studied, the compounds being prepared conventionally from acetalated mannitol derivatives.[20]

Some spectroscopic analyses of alditol derivatives are mentioned in Chapters 21 and 22, while Chapter 6 includes a method of distinguishing stereoisomers of 1-substituted glycerols by n.m.r. analysis of isopropylidene derivatives.

1.3 Amino-Alditols. - 1-Deoxy-nojirimycin (21) has been isolated as a sweet-flavoured material from the root of the mulberry tree.[21] It has been prepared from a 6-amino-2,3-epoxide (22) prepared from D-mannose (H.Setoi *et al.*, Tetrahedron Lett., 1985, 26, 4617), the trans-dioxalan ring controlling formation of the 6-membered ring. The manno isomer (23) of (21) was also prepared via a 6-amino-D-fructose derivative as outlined in Scheme 6, the stereochemistry at

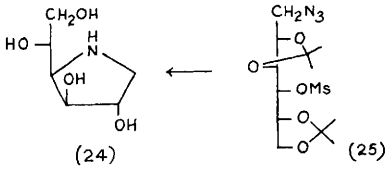


Reagents: i, Bu^tMe_2SiCl - imidazole - DMF; ii, H_3O^+; iii, Collins reagent; iv, H_2-Pd; v, $\Delta(MeOCH_2CH_2OH)$

Scheme 6

C-5 being determined by reduction of the intermediate imine from its less hindered side. Both (21) and (23) were less effective immunostimulants than swainsonine.[22] The synthesis of 5-amino-5-deoxy-D-galactopyranose (i.e., galacto-nojirimycin) and its 1-deoxy analogue together with L-altro isomers is mentioned in Chapter 9.

Full details of the synthesis of 1,4-dideoxy-1,4-imino-D- and -L-arabinitol have been published (see Vol. 19, p.170).[23] 1,4-Dideoxy-1,4-imino-D-glucitol (24) has been synthesized from 1,4-di-O-mesyl-2,3:5,6-di-O-isopropylidene-D-glucitol via its 1-azido-1-deoxy derivative (25), using 3,4- and 4,5-oxiran intermediates to retain



(24) (25)

stereochemistry at C-4.[24] This same azido-glucitol (25) has been used to synthesize 1,4-diamino-1,4-dideoxy-D-galactitol and 1,5-diamino-1,5-dideoxy-L-altritol by standard reactions.[25]

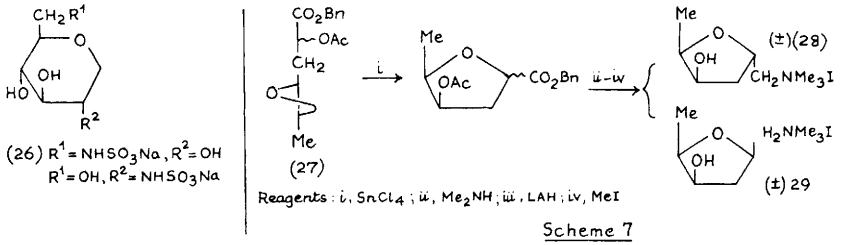
Dimethyl galactarate serves as a source of 1,6-diamino-1,6-dideoxy-galactitol, using a di-amide derivative to introduce the amino groups in a conventional sequence, although troublesome side-reactions made the initial silylation of hydroxy groups difficult.[26] The procedure has been extended to the synthesis of 1-amino-1-deoxy-alditols and other diterminal diamino dideoxyalditols.[27] 3-O-acryloyl- and 3-O-methacryloyl-1,5-bis(diethylamino)-1,5-dideoxy-2,4-O-methylene-xylitol have been synthesized conventionally from 1,5-dideoxy-1,5-dihalo precursors.[28]

Reductive amination of 2,3:5,6-di-O-cyclohexylidene-D-mannofuranose using hydroxylamine or ethanolamine gave the corresponding 1-amino-1-deoxy-D-mannitol derivatives.[29] Surface-active 2-acylamido-2-deoxy-D-glucitols have been prepared by borohydride reduction of 2-acylamido-2-deoxy-D-glucoses.[30]

6-Amino-1,5-anhydro-6-deoxy-D-glucitol, prepared in standard reactions from D-glucose, has been used to prepare compounds (26) with cyclamate-like structure, but these were only slightly sweet with a bitter after-taste.[31]

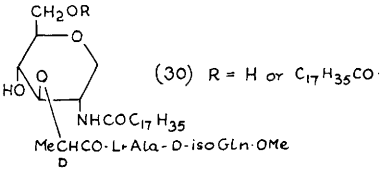
The oxiran-aldonates (27) undergo intramolecular rearrangement via orthoester intermediates to give 2,5-anhydro-aldonates, which were used to make DL-epiallomuscarine (28) and DL-epimuscarine (29) (Scheme 7).[32]

A 1-thiolacetate derivative of muramic acid has been converted

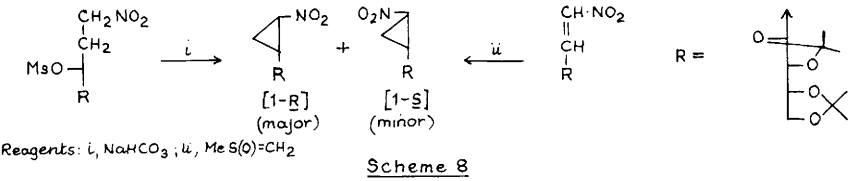


Scheme 7

to the corresponding 1-deoxy analogue, and hence to glycopeptides (30), but these compounds showed no immunoadjuvant activity.[33]



1.4 Miscellaneous Alditol Derivatives and Reactions. - Carbohydrate nitro-cyclopropanes have been prepared from nitro-alditols, as indicated in Scheme 8.[34]



Scheme 8

Hakamori methylation of 2-acetamido-2-deoxy-D-glucitol gave the expected N-methylacetamido-pentamethyl ether, and two minor products, the corresponding N-acetamido and N-methylpropanamido pentamethyl ethers. Further Hakamori methylation yielded N-methyl-isobutyramido- and traces of N-methylpivalamido analogues.[35]

Photo-oxygenation of polyhydroxyalkyl-furans derived from hexoses with ethyl acetoacetate or pentane-2,4-dione gave 1,4-endo-peroxides which could either be rearranged to mono- and di-epoxides or reduced with dimethylsulphide to give unsaturated γ-diketones, which are ulosonic acid or diulose derivatives of higher sugars.[36]

Full details of the catalytic oxidative procedure for cleaving 1,2:5,6-di-O-isopropylidene-D-mannitol to 2,3-O-isopropylidene-D-glyceraldehyde using a bismuth catalyst have been published (see Vol. 15, p. 167).[37]

C_3-C_5 Polyols accelerate the degradation of the β-lactam anti-

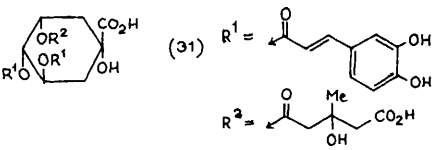
biotic ampicillin in aqueous solution; nucleophilic attack of a hydroxy anion on the lactam ring was thought to be facilitated by hydrogen bonding among the adjacent hydroxyls on the polyol and the amide and carbonyl on the β-lactam.[38]

Other chapters record a conversion of D-mannitol to D-mannose (Chapter 2), ester formation between borate and hexitols (Chapter 7) and platinum complexes of 1,2-diamino-1,2-dideoxy-D-glucitol (Chapter 17).

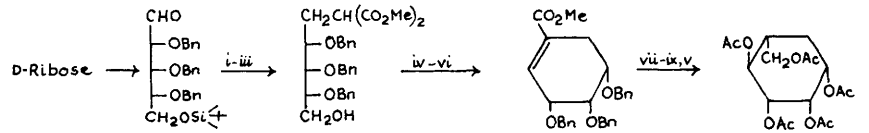
2 Cyclitols

The Ferrier synthesis of deoxyinoses from 6-deoxy-hex-5-enopyranose derivatives has been discussed in a symposium report.[39]

3,4-Dicaffeoyl-5-(3-hydroxy-3-methylglutaroyl)quinic acid (31), a new lipoxygenase inhibitor, has been isolated from Gardenia fructus.[40]



Many papers reflect increasing interest in the synthesis of pseudo-sugars. A synthesis of acetylate pseudo-β-L-mannopyranose (32) starts from D-ribose and uses an inter- and an intra-molecular Knoevenagel reaction to lengthen the chain and then form the ring (Scheme 9).[41] A route to racemic pseudo-hexuronates has been developed from the readily available tricyclic bromo-lactone (33), as outlined in Scheme 10.[42] A synthesis of ψ-β-D-fructofuranose (34)

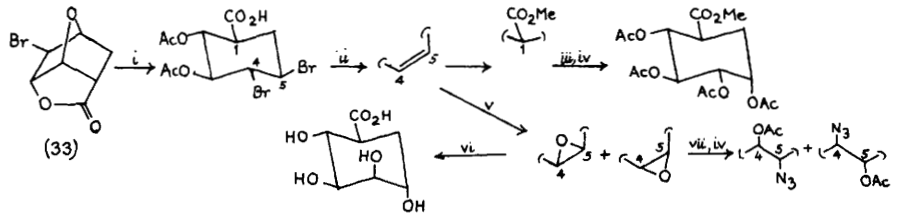


Reagents: i, $CH_2(CO_2Me)_2$-Py-Ac_2O; ii, H_2-Raney Ni; iii, F^-; iv, PCC; v, Ac_2O-Py; vi, NaCl-DMSO; vii, LAH; viii, BH_3-THF; ix, H_2O_2

Scheme 9

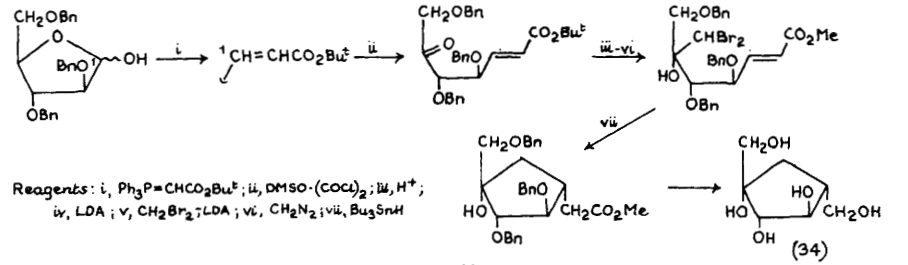
starts from 2,3,5-tri-O-benzyl-D-arabinofuranose, using a Wittig chain-extension reaction and the stereospecific ring closure of an alkenyl dibromide shown in Scheme 11; the corresponding 6-phosphate was also made.[43]

Derivatives of pseudo-D-glucosamine and pseudo-L-idosamine have been synthesized from the cyclohexanone (35) by conventional proced-



Reagents: i, HBr-HOAc; ii, Zn; iii, OsO_4-H_2O_2; iv, Ac_2O-Py; v, MCPBA; vi, H_2SO_4; vii, NaN_3

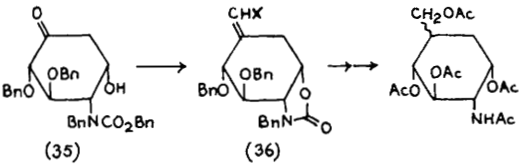
Scheme 10



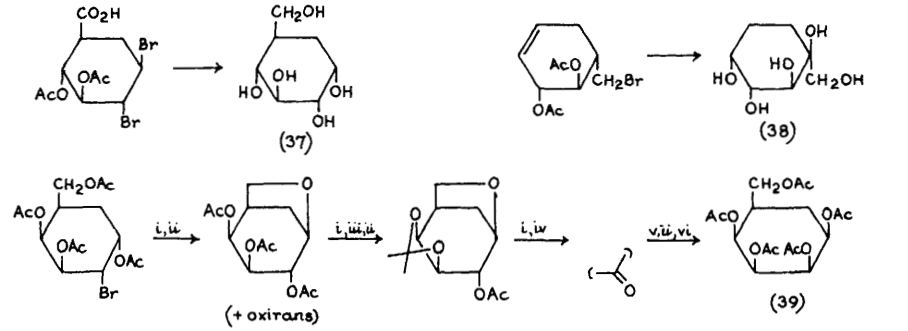
Reagents: i, $Ph_3P{=}CHCO_2Bu^t$; ii, DMSO-$(COCl)_2$; iii, H^+; iv, LDA; v, CH_2Br_2-LDA; vi, CH_2N_2; vii, Bu_3SnH

Scheme 11

ures via the Wittig products (36)(Scheme 12).[44] Racemic forms of ψ-α-glucopyranose (37),[45] ψ-β-fructopyranose (38),[46,47] and ψ-β-talopyranose (39)[48] have been prepared from cyclohexane precursors. The ψ-talo isomer, prepared as shown in Scheme 13, is the last



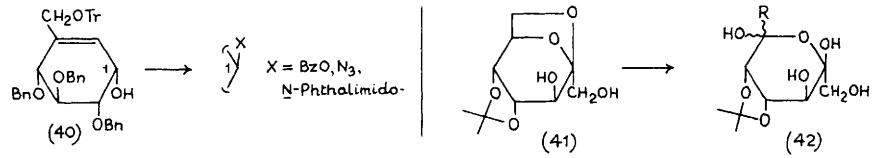
Scheme 12



Reagents: i, NaOMe-MeOH; ii, Ac_2O-Py; iii, $Me_2C(OMe)_2$-TsOH; iv, RuO_2-$NaIO_4$; v, H_2-Pt; vi, Ac_2O-AcOH-H_2SO_4

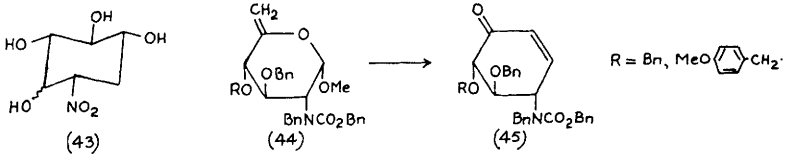
Scheme 13

diastereomer of this series to be synthesized; the oxirans produced were used to prepare α-galacto and α-talo isomers. The cyclohexene derivative (40), prepared from D-glucose, undergoes ready substitution at the allylic position, giving access to both anomers of 5,6-unsaturated ψ-glucosides.[49]

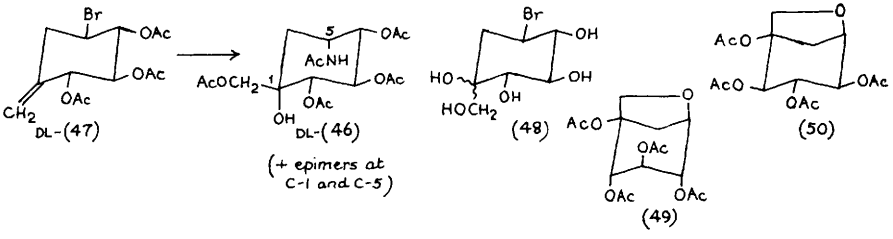


Further examples of the 1,6-anhydro-pyranose → cyclitol rearrangement (see Vol. 18, p. 170) have been published, e.g., (41) → (42).[50]

Cyclization of 5,6-dideoxy-6-nitro-D-xylo-hexofuranose led to a mixture of myo- and epi-isomers (43) which were separated and converted to the corresponding amino compounds.[51] Examples of the use of the Ferrier reaction for preparing cyclitols and amino-cyclitols from D-glucose and D-glucosamine have been published, e.g., (44) → (45).[52]

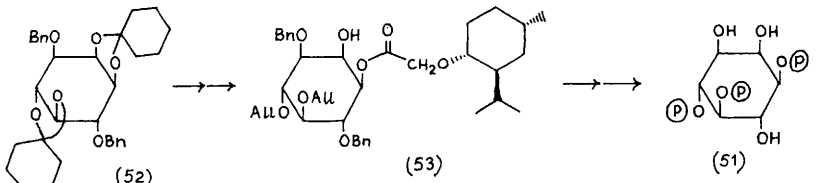


Syntheses of DL-penta-N,O-acetyl-valiolamine (46) and related amino-cyclitols have been reported, using the racemic methylene derivative (47).[53] The same route, involving the epimeric cyclitols (48), has been applied to make a series of five diastereomers of C-hydroxymethyl-6-deoxy-inositol, which is the 5-hydroxy analogue of valiolamine; sodium methoxide treatment of (48) gave a mixture of oxirans and the corresponding pseudo-1,6-anhydride, i.e., (49) or (50), the 1,6-anhydride becoming predominant at equilibrium.[54]



New syntheses have been reported for (-)-fortamine and (+)-2-deoxy-fortamine, starting from resolved 3S,4S-N-carbomethoxy-3-aminocyclohexen-4-ol[55] (for a racemic version see Vol. 17, p.166).

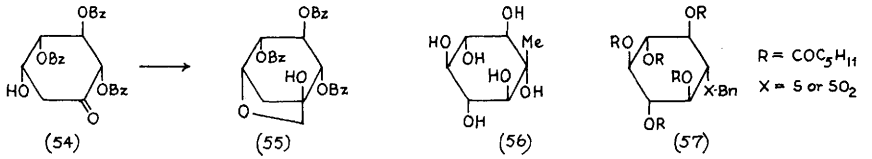
Optically active myo-inositol 1,4,5-triphosphate (51), the cellular second messenger, has been prepared from the racemic inositol precursor (52) via the chiral ester intermediate (53) which could be resolved (Scheme 14).[56] The identity and conformation of (51)



Scheme 14

(which has a single axial C-2 substituent) has been confirmed by ^{1}H, ^{13}C, and ^{31}P n.m.r. spectroscopy.[57] Another report gives ^{1}H and ^{31}P n.m.r. data on a variety of phosphorylated myo-inositols, from mono- to tetra-phosphates.[58]

A series of reactions of the deoxy-inosose (54) have been described; standard reactions at the free hydroxy group and ketone carbonyl occur. Reaction with diazomethane gave a spiro-oxiran intermediate as well as the 6-oxa-bicyclo[3,2,1]-octane (55).[59]



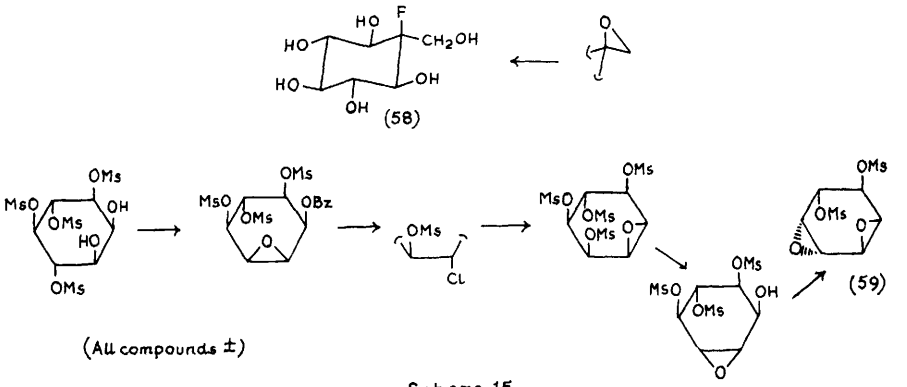
A number of per-esters of myo-inositol and mytilitol (56) have been described, but, unlike derivatives of scyllitol, these were not liquid crystals.[60] The synthesis and mesomorphic properties of the mono-thioscyllitols (57) have been reported.[61]

An improved synthesis of 1,2-O-cyclohexylidene-myo-inositol has been described, using 1,1-dimethoxycyclohexene in DMSO with a perfluorinated, strongly acidic resin.[62]

The 2-deoxy-2-fluoro-2-hydroxymethyl-myo-inositol (58) has been synthesized via the corresponding 2-spiro-oxiran analogue.[63]

A number of racemic cyclitol oxiran derivatives have been prepared from a myo-inositol tetra-mesylate, leading to the di-oxiran (59)(Scheme 15).[64]

The total synthesis of neosurugatoxin, which contains myo-inositol, is covered in Chapter 19, and a number of pseudo-sugar



Scheme 15

nucleosides are mentioned in Chapter 20. Pseudo-sugar crystal structures are referred to in Chapter 21, and ^{11}B n.m.r. studies on cyclitol borate complexes are mentioned in Chapter 22.

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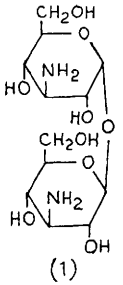
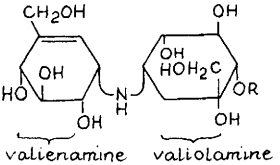
19
Antibiotics

1 Amino-Glycoside Antibiotics

New representatives of known groups of compounds have been reported. Antibiotic BMY-28251, obtained from a Bacillus pumilis strain, has been identified as 3,3'-neotrehalosdiamine (1), the first example of an α,β-trehalose antibiotic.[1] New components of a validamycin



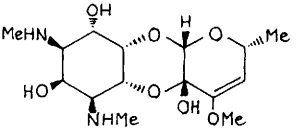
(1)



valienamine valiolamine

(2) R = β-D-Glc-p

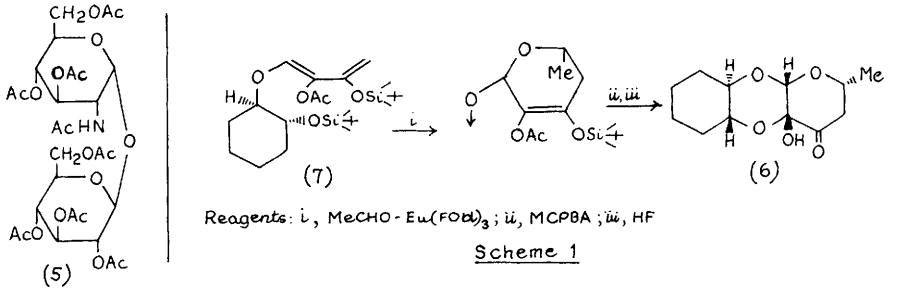
(3) R = H



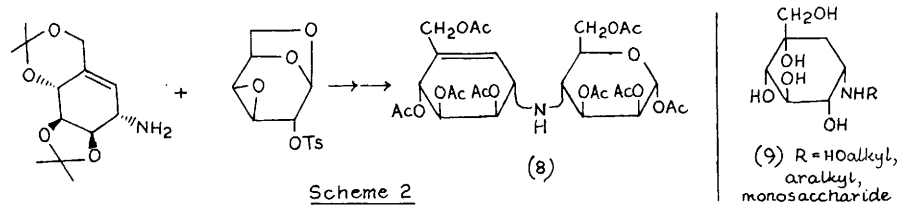
(4)

complex, validamycin G (2) and validoxylamine G (3), have been characterized.[2] Antibiotic AC 4437, obtained from a Streptomyces strain, is proposed to be the de-(N-methyl-L-glucosamine) derivative of dihydrostreptomycin.[3] 3-N-Methyl-paromomycin, a new member of the paromomycin group, has been isolated from a Streptoverticillium source,[4] and acmimycin, a spectinomycin analogue, is thought to have the same structure as spenolimycin (4).[5]

Many analogues of natural compounds have been prepared, either by modifying natural material or by synthesis from mono-saccharide or non-carbohydrate precursors. Dihydrostreptomycin analogues in which the guanidino groups are modified have been synthesized; the resulting pattern of antibiotic activity is unrelated to that of other amino-glycoside antibiotics, and in particular, unlike kanamycin derivatives, an aminohydroxybutanoyl group did not confer any resistance to inactivation.[6] The peracetylated pseudo-disaccharide analogue (5) of (neo)trehalosamine has been prepared from a racemic inosamine derivative.[7] The racemic spectinomycin analogue (6) has been synthesized from the cyclohexyl-butadienyl ether (7) as outlined in Scheme 1.[8] A D-manno-analogue (8) of acarviosin has been prepared from the "manno" isomer of valienamine and 1,6:3,4-dianhydro-D-galactopyranose (Scheme 2). A series of N-substituted valiol-

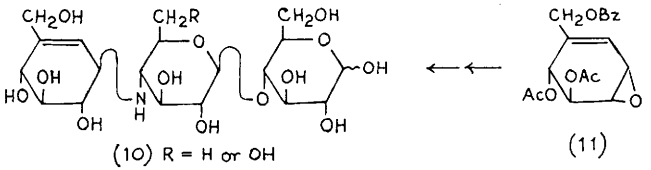


Scheme 1



Scheme 2

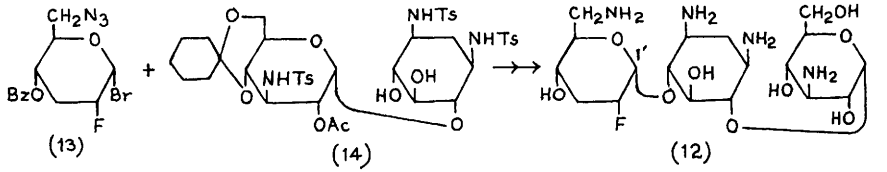
amine derivatives (9) have been synthesized, which are structural analogues of key pseudodisaccharides present in natural α-glucosidase inhibitors; these derivatives all proved to be more potent than the parent valiolamine and the corresponding N-substituted valienamine.[10] A synthesis of peracetylated DL-valiolamine and related branched-chain aminocyclitols is mentioned in Chapter 18. The pseudotrisaccharides (10) have also been prepared as potential glucosidase inhibitors, using conventional reactions from 1,6-anhydro β-lactose to form 4′-amino-4′-deoxy-cellobiose derivatives which could then be coupled to the cyclohexadiene mono-epoxide (11).[11]



A synthesis of the pseudotrisaccharide destomycin C has been described, using mannose and deoxystreptamine to form a pseudodisaccharide which was then coupled to destonic acid to form the orthoester linkage; inversion at the mannose C-4 centre gave the antibiotic.[12]

Syntheses from antibiotic precursors have been recorded for 6″-deoxy-6″-fluoro-kanamycin A and -amikacin using DAST, and also for 1-N-[(R) and (RS)-3-amino-2-fluoropropanoyl]kanamycin.[13] DAST was also used to make 2′,3′-dideoxy-2′-fluorokanamycin A (12) and its

1-epimer, coupling the fluoro sugar (13) with the pseudodisaccharide (14)(Scheme 3); the analogue (12) was only slightly less active than 3-deoxykanamycin, but the 1-epimer was inactive.[14] N-Palmitoyl-kanamycin A derivatives have been reported.[15]



Scheme 3

Carbenicillin derivatives of several aminoglycoside antibiotics have been described, using disodium carbenicillin, forming the products by acylation of the carbohydrate amino groups by the β-lactam ring, acylation occurring preferentially in the 2-deoxystreptamine ring; although suitably non-toxic, products were also almost inactive.[16]

Synthesis of amino-sugars present in amino-glycoside antibiotics is also referred to in Chapter 9.

A 2D ^{1}H n.m.r. study of neomycin B has been reported;[17] the technique was also valuable in analysing kanamycin derivatives.[13] A comparative study of desorption chemical ionization m.s. with molecular secondary ion m.s. as applied to amino-glycoside antibiotics has been published; a combination of these methods allowed unequivocal characterization of compounds containing an aminoacyl group.[18]

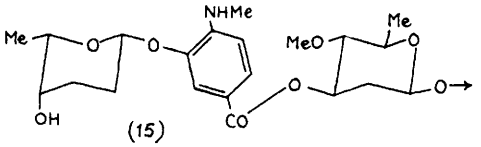
A large number of complexes formed between aminoglycoside antibiotics and trivalent metal ions with an organic indicator have been studied spectroscopically, and kinetic parameters have been determined; the antibiotic appears to complex first with the organic reagent and then the metal ion.[19]

A polarographic method has been described for the quantitative determination of some aminoglycoside antibiotics, using their nitroso derivatives.[20]

2 Macrolide Antibiotics

A preliminary communication describes a novel macrolide antifungal agent, notonesomycin A, which was isolated from a complex obtained from S. aminophilus subsp. notonesogenes; it is thought to contain two deoxysugars linked through a phenolic acid residue (15) attached to a 32-macrolide ring (the evidence for this was not given in

this paper).[21]



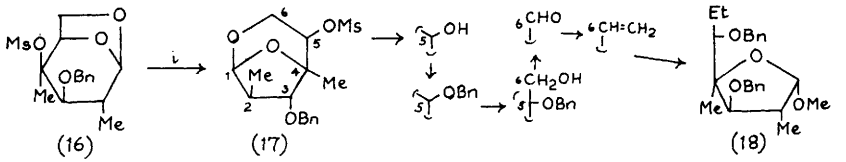
(15)

A new component of the algamycin complex has been identified, algamycin G (containing D-mycinose and the branched-chain sugar D-algarose), which is produced along with algamycin F by a strain of S. avidinii.[22] Two major macrolide components of chinese nystatin, nystatin A_3 and polyfungin B, have been identified; they contain two monosaccharide units, 2,6-dideoxy-α-L-ribo-hexopyranose and 3-amino-3,6-dideoxy-β-D-mannopyranose, linked glycosidically to a 38-membered hexa-unsaturated macrolide ring.[23]

A large number of ester derivatives of tylosin-related antibiotics have been prepared, in which the hydroxy groups at C-3 and C-4" (mycarose) were acylated either chemically or enzymatically; most derivatives showed excellent in vitro activity, but only the 3,4"-diacyl derivatives of tylosin and macrocin showed any in vivo efficacy relative to the parent compounds.[24]

A study of the biosynthesis of the sugar units in chlorothricin has shown that formation of the 2,6-dideoxy-D-arabino-hexose units involves replacement of the 2-hydroxy group in glucose by hydrogen with inversion, contrasting with retention previously observed in an analogous case for granaticin.[25]

The 2,4-di-C-methyl-D-galactopyranose derivative (16) has been rearranged to the furanose isomer (17) and hence to the derivative (18)(Scheme 4) required for the synthesis of an erythronolide ring fragment.[26]



(16) (17) (18)

Reagents: i, $MeNO_2$ · Mol. Sieve 4A

Scheme 4

A study of the biosynthesis of avermectins by S. avermitilis using [1-^{13}C]-glucose showed products labelled at C-1 in both oleandrose units of the disaccharide sidechain.[27]

3 Anthracycline and Related Polycyclic Antibiotics

A new anthracycline antibiotic, viriplanin A, has been isolated from Ampullariella regularis; it is related to arugamycin and decilorubicin, containing 2-deoxy-L-fucose, 4-O-mesoconoyl-L-diginose and deilonitrose attached to the aglycone viriplanol.[28]

A potent new anthracycline antibiotic, oxaunomycin, has been identified as 7-O-(α-L-daunosaminyl)-β-rhodomycinone; obtained from a blocked mutant of a Streptomyces strain producing baumycin, it is ~100 times more cytotoxic against L1210 leukaemia than doxorubicin.[29]

Structural studies on the antitumour antibiotics rhodilunancins A and B obtained from a S. violaceus variety show that they are identical to cosmomycins A and B respectively (see Vol.19,p. 180).[30]

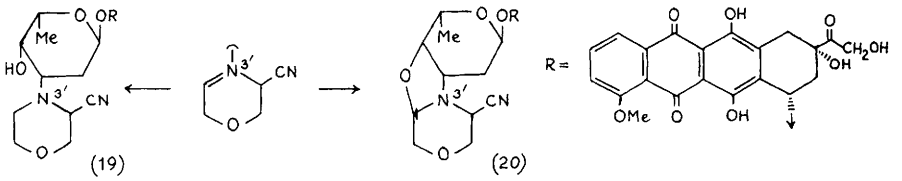
A mutant strain of S. violaceochromogenes has yielded an antibiotic cinerubin X, identified as an α-L-cinerulosyl(1→4)-α-2-deoxy-L-fucosyl(1→4)-α-L-rhodinosyl-ε-pyrromycinone,[31] and microbial glycosidation of α-citromycinone using a mutant strain of S. galilaeus has yielded a new antibiotic CG12, which is 10-O-(cinerulosyl-2-deoxyfucosyl-rhodosaminyl)-α-citromycinone.[32]

Minor cogeners of elloramycin obtained from S. olivaceus have been characterized; elloramycins B-F contain either the same 2,3,4-tri-O-methyl-α-L-rhamnopyranosyl monosaccharide unit present in elloramycin, or its 2,4- or 3,4-di-O-methyl analogue, with or without minor modifications to the aglycone.[33]

Further work on the synthesis of C-glycosyl isosters of anthracyclines has been reported, extending functionalization of the aglycone (see Vol. 18, p.181, ref.42).[34]

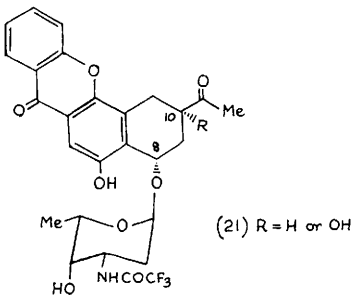
A total synthesis of 9-aza-N-(trifluoroacetyl)-4-demethoxydaunomycin has been reported, including its 7-epimer; both were inactive as antitumour agents.[35]

N'-Substituted derivatives of doxorubicin and daunorubicin have been reported,[36,37] including analogues of the hyperactive 3"-cyano-4"-morpholinyl-doxorubicin (see Vol.18, p.179); an iminium intermediate which leads to this latter product (19) can also undergo cyclization with the sugar 4'-hydroxy group, giving the bicyclic

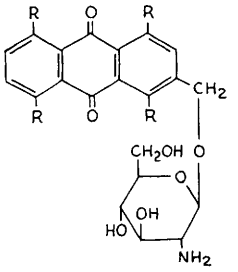


adduct (20).[37]

10-Acetyl-7,8-dihydroxy-xantho[2,3-f]tetralin glycosides of daunosamine have been synthesized as angular chromophore analogues of anthracyclines; whereas Koenigs-Knorr coupling of the cis-8,10-dihydroxy epimer worked satisfactorily to give (21)(R = OH), the corresponding trans isomer did not, a fact attributed to facile intramolecular hemiacetal formation.[38] 2'-Fluoro-3'-deamino



(21) R = H or OH



(22) R = H or OH

analogues of daunorubicin and doxorubicin have been prepared; the expected strengthening of the glycosidic bond in these derivatives was reflected in their increased antitumour activity with decreased toxicity relative to the parent compounds.[39]

A series of anthraquinonyl glucosaminides (22) have been synthesized conventionally to test the role of the aglycone hydroxy groups in antitumour activity.[40]

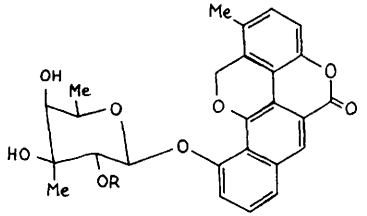
Furanoside analogues of daunorubicin or adriamycin have been prepared, derived from D-ribofuranose[41] and daunosamine;[42] the latter sugar coupled to daunomycinone gave compounds which were less active than the pyranosyl analogue, but were much less toxic and therefore had a more favourable therapeutic index.

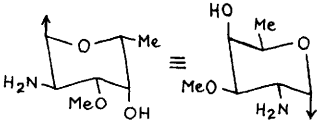
4-Demethoxydaunorubicin has been synthesized.[43]

The total synthesis of the disaccharide unit in olivomycin A, using L-threonine as the precursor, is mentioned in Chapter 3.

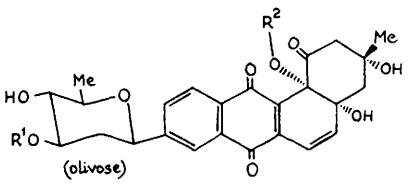
A number of new antibiotics have been reported which have related polycyclic aromatic aglycones O- or C- glycosically linked to sugars. An unidentified strain of actinomycete (J 907-21) has yielded elsamycin A (23) and B (24), which are relatives of chartreusin; the greater activity of elsamycin A correlates with its greater water solubility imparted by the aminosugar.[44] New angucycline antibiotics, urdamycins A-F, have been described. The main component, urdamycin A, has the structure (25).[45,46]

Another component of the lactoquinomycin complex has been

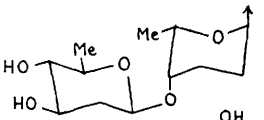


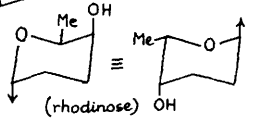
(23) R = 

(24) R = H

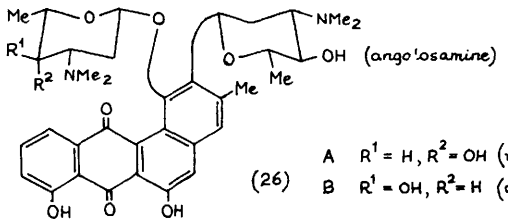


(25)

R^1 = 

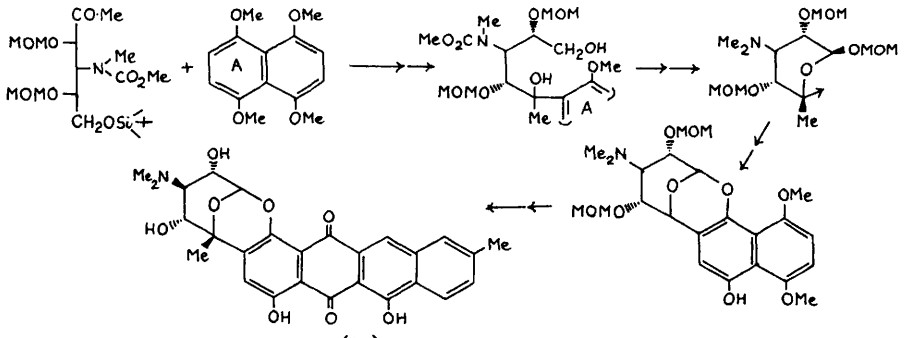
R^2 = 

identified; lactoquinomycin B (produced by S. tanashiensis) is the aglycone 4a/10a epoxide derivative of lactoquinomycin A (see Vol.19, p.186).[47] New quinone antibiotics, benzanthrins A and B, have been isolated from nocardia lurida, and characterized as isomeric diglycosides (26) of a trihydroxy-benz [a] anthraquinone chromophore;



(26) A R^1 = H, R^2 = OH (rhodosamine)
B R^1 = OH, R^2 = H (angolosamine)

nogalamycin is so far the only other example of an antibiotic containing both O- and C-linked sugars.[48] A synthesis has been develop-

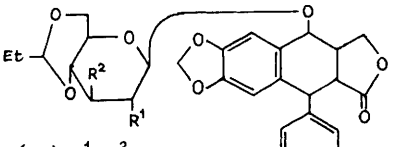


(27)

Scheme 5

ed for the nogalamycin analogue (27), forming the C- and O-linked glycoside as indicated in Scheme 5.[49]

Analogues of the anticancer podophyllotoxin etoposide (28) have been prepared by coupling partially protected aglycone and sugar moieties; both the amino analogues (29) were more active than the parent toxin. The α-anomer of the 2-amino-glucoside and the 2-N-methyl analogue of its L-enantiomer were also reported.[50]

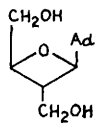


(28) $R^1 = R^2 = OH$
(29) $R^1 = OH, R^2 = NH_2$
$R^1 = NH_2, R^2 = OH$

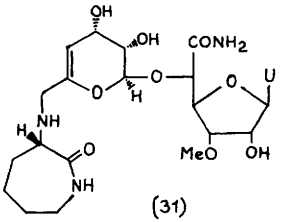
4 Nucleoside Antibiotics

A highly novel analogue of a nucleoside possessing a 4-membered oxetan ring instead of the normal furanose ring, oxetanocin (30), has been isolated from Bacillus megaterium NK84-0218, and identified spectroscopically, including X-ray crystal analysis.[51,52]

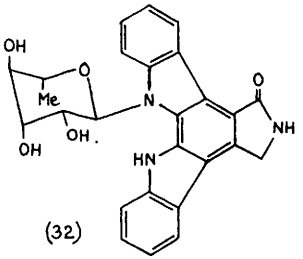
Capuramycin, a new antibiotic obtained from an S. griseus strain, is the allouronic acid-uracil derivative (31), containing a caprolactam substituent.[53] New nucleoside analogues of gougerotin have



(30)



(31)

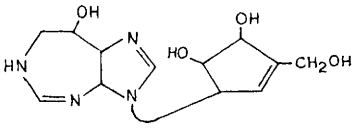


(32)

been isolated from a culture of B. circulans; bagougeramines A and B have the same 1-(4-amino-4-deoxy-β-D-glucopyranosyluronic acid)-cytosine unit as gougerotin, but a guanidino-D-alanine aminoacid replaces serine in the peptide side-chain.[54]

Some novel protein kinase C inhibitors, produced by Nocardiopsis sp. K252 and sp. K290, include the component K252d (32), which is the interesting α-L-rhamnosyl derivative (in the unusual $^4C_1$ conformation) of a double-headed carbazole heterocycle.[55] Another paper

reports a unique adenosine deaminase inhibitor, adecypenol (33), obtained from a Streptomyces strain, which contains the same cyclopentene structure as neplanocin A and the same base as coformycin, but the stereochemistry was not established.[56]



(33)

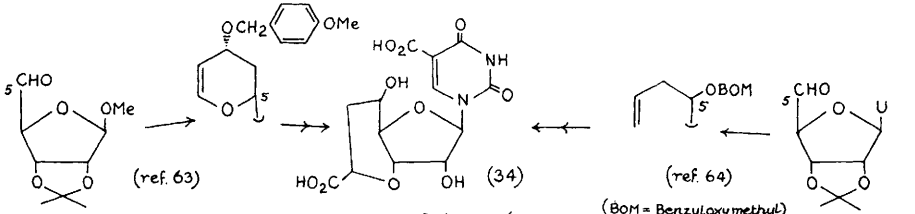
Further representatives of the nikkomycin group of antibiotics have been described (see Vol. 19, p.182), involving more variants in the aminoacid sidechains attached to the 5-amino-allouronic acid core.[57]

The total synthesis of tunicamycins, corynetoxins, and some analogues have been discussed,[58] and a published symposium paper includes the enantioselective synthesis of nucleoside analogues and fortimicin aminocyclitols using chiral synthesis achieved by asymmetric hydrolysis of symmetrical di-esters with pig-liver esterase.[59]

A synthesis of sinefungin has been described, using a nitro-aldol condensation between a dialdose derived from adenosine and an ω-nitro-aminoacid derivative to build the required C_{10}-carbon skeleton of the sugar unit.[60]

A "much improved" synthesis of cadeguomycin using a standard sugar/base condensation procedure has been reported,[61] and the same group has described a synthesis of its arabino- epimer.[62]

Two separate syntheses of octosyl acid A (34) have been published; both use dialdose derivatives to construct the carbon chain. In one route a Diels-Alder cycloaddition procedure was adopted,[63] whereas the other incorporated a Grignard addition step (Scheme 6).[64]



Scheme 6

A total synthesis of ascamycin results from the 5'-aminosulphation of a 2-chloro-adenosine derivative followed by acylation of the resulting amino-group with alanine.[65] The synthesis of bredinin has

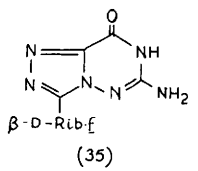
been improved.[66]

A number of 5-(2-subsituted-vinyl)-6-aza-2'-deoxyuridines have been prepared conventionally from the appropriately substituted uracil base, or more satisfactorily by modifying preformed 5-hydroxymethyl-6-aza-2'-deoxyuridine via the corresponding 5-formyl compound; a 5-(3-furanyl) analogue was best made by 2'-deoxygenation of the ribose analogue, via a 3',5'-tetraisopropyldisiloxanyl intermediate.[67]

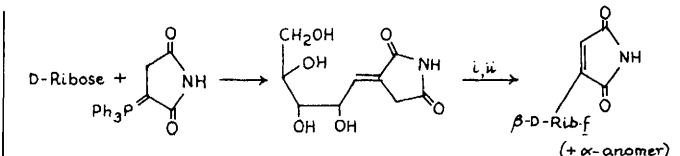
A process has been described which is suitable for the large scale preparation of the antitumour -antiviral agent selenazofurin (see Vol. 17, p.197), giving 41-47% overall yields from perbenzoylated β-D-ribofuranosyl-cyanide, in turn best made from the 1-acetyl analogue using the TMS-CN/$SnCl_4$ procedure.[68]

Thymidine or 2'-deoxyuridine have been converted to corresponding 3'-amino, 5'-amino, and 3',5'-diamino analogues by a previously reported methodology; the resulting amino nucleosides were also complexed with platinum salts, and their biological activity studied.[69]

A number of 3-β-D-ribofuranosyl-1,2,4-triazolo[3,4-f]1,2,4-triazenes, related to formycin, have been synthesized, e.g., (35), using a 2,5-anhydro-allonic acid derivative.[70] A new synthesis of



(35)



Scheme 7

showdomycin and its α-anomer using a Wittig reagent with ribose is outlined in Scheme 7.[71] Syntheses have been developed for neplanocin A and quenosine from a common aminodihydroxy-cyclopentylcarboxylic acid derivative.[72] A synthesis of (±) and (-)-aristeromycin is mentioned in Chapter 18.

The carbocyclic analogue of puromycin has been prepared from the racemic carbocyclic nucleoside precursor, resolving the diastereoisomers formed after acylation by p-methoxyphenylalanine; the D-form is a bacterial growth inhibitor and an excellent substrate for peptidyl transferase, whereas the L-form is inactive.[73] The enzymic synthesis of 7-hydroxyguanine riboside and 2-deoxy-riboside has been described; both showed antitumour activity, the latter more so.[74]

Tubercidin isomerizes slowly with acid to give α-furanoside and cleavage products; 2-deoxy-analogues also gave both anomeric pyranosides and α-furanosides, the β-pyranosides being most stable.[75]

The crystal structure of neplanocin C is mentioned in Chapter 22.

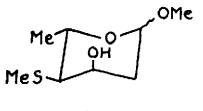
5 Glycopeptide Antibiotics

New glycopeptide antibiotics, kibdelins A-D, have been reported, elaborated by Kibdelosporangium aridum subsp. largum. They contain the same mannosyl aglycone as the aridicins produced by the parent strain of these microorganisms, but have 2-amino-2-deoxy-D-glucose in place of 2-amino-2-deoxy-D-glucuronic acid; the components differ in the acyl group attached to the sugar amino group, being derivatives of C_{10} or C_{12} fatty acids.[76] A study of the biosynthesis of aricidin antibiotics reveals that oxidation to glucuronic acid occurs as a terminal step, the first-formed peptide core being first mannosylated then glucosaminylated.[77]

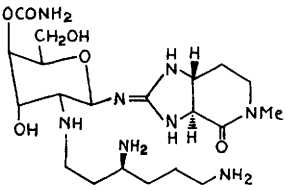
A ^{13}C n.m.r. study of actinoidins has been recorded, particularly of the glycosidic linkages involved; α-D-mannosyl, α-L-actinosaminyl, and α-L-acosaminyl-β-D-glucosyl (β-acobioside) units were identified from 2D $^{13}C/^{1}H$ correlated spectra, using phenyl or methyl glycoside analogues as references.[78] The synthesis of phenyl acobioside has been separately described.[79] The N-methyl-fucosamine present in neocarzinostatin (see K.Edo et al., Tetrahedron Lett.1985, 26, 331) has been assigned to the D-series by synthesis.[80]

6 Miscellaneous Antibiotics

Novel sulphur-containing sugars have been detected in antitumour antibiotics PD 114759 and PD 115028. Methanolysis yielded unstable glycosides considered to be methyl 4-alkylthio-2,4-dideoxy-3-O-methyl-α- and -β-pentopyranoside (from n.m.r. data), and methyl 2,4,6-trideoxy-4-methylthio-α- and -β-lyxo-hexopyranoside (36)(L-series assumed); n.m.r. evidence also suggested a third thio sugar was present, a 4,6-dideoxy-4-mercapto-hexopyranose, which accounts



(36)



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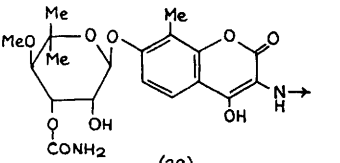


(38)

for all the sulphur present in the antibiotics. Great interest attaches to the role these sulphur sugars may play in the remarkable activity of these antibiotics.[81]

A new streptothricin antibiotic, albothricin (37), has been isolated from the culture broth of strain SIPI-2985.[82]

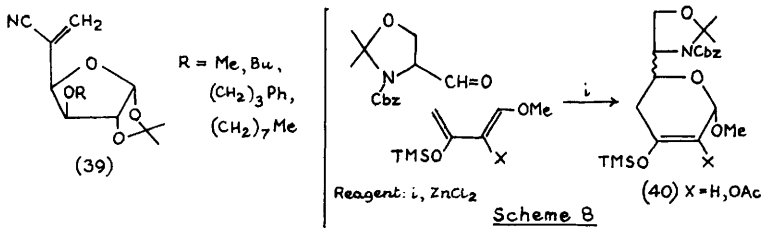
Nine additional minor components of the avilamycin complex (orthosomycins), avilamycins F-N, have been characterized; all are minor variants on previously identified members of the complex.[83]

Testing fragments of novobiocin for activity against E. coli indicated that the novenamine unit (38), which includes the branched-chain sugar noviose, is the active moiety in the antibiotic.[84]

Pentagalloyl-glucose and related gallotannins have been shown to be potent inhibitors of glucan synthesis by glucosyl-transferase from a cariogenic bacterium, S. mutans, an appropriate target for preventing dental caries.[85] Amylase inhibitors have been prepared from 1-deoxynojirimycin using soluble starch and bacterial saccharifying amylase; up to eight glucose units were transferred, all linked α-1$\rightarrow$4. Only mono- and tri-glucose derivatives inhibited β-amylases, whereas all could inhibit α-amylases.[86]

The total synthesis of the marine toxin neosurugatoxin has been reported, which involved the synthesis of a D-xylopyranosyl-myo-inositol derivative and its esterification with a polycyclic carboxylic acid.[87]

A series of α-methylidene-urononitriles (39) have been prepared from corresponding nitro-enoses, which were mostly cytotoxic, some being antiviral as well.[88]



Scheme 8

An approach to the synthesis of the 6-amino-hepturonic acid component in amipurimycin has been described, coupling a formyl-oxazolan derived from L-serine with a butadiene diether in a Diels-Alder reaction to give the product heptenose derivative (40) (Scheme 8); the erythro : threo ratio could be controlled from the zinc chloride concentration and the solvent.[89]

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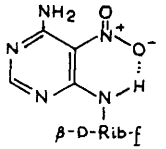
20
Nucleosides

1 General

The novel cytokinin 9-β-D-ribofuranosyl-1'-methylzeatin, referred to last year, has been shown to have R-chirality in the 1'-methylzeatin unit.[1] Clitocine, a new insecticidal nucleoside from the mushroom Clitocybe inversa, has the structure (1),[2] and the novel nucleoside 5-carboxymethyluridine has been isolated from the urine of certain human cancer patients.[3] Inosine has been identified as the hypotensive agent contained in the dried body of an Asian animal in the Naja genera.[4]



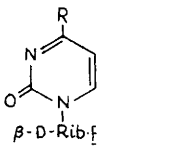
(1)

Ohno has reviewed the work of his group on the enantioselective synthesis of, inter alia, nucleosides, C-nucleosides and carbocyclic nucleoside analogues using chiral synthons derived by asymmetric hydrolysis of meso-diesters with pig liver esterase.[5] Although acyclonucleosides are not discussed in detail in these volumes, we note an extensive review of the chemistry and antiviral activity of such compounds.[6]

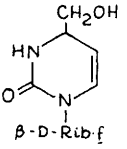
2 Synthesis

Conventional condensation procedures have been used to prepare β-D-ribofuranosyl derivatives of 5-and 6-alkyl-3-deazacytosine and -uracil,[7] the pyrimidine -2-ones (2), which were reduced to dihydroderivatives, one of which (3) showed good acid stability and powerful inhibitory activity against cytidine deaminase,[8] 4-cyano-5-methylimidazole and the 5-cyano-4-methyl isomer,[9] and 3-amino- and 3,5-diaminopyrazole-4-carboxylic acid.[10] The pyrazole nucleoside (4) was produced as the only isomer from Koenigs-Knorr

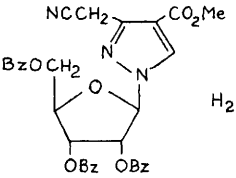
procedures, and this was converted to 2-β-D-ribofuranosyl-6-aminopyrazolo[4,3-c]pyrimidin-4(5H)one (5); similar work in the 2'-deoxy- series gave a mixture of both N-glycosylated isomers of β-configuration.[11]



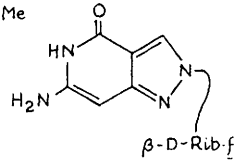
(2) R=H, CH_2OH



(3)

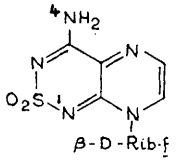


(4)

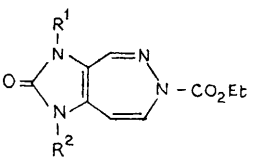


(5)

Standard procedures were used to prepare the pyrazino[2,3-c]-1,2,6-thiadiazine -2,2-dioxide riboside (6), together with the N^1-ribosyl isomer and an N^3, N^4 -diribosylated product,[12] the N^7 -riboside of uric acid,[13] 1-β-D-ribofuranosyl-lin-naphthotriazole,[14] 1-β-D-ribofuranosyl-2-trifluoromethylnaphth[2,3-d]-imidazole,[15] and the nucleosides (7) and (8) as a separable



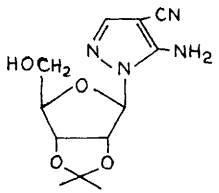
(6)



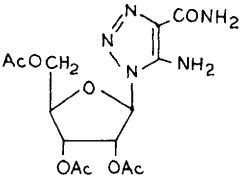
(7) R^1 = β·D·Rib·f, R^2 = H
(8) R^1 = H, R^2 = β·D·Rib·f

mixture.[16] Work reported earlier (see Vol. 18, p.192) on the use of N-octylthiocarbonyl pyrimidines in nucleoside synthesis has been further discussed.[17] A series of 3-deazapurine nucleosides has been prepared from uridine and the deazapurine base by enzymic phosphorolysis in conjunction with purine nucleoside phosphorylase.[18]

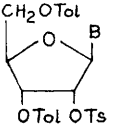
The pyrazole nucleoside (9) has been prepared from 2,3-O-isopropylidene-D-ribofuranosyl hydrazine, and the triazole (10) from tri-O-benzoyl-β-D-ribofuranosyl azide; both were converted



(9)



(10)

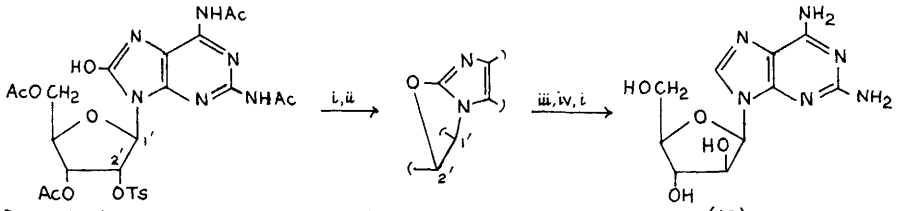


Tol = p-Toluoyl

(11) B = Ad or U

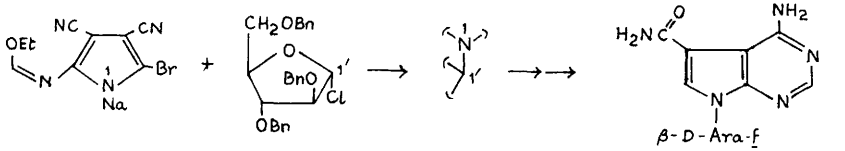
to heterocyclic analogues of coformycin. The 2'-O-tosyl nucleosides (11) have been prepared exclusively as β-anomers by reaction of the silylated base with the β-methyl riboside in the presence of stannic chloride, indicating that the steric bulk of the tosyloxy group can act to direct a ribosylation reaction.[20]

2,6-Diamino -9-β-D-arabinofuranosylpurine (12) has been prepared via a cyclonucleoside as outlined in Scheme 1,[21] whilst the sodium salt glycosylation procedure shown in Scheme 2 proceeded to



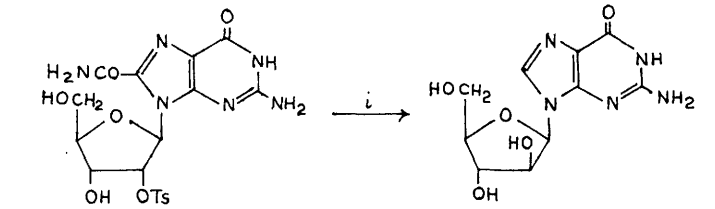
Scheme 1

give exclusively a β- product, which was converted into the arabino analogue of toyocamycin (13); a similar sequence in



Scheme 2

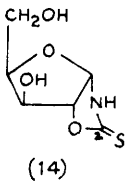
the 2'-deoxy- series also gave exclusively a β-nucleoside.[22] Ara-G has been prepared as indicated in Scheme 3.[23] Some 4-substituted 1-β-D-xylofuranosyl and 1-α-D-arabinofuranosyl



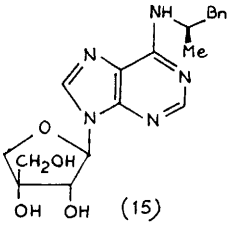
Scheme 3

pyrazole[3,4-d]pyrimidines have been prepared conventionally.[24] β-D-Xylofuranosyl nucleosides of the five naturally occurring bases have been synthesised by standard glycosylation, whilst the corresponding α-D-nucleosides were prepared from the oxazoline

(14) or the corresponding 2-amino-compound, building up the heterocycle around the nitrogen atom at the anomeric centre.[25]



(14)

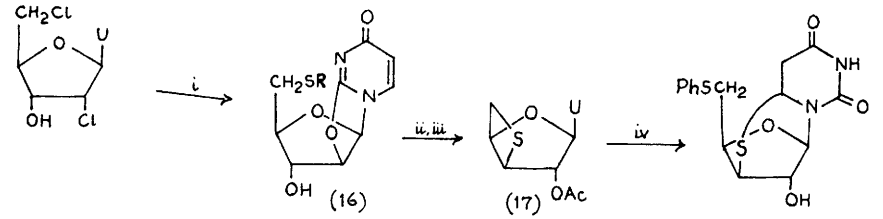


(15)

The β-D-apiofuranosyl nucleoside (15), designed as an adenosine receptor agonist, has been reported.[26] Some other references to nucleoside synthesis can be found in Chapter 19.

3 Anhydro- and Cyclonucleosides

Reaction of 2',5'-dichloro -2',5'-dideoxyuridine with thiols gives the 2,2'-anhydro systems (16) (Scheme 4); in the case where R = Ac

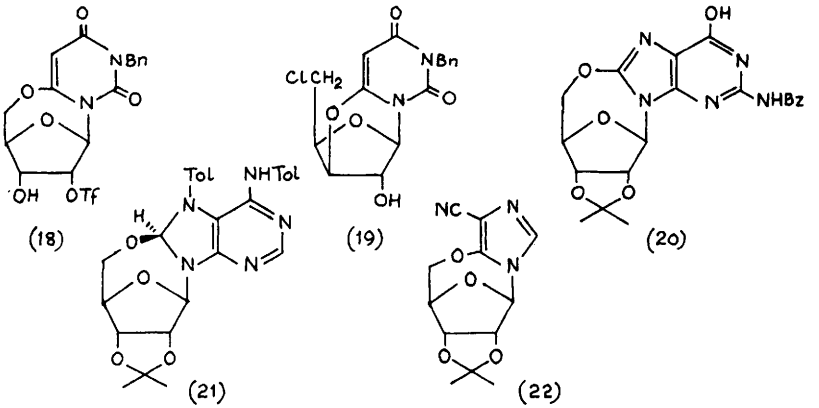


Reagents: i, RSH ; ii, NaOMe ; iii, Ac_2O ; iv, NaSPh - EtOH - Δ

Scheme 4

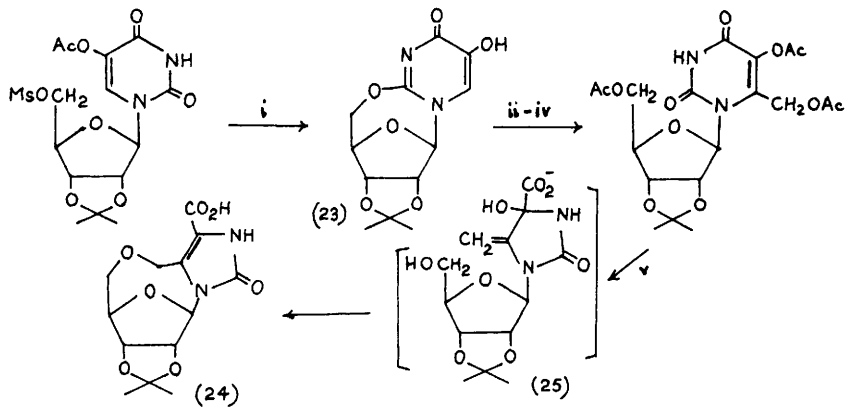
base treatment gives the thietan system (17), which reacts as shown with phenylthiolate ion.[27] The triflate (18) was the major product (9:1) in the partial esterification of the stannylene derivative; both (18) and the 3'-O-triflyl isomer gave the same 6,3'-anhydride (19) on treatment with lithium chloride in HMPA, indicating a triflate migration in the case of (18).[28]

8,5'- Cyclopurine nucleosides such as (20), and 6,5'-cyclocytidine have been formed by intramolecular oxidative photocyclization of the corresponding nucleosides in the presence of pyrimidino[5,4-g]pterin-N-oxide.[29] Treatment of guanosine with 2,4-dinitrophenoxyamine gave a 7-amino derivative which can be converted to 8,5'-O-cycloguanosine and 8-hydroxyguanosine in aqueous media.[30] Further details and examples have been given of the formation of 5,5-disubstituted 5,6-dihydro -6,2': 6,5'-di-O-cyclouridines (see Vol. 17, p.188);[31] the formation of 8,5'-



O-cycloadenosine derivatives such as (21) in the acylation of isopropylidene adenosine, reported last year (see Vol. 19, p.198), and the factors involved in the cyclization have been further studied.[32] The 5,5'-anhydronucleoside (22) was obtained in fairly low yield on deamination of the corresponding 5-aminoimidazole.[33]

The 2,5'-anhydro-5-hydroxyuridine (23) has been prepared (Scheme 5); this, in contrast to the acyclic precursors, underwent hydroxymethylation at C-6 to give a product which was subsequently converted by ring -contraction to the novel 5'-cyclonucleoside (24), presumably via intermediate (25).[34]

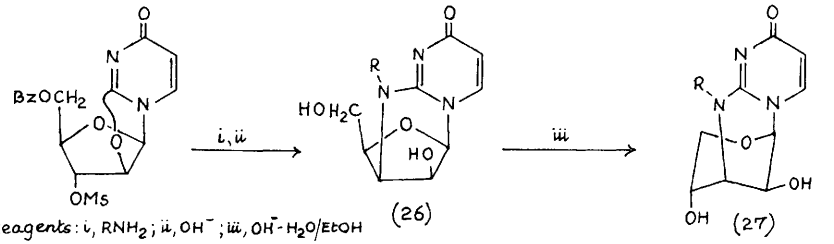


Reagents: i, OH^--EtOH; ii, OH^--HCHO; iii, Ac_2O-Py; iv, AgOAc-Py; v, OH^-

Scheme 5

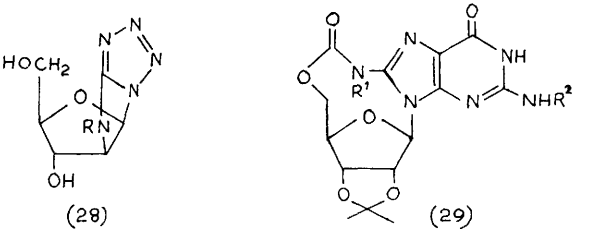
2,3'-Iminocyclonucleosides of type (26; R = H, alkyl, Ph, NHMe,

CH_2CO_2Et) have been obtained as shown in Scheme 6. On treatment

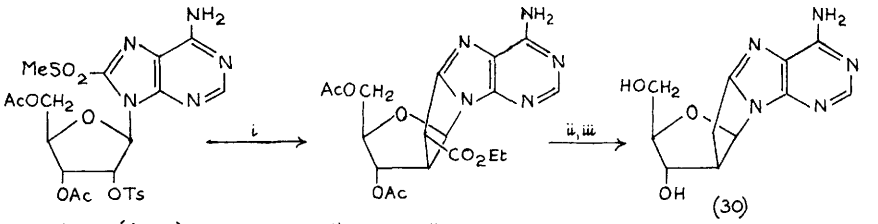


Scheme 6

with base these compounds underwent ring expansion to the pyranoses (27), the first case of such a reaction for pyrimidine cyclonucleosides.[35,36] The tetrazole iminocyclonucleoside (28) has been prepared by intramolecular displacement of a 2'-O-triflyl group.[37] Further details have been given of 8,5'-imino purine cyclonucleosides (see Vol. 17, p.192), together with reports of intramolecular carbamates of type (29) in the guanosine series.[38]



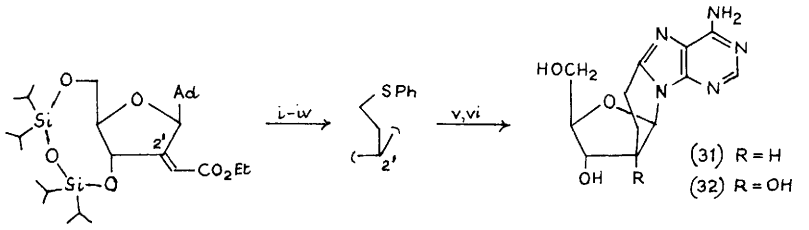
Carbon-bridged purine cyclonucleosides have attracted attention this year. 2'-Deoxy-8,2'-methanoadenosine (30) has been prepared as outlined in Scheme 7,[39,40] and the guanosine analogue is



Scheme 7

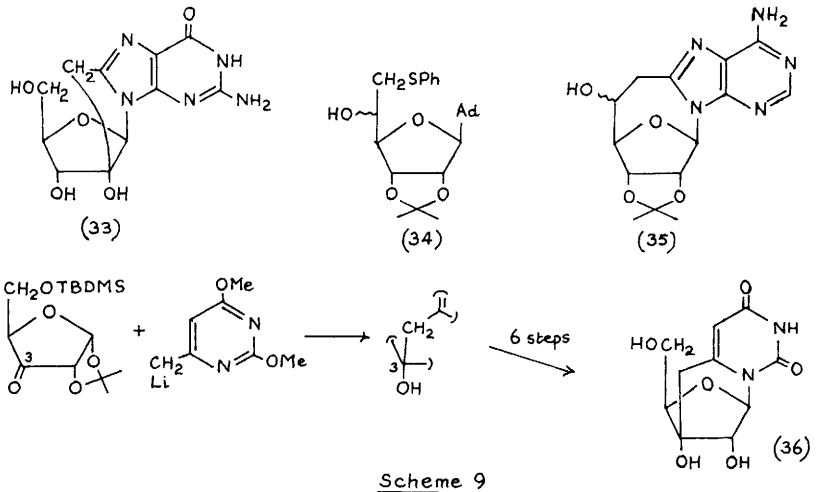
similarly accessible.[40] 2'-Deoxy-8,2'-ethanoadenosine (31) has been synthesized by a route (Scheme 8) involving photochemical

cyclization, and the 8,3'-analogue can be prepared similarly.[41]



Scheme 8

The same key cyclization was employed, at a higher oxidation level, for the synthesis of 8,2'-ethanoadenosine (32) and the 8,2'-methano analogue,[42] and for the preparation of 8,2'-methanoguanosine (33).[43] Photolysis of (34) in the presence of trimethylphosphite gave the 8,6'-methano system (35), but only in low yield, with the major product being the 6'-deoxy nucleoside.[44]



Scheme 9

6,3'-Methanouridine (36) has been synthesized from D-xylose by a sequence involving intramolecular glycosylation (Scheme 9).[45]

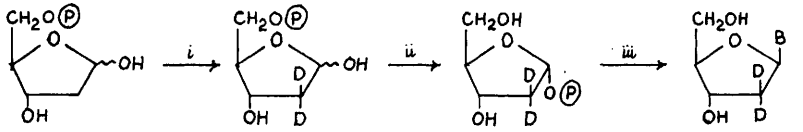
4 Deoxynucleosides

Standard procedures have been used to prepare 2'-deoxy-α- and β-D-ribofuranosides of 5-cyclopropyluracil,[46] 5-trimethylgermyluracil,[47] 8-aza-7-deazaguanine,[48] and 6-oxoallopurinol.[49] 2'-

Deoxy-5-azacytidine has been prepared,[50] as has its 6-oxo-analogue.[51]

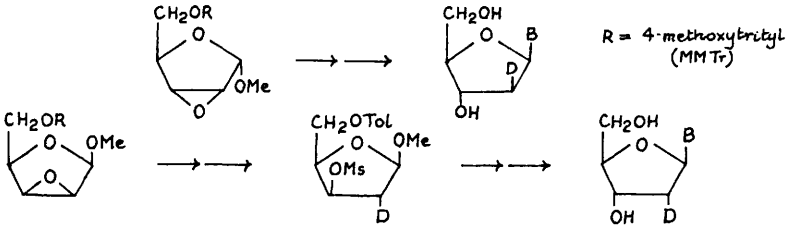
The 2'-deoxy-, 3'-deoxy- and 5'-deoxy-β-D-ribofuranosides with the same aglycone as (15) have been prepared,[26] and a series of 3-deazapurines have been linked enzymatically to 2-deoxy-, 5-deoxy- and 2,5-dideoxyribose.[18]

An enzymic synthesis of 2'-deoxyribonucleosides doubly deuteriated at the 2'- position is outlined in Scheme 10,[52] whilst Scheme 11 indicates in outline chemical methods for stereo-



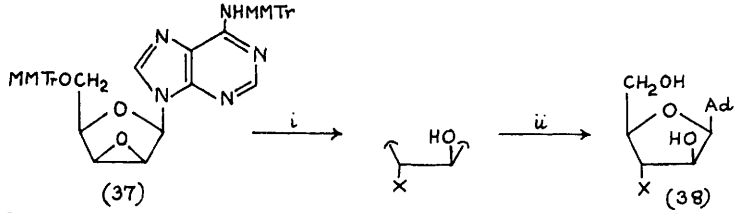
Reagents: i, 2-deoxyribose-5-phosphate aldolase - D_2O ; ii, Phosphopentomutase; iii, Purine nucleoside phosphorylase or thymidine phosphorylase

Scheme 10



Scheme 11

specific mono-deuteriation at the same position.[53] Reduction of the epoxide (37) has led to a convenient synthesis of 9-(3'-deoxy-β-D-threo-pentofuranosyl)adenine (38; X=H), a constituent of agrocin 84, and its monodeuterio analogue (38; X=D) (Scheme 12).[54]

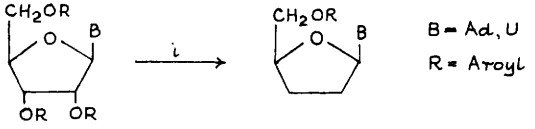


Reagents: i, $LiAlX_4$ (X = H,D) ; ii, HOAc (RT)

Scheme 12

A photosensitized electron- transfer reaction has been used for the selective deoxygenation of secondary alcohols in ribonucleosides, as outlined in Scheme 13. Best yields were obtained with

m-[trifluoromethyl]benzoyl esters, but simple benzoyl esters gave good yields in reasonable times if magnesium perchlorate was present.[55]



Reagents: i, hν - N-methylcarbazole - PriOH - H_2O

Scheme 13

Methods for the preparation of [8-^{13}C]-deoxyadenosine have been compared,[56] and 5,6-dideoxyheptofuranosyl nucleosides have been prepared by Wittig chain extension of 5'-aldehydes.[57]

5 Halonucleosides

2-Deoxy-2-fluoro-β-D-arabinofuranosyl derivatives of guanine[58] and some 5-alkyluracils[59] have been prepared conventionally. 2',3'-Dideoxy-3'-fluoro-D-ribofuranosylbenzimidazole has been synthesized.[60]

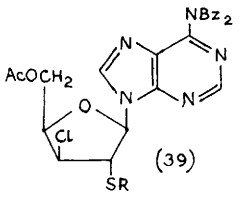
The isomer (39) was the major product formed when the 2',3'-alkene was treated with sulphenyl chlorides; presumably the ribo-thiiranium ion predominates, and is opened stereoselectively.[61]

A Kiliani reaction of L-erythrose with labelled cyanide was used to prepare 5'-chloro-5'-deoxy-[5'-^{13}C]-adenosine, and hence labelled adenosyl cobalamin.[62]

6 Nucleosides with Nitrogen-substituted Sugars

When mesylate (40) was treated with azide ion, substitution occurred predominantly with retention via a 2,3'-anhydride if R = H, Me, whereas for R = I, F, direct substitution predominated.[63] 3'-Azido-3'-deoxy analogues of BVDU have been reported,[64] and 2'-azidopentopyranoses of type(41) have been prepared in racemic form.[65] When the 2'-O-triflyl precursor of (28) was treated with azide ion, a 2'-azido-2'-deoxyarabinofuranosyl nucleoside was formed.[37] A series of 5-amino-and 5-acylamino -5-deoxyribofuranosyl derivatives of thymine has been prepared,[66] as has the 5'-amino-5'deoxy derivative of ribavirin.[67]

Pyrimidine nucleosides of N-acetylneuraminic acid have been prepared, with β-anomers predominating under Koenigs-Knorr conditions.[68]



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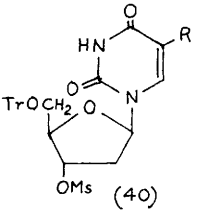

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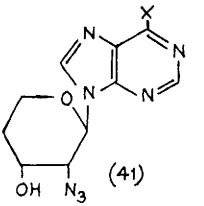

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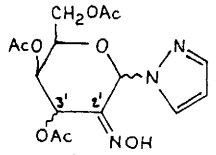

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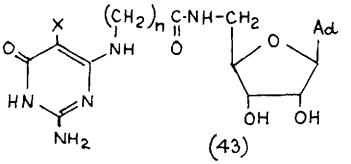

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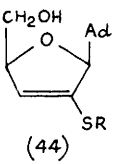


(44)

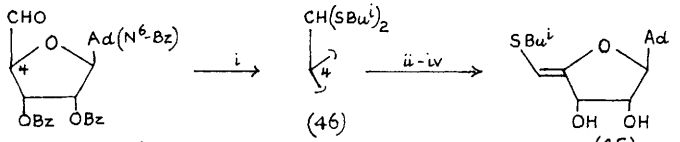
In work similar to that reported last year (Vol. 19, p. 201), 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso-α-D-galactopyranosyl chloride was shown to react with pyrazole to give products of type (42); additional chemistry was carried out at C-2' and C-3'.[69]

Some bridged adenosine - isocytosine derivatives (43; n = 2-7) have been reported, but without the anticipated anti-bacterial activity.[70]

7 Thionucleosides

When the product mixture containing (39) was deprotected and then treated with methoxide ion, the 2'-ene thioethers (44) were obtained.[61]

The unsaturated thioether (45) has been prepared as outlined in Scheme 14.[71] When N^6-benzoyl-2',3'-O-isopropylidene adenosine



Reagents: i, Me_3SiSBu^i - Me_3SiOTf; ii, Br_2; iii, DBU; iv, NH_3-MeOH

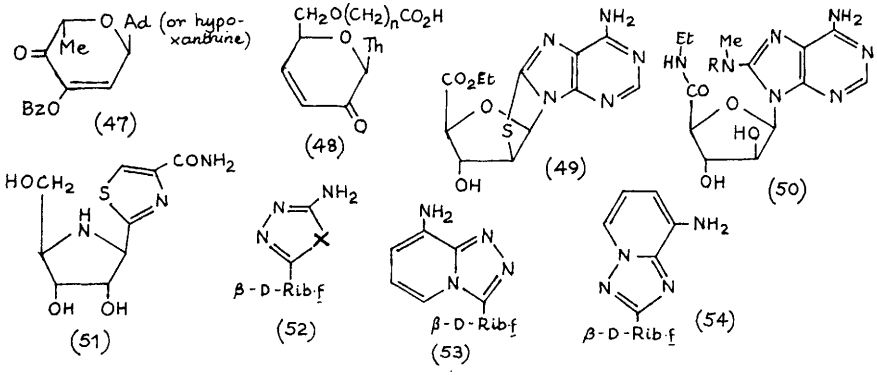
Scheme 14

was treated with tributylphosphine and dialkyl disulphides in the presence of excess of the corresponding alkylthiols, the 5'deoxy-5'-thioalkyl derivatives were formed; when a similar reaction was carried out on the hydrated form of 2',3'-O-cyclohexylideneuridine-5'-aldehyde, a dithioacetal similar to (46) was produced.[72]

8 Nucleosides of Unsaturated Sugars, Ketosugars and Uronic Acids

The unsaturated ketonucleosides (47) have been prepared from the α-L-rhamnopyranosyl nucleosides, and the 5'-epimers were produced from 6-deoxy-β-D-glucopyranosyl nucleosides.[73] The theophylline nucleosides (48; n = 5,6) were synthesised in a multistep sequence.[74] 2',3'-O-Isopropylidene-4'-keto-α-L-rhamnopyranosyluracil has been reported.[75]

Thymidine-5'-carboxylic acid and 2'-deoxyuridine-5'-carboxylic acid, previously known as synthetic compounds, have been isolated from the ascidian A. Fuscum.[76] Some N^6-alkyladenosine-5'- uronamides have been reported.[77] 8-Bromoadenosine-5'-carboxylic acid was prepared by oxidation of the hydroxymethyl compound;[78] its esters could be converted into 5'-uronamides and thence into 8-alkylamino derivatives.[79] 8-Bromoadenosine-5'-carboxylic acid was also converted in two steps into the 8,2'-S-anhydronucleoside (49),[80] and arabinofuranosyluronamides (50) have been prepared from the 8-2'-anhydrosystem.[81] Some N^6-alkyladenin-9-yl-β-D-glucofuranuronosides were prepared in Vorbrüggen-type procedures.[82]



9 C-Nucleosides

The approach to C-nucleosides involving [4+3] cycloaddition to furans, developed by Noyori and his group, has been reviewed.[83]

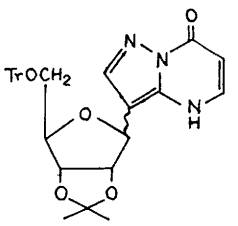
A process suitable for large-scale synthesis of the antitumour and antiviral agent selenazofurin has been reported; this includes a new direct preparation of the useful intermediate 2,5-anhydro-

3,4,6-tri-O-benzoyl-D-allononitrile by treatment of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose with TMSCN and stannic chloride.[84] An improved route to tiazofurin has been described, along with 5'-O-sulphamoyl and -carbamoyl derivatives,[85] and the 5'-amino-5'-deoxy- and 5'-deoxy-5'-thio analogues.[67] The tiazofurin analogue (51) containing a pyrrolidine ring is the first example of a C-nucleoside analogue with this feature.[86] The thia- and oxadiazoles (52; x = O,S) have been prepared from 2,5-anhydro-D-allonic acid,[87] and some 2-β-D-ribofuranosylpyridines have been reported.[88]

The 5'-deoxy-5'-halo derivatives of formycins A and B have been shown to inhibit certain enzymes of purine metabolism,[89] and the β-D-xylofuranosyl analogue of formycin has been prepared from D-mannose in a stereoselective manner.[90] The S-triazolo[4,3-a]-pyridine analogue of formycin (53) and the S-triazolo [1,5-a]-pyridine (54) have both been synthesized from 2,5-anhydro- D-allononitrile.[91] Some furo[3,2-d]pyrimidine C-nucleosides, isosteres of adenosine, have been prepared,[92] and previously reported pyrrolo- and thieno[3,2-d]-pyrimidines have been modified at C-2' (deoxygenation, stereochemical inversion, halogenation) via the 3',5'-cyclic disiloxanyl derivatives.[93] An alternative approach to the synthesis of pyrrolo[3,2-d]-pyrimidine C-nucleosides has been described.[94]

Further studies have been reported on the palladium-mediated coupling of furanoid glycals to give C-nucleosides (see Vol.17, p.195); α- or β- compounds are available depending on the nature of the substituents at O-3 and O-5.[95]

When (55) was subjected to acid hydrolysis for deprotection, only the β-D-pyranoside could be isolated.[96] Four different nitrogen heterocyclic systems were formed by annulation on to C-1 of the anhydro-L-mannose derivative (56).[97] The homo-C-nucleo-



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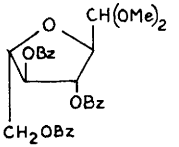

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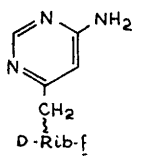

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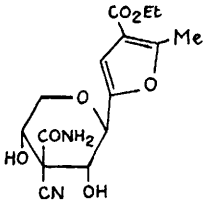


(58)

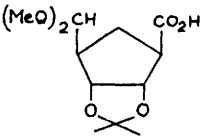
side (57) has been synthesized via a Wittig reaction of 2,3-O-isopropylidene -5-O-trityl-D-ribofuranose,[98] and C-glycosyl-

furans such as (58) have been prepared from cyanoacetamide and a dialdehyde.[99]

10 Carbocyclic nucleoside analogues

The chemistry and biological properties of carbocyclic nucleoside analogues have been reviewed.[100]

The racemate (59), formed by cleavage of a Diels-Alder adduct, has been converted into the carbocyclic C-nucleoside analogue (60); the "2'-deoxy" compound and its α-anomer were also



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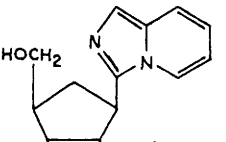
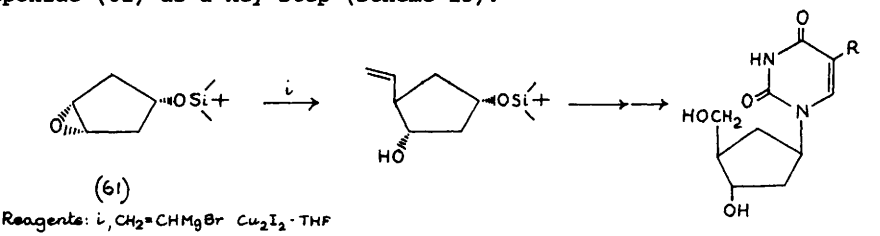


(60)

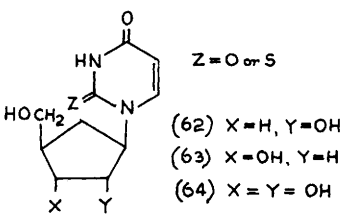
prepared.[101] A Curtius rearrangement of (59) with diphenylphosphoryl azide gave a route to the carbocyclic analogue of uridine; again both anomers of the 2'-deoxy system were also prepared, and converted into carbocyclic analogues of BVDU.[102] A stereospecific route to (+)-carbocyclic 2'-deoxyuridines involves the opening of epoxide (61) as a key step (Scheme 15).[103]



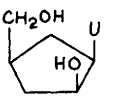
(61)

Reagents: i, $CH_2=CHMgBr$ Cu_2I_2 · THF

Scheme 15



(62) X = H, Y = OH
(63) X = OH, Y = H
(64) X = Y = OH



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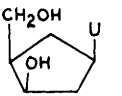
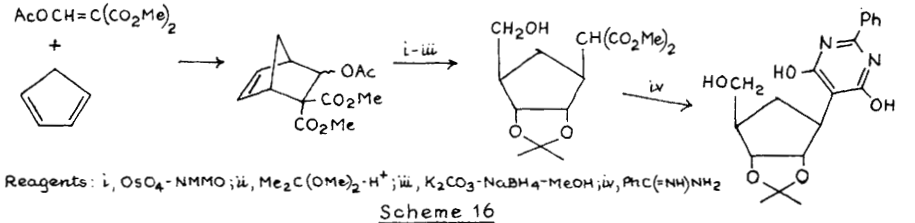


(66)

Carbocyclic uracil and 2-thiouracil analogues (62)-(64) have been reported, using modifications and improvements on earlier work.[104] The stereoisomers (65) and (66) have also been

synthesized, as have their 2-thio analogues, starting from endo -5-norbornen-2-yl acetate,[105] and an alternative way of using the same starting material to synthesize (66) has also been described by other workers.[106]

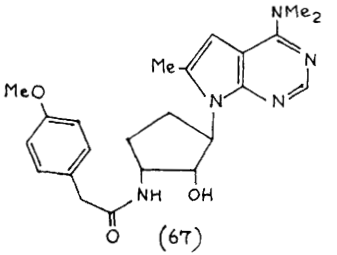
A new synthon for carbocyclic C-nucleosides has been prepared and used as indicated in Scheme 16.[107]



Reagents: i, OsO_4-NMMO; ii, $Me_2C(OMe)_2$-H^+; iii, K_2CO_3-$NaBH_4$-MeOH; iv, $PhC(=NH)NH_2$

Scheme 16

Carbocyclic analogues of 5'-amino-5'-deoxy- and 3'-amino-3'-deoxythymidine have been prepared from previously known cyclonucleosides,[108] and the puromycin analogue (67) has been reported.[109] A synthesis of aristeromycin is mentioned in Chapter 19.



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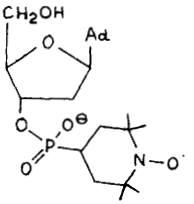


(68)

11 Nucleoside phosphates and phosphonates

As in previous volumes, standard syntheses of oligonucleotides are not discussed. A review has appeared (in Czech) on chemical and enzymic synthesis of ^{32}P-labelled nucleoside mono-, di- and triphosphates and 2'-deoxynucleoside phosphates.[110]

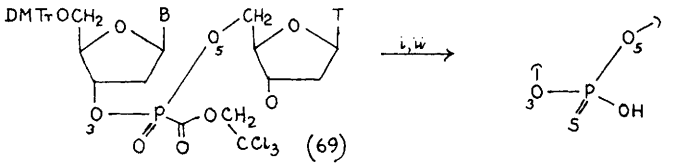
Guanosine -5'-monophosphate has been prepared by reaction of 2',3'-O-isopropylideneguanosine with PCl_3 and anthraquinone in dioxan and a stream of oxygen, followed by hydrolysis.[111] Phosphodiesters have been obtained by condensation of nucleotides in aqueous medium with an alcohol in the presence of a water-soluble carbodiimide.[112] The spin-labelled 2'-deoxyadenosine derivative (68) has been prepared.[113]

A review has been given of the use of the p-nitrophenylethyl

and p-nitrophenylethoxycarbonyl protecting groups in nucleoside and nucleotide synthesis; the latter group gives new approaches to oligonucleotide synthesis if it is used instead of acid-labile mono- and dimethoxytrityl groups.[114] The 2-(2-pyridyl)ethyl group has been advocated for the protection of internucleotide phosphates; it is removable by methyl iodide in acetonitrile.[115]

A series of 3'-phosphoramidite derivatives of 2'-deoxyribonucleosides protected at O-5' have been synthesized in connection with oligonucleotide synthesis,[116] and the non-aqueous oxidation of nucleoside phosphites to phosphates has been studied, with bis-(trimethylsilyl)peroxide in the presence of trimethylsilyl triflate being proposed as the best reagent.[117]

A simple method has been reported for the synthesis and h.p.l.c. separation of the diastereoisomers of the α-thio analogues of ATP and dATP,[118] and some dinucleoside phosphorothioates have been synthesized via the separable diastereomers (69), followed by stereospecific conversion (overall retention) into phosphorothioates (Scheme 17).[119] Nucleoside 3', 5'-cyclic



Reagents: i, Zn-Py-TMSCl; ii, S_8

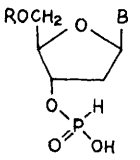
Scheme 17

phosphorothioates have been conveniently synthesized by treatment of the nucleoside (N-protected if necessary) with bis(p-nitrophenyl)phosphorochloridothioate, and cyclization of the 5'-bis (p-nitrophenyl)phosphorothioates with potassium t-butoxide in DMF; the Sp isomer predominated (ca. 4:1) in each case.[120]

Treatment of cyclic AMP tributylammonium salt with alkyl halides in dimethylacetamide produces the corresponding triesters, with axial alkoxy groups predominating.[121] 2'-Bromo-and 2'-chloro-2'-deoxy analogues of c-AMP have been prepared, and prevent the development of disseminated intravascular coagulation.[122]

Two good methods have been developed for the synthesis of 2'-deoxynucleoside -3'-hydrogenphosphonates (70).[123] A chiral derivatizing agent was used as a blocking group for the 3'-OH function to facilitate the resolution of diastereomers of methylphosphonate dinucleotides by column chromatography.[124]

The cyclonucleoside phosphonate (71) has been prepared from 2,3'- anhydro-1-β-D-fructofuranosyluracil via the 4',6'-TIPDS



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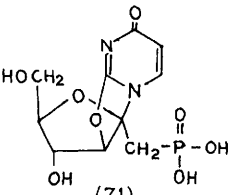
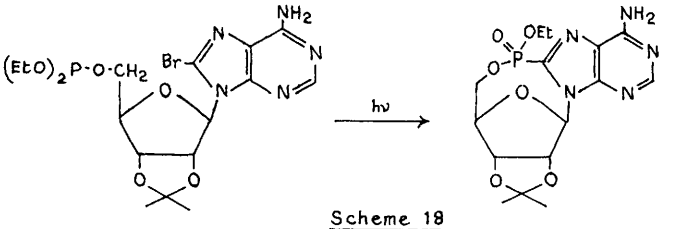


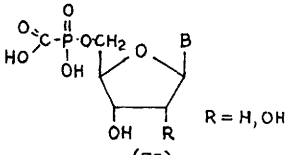
(71)

derivative.[125] Appropriately protected intermediates were ring-opened and deoxygenated to give 1'-phosphonomethyl derivatives of arabinofuranosyl- and deoxyribofuranosyluracil.[126] When tri-O-acetyl-8-bromoadenosine was photolysed in the presence of triethyl phosphate, the 8-(diethylphosphono)adenosine was formed, and an intramolecular version of this reaction was also carried out (Scheme 18).[127] The synthesis and antiviral activity of some nucleoside 5'-phosphonoformates (72) have been reported.[128]

The kinetics of hydrolysis of AMP at high temperatures in the pH range 5.9-8.7 have been studied.[129]



Scheme 18



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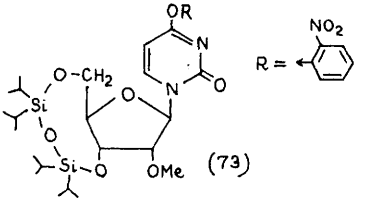


(73)

12 Ethers and Esters of Nucleosides

The $O^{2'}$-methyl ethers of adenosine and uridine have been prepared by the reactions of 2',3'-O-(dibutylstannylene) nucleosides with diazomethane.[130]

$O^{2'}$-Methyluridine, $O^{2'}$-methylcytidine, N^4,$O^{2'}$-dimethylcytidine, and N^4,N^4,$O^{2'}$-trimethylcytidine have been obtained from the common intermediate (73).[131] When ribonucleosides were treated with trimethylsulphonium hydroxide in the presence of magnesium or

calcium ions, selective methylation at O-2' took place, most successfully with 3-alkyluridines.[132]

Separable mixtures of 2'- and 3'-O-(4-methoxybenzyl) nucleosides were obtained through the use of 4-methoxyphenyldiazomethane and stannous chloride,[133] and 2'-O-(3,4-dimethoxybenzyl) nucleosides have been prepared for use in oligonucleotide synthesis; the group can be added selectively in the case of adenosine, or, in the case of N-protected uridine, via the 3',5'-TIPDS derivative.[134] N^2-Phenylacetyl -5'-O-(9-phenylxanthen-9-yl)-2'-deoxyguanosine has been prepared as a crystalline compound suitable for oligonucleotide synthesis.[135]

2'-Deoxy -3'-O-triisopropylsilylribonucleosides have been synthesized by reaction of 5'-O-aryl derivatives with the reagent combination iPr_3SiCl-DMF-pyridine-$Pb(NO_3)_2$, followed by deacylation.[136] The 2',3'-O-TIPDS derivative of ara-uridine has been prepared, and shown not to be mutually interconvertible with its 3',5'-isomer.[137] A study has been made on the formation and stability of 3',5'-O-dialkylsilandiyl deoxyribonucleosides.[138]

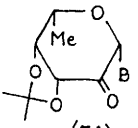
Guanosine and 2'-deoxyguanosine can be acylated in high yield on the sugar unit but not the heterocycle by use of an acid anhydride and DMAP in acetonitrile/triethylamine.[139] 2'-Deoxyribonucleosides have been converted efficiently into their 5'O-aroyl derivatives by treatment in pyridine with a dilute solution of the aroyl chloride in pyridine,[140] whilst in the ribonucleoside series peracylated systems can be selectively unblocked at O-2' and O-3' in yields above 80% by the use of sodium methoxide in THF.[141] Additionally, peraroylated ribonucleosides can be selectively deprotected at O-2' only, using potassium t-butoxide in THF or dichloromethane at low temperatures.[142] Selective acylation of uridine gave 2'- and 2',5'-di--O-acyl derivatives in excellent yields under controlled conditions. The 2'-O-acyl groups migrated to O-3' on silica gel.[143] Treatment of ribonucleosides with dibutyl tin oxide and phenyl isocyanate gave the 3'-O-phenylcarbamoyl system preferentially, whereas the selectivity was for the 2'-oxygen with phenylisocyanate and tertiary amines (see also Vol. 16, p.216).[144]

Three 3'-esters and twelve 5'-esters of 5-ethyl -2'-deoxyuridine have been synthesized as potential antiviral prodrugs. Most were as active as the parent compound, indicating ready hydrolysis.[145]

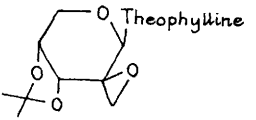
13 Miscellaneous Nucleoside Analogues

Some 5'- and 3'-O-aminonucleosides have been synthesized by methods including the opening of O^2,5'-cyclonucleosides with hydroxyphthalimide.[146] Further UDPG analogues, similar to one reported last year (see Vol.19, p.209), have been described.[147]

The reactions of ketonucleoside (74; B=thyminyl, theophyllinyl) with dimethylsulphoxonium methylide have been investigated. Under certain conditions the α-L-galacto product (75) was produced, indicating epimerization at C-1'.[148]



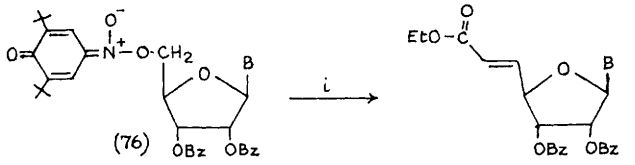
(74)



(75)

14 Reactions

A review (in Japanese) is available concerning regioselective chain extension from the 5'- position of nucleosides.[149] Such compounds are accessible via the aci-nitro esters of type (76), which are prepared by Mitsunobu reaction of the 5'-ol with the p-nitrophenol, on reaction with phosphoranes (Scheme 19).[150]



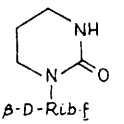
(76)

Reagent: i, $Ph_3P{=}CHCO_2Et$

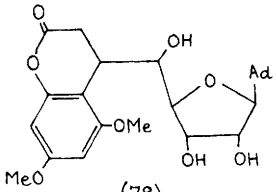
Scheme 19

It has been shown that tetrahydrouridine (77), and other ribofuranosides of fully reduced cyclic ureas, undergo a rapid acid-catalysed isomerization to the β-D-ribopyranosyl isomers, which predominate at equilibrium. In the case of tetrahydrouridine, the pyranose isomer was synthesized by the Vorbrüggen procedure, and shown to be the same as material produced by isomerization of (77).[151]

The 4,4',4"-tris(benzoyloxy)trityl group has been used to protect the amino functions of the bases in deoxyribonucleosides, and it was found that this group confers increased acid stability to the N-glycosyl bond in deoxyadenosine.[152]



(77)



(78)

Further work has been reported on the periodate-borohydride cleavage of guanosine to the triol (see Vol.18, p.205), and the same reaction has been applied to 5'-modified guanosines.[153]

A study has been made of the degradation of adenosine in aqueous alkali, to give ultimately adenine and D-ribose.[154] As part of a detailed kinetic study, 5-bromouridine was found to give with aqueous alkalis some 6,5'-anhydro-6-hydroxyuridine, which then decomposed to non-chromophoric products; the major course of the reaction was ring contraction to give 1-β-D-ribofuranosyl-2-oxo-4-imidazoline-4- carboxylic acid.[155] β-D-Arabino- and β-D-lyxofuranosyluracil react with aqueous alkali much more rapidly than does uridine, and the mechanism of decomposition seems to involve participation of the 'up' 2'-hydroxy group.[156] The rates and products of aqueous degradation of ara-cytidine and 5-azacytidine have been studied.[157]

A further report has appeared on the reaction of the antitumour agent N^2-methyl-9-hydroxyellipticinium acetate with nucleosides and nucleotides (see Vol.19, p.209).[158] In work designed to model the skin-sensitization reaction of psoralens(furocoumarins), the photoadduct (78) was identified as a product of photolysis of adenosine and 5,7-dimethoxycoumarin.[159]

In connection with work on the mechanism of action of cisplatin, the first example has been found of a facile reaction between thymidine and substituted thymidines and a cis-platinum (II) complex to give an adduct characterized by ^{31}P and ^{1}H n.m.r. methods.[160]

15 Spectroscopic and Conformational Studies

F.t.-i.r. and laser Raman spectra have been recorded for cytosine and cytidine; comparison of the spectra permitted identification of bands characteristic of the sugar and of the pyrimidine.[161] A similar study has been done on guanine and guanosine.[162]

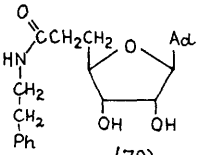
From an analysis of ^{13}C chemical shifts and $^{1}J_{CH}$ values for a series of β-D-nucleosides, it has been shown that the sugar carbons and the configuration of the 2'-hydroxy group can be unambiguously assigned.[163] Somewhat similar criteria have been used to determine the configuration of 2'-deoxyfuranosyl C-nucleosides, [164] and ^{1}H n.m.r. has been used for assigment of configuration to carbocyclic analogues of 2'-deoxyribo-C- and N-nucleosides.[165]

The conformation of 4-O-ethyl -2'-deoxythymidine has been studied by ^{1}H-n.m.r.,[166] and 8-bromo -2',3'-O-isopropylideneadenosine has been shown to have a rigid syn-conformation in apolar solvents due to an OH-5'→N-3 hydrogen bond, on the basis of ^{1}H-n.m.r. studies.[167] The solution conformations of deoxynucleotidyl (3'→5') arabinofuranosyl nucleosides have been studied by n.m.r.,[168] whilst the conformational mobility of deoxynucleosides has been investigated using solid-state ^{2}H-n.m.r. of the 2'-dideuterio derivatives (Scheme 10).[52]

The ^{13}C-n.m.r. spectrum of wyosine and some N-methyl derivatives has been assigned.[169]

A study of the mass spectra of halonucleosides has permitted differentiation between positions of halogenation,[170] and the mass spectral fragmentation of trimethylsilyated nucleoside 5'- phosphoramidates has been elucidated and compared with the patterns of the 3'-isomers.[171] Negative-ion FAB mass spectra have been used to identify products and impurities during the synthesis of nucleoside 3'-phosphoramidites.[172] Further references to mass spectrometry of nucleosides are given in Chapter 22.

U.v., c.d., and ^{1}H n.m.r. spectroscopy were used to study stacking interactions in (79; Ar = Ph or indol-3yl), models of aminoacyladenylates, to provide insights into the substrate specificities of t-RNA synthetases.[173]



(79)

Studies of the solution ordering of guanosine -2'-monophosphate dianions, with alkali metal ion as structure directors, support the stacked tetramer model for nucleoside ordering.[174]

X-ray structures of nucleosides are mentioned in Chapter 22.

Some structures with similarity to nucleosides are referred to in Chapters 10 and 11.

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21

N.M.R. Spectroscopy and Conformational Features

1. Theoretical and general considerations

Reviews on high resolution solid state ^{13}C-n.m.r. spectroscopy and its application in carbohydrate chemistry[1] and on 2D n.m.r. techniques for structure analysis of carbohydrates[2] have appeared.

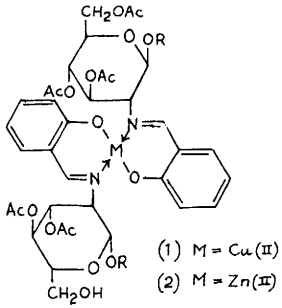
Empirical force field calculations on the simplest acyclic diols show that there is a tendency for 1,2-diols to adopt the gauche O-C-C-O conformations. In protic media, these conformations are stabilized by specific activation.[3] The stereochemical properties of the glycosidic linkages in flexible pyranose rings have been studied by PCILO quantum chemical methods. The energies of thirty six conformers were calculated, as were the influences of solvent on the equilibrium and hence the magnitude of the exo-anomeric effect. The calculations showed that the exo-anomeric effect is in the range 5.9 - 9.1 kJ mol^{-1} for an isolated molecule, which is lowered by a factor between 3 and 4 in aqueous solution.[4] The barriers to pseudorotation in 2-deoxy-2-fluororibofuranose and deoxyribofuranose as models for nucleosides have been calculated by ab initio methods, the former being shown to have a higher barrier between the N and S states, and to prefer the N-state due to internal hydrogen bonding between the fluorine and 3-hydroxy group.[5] A detailed theoretical determination of the dynamics and energetics of the pseudorotation cycle of D-ribofuranose has been carried out; the relative energy of different conformations was found to be primarily determined by the torsional energy terms.[6] A method for determining furanose ring coordinates in the pseudorotational circuit for different amplitudes of pucker has been devised using geometries generated by a procedure based on ring closure and the empirical dependence of endocyclic bond lengths and angles on the amplitude of the pucker.[7] Conformational energy calculations on oligosaccharides using various methods have enabled a comparison to be made, and led to a strategy for such calculations. Several conformers exist in complex equilibrium in oligosaccharides which were best described by the MM2CARB method.[8]

The COLOC n.m.r. technique for assignment of signals by correlation of long-range couplings has been applied to some acetyl and trityl derivatives of glucose, glucal, glucuronic acid, and sucrose.[9]

A pattern recognition technique, using a readily available computer program, has been demonstrated for assignment of carbohydrate structure from ^{13}C-n.m.r. data for sixteen isomeric glycosides with arabino, ribo, gluco, or galacto configurations.[10]

Configuration-dependent conformational transmission in trigonal bipyramidal phosphorus(V) compounds enhances the gauche (-) conformation population around the C-5 - C-6 linkage in phosphorylated tetramethyl-α-D-galactopyranoside.[11]

Solid state ^{13}C-n.m.r. by the c.p.-m.a.s. technique has been used to study the metal-sugar complexes (1) and (2). Related copper(II) complexes of Schiff's bases from chitosan were also studied.[12]



(1) M = Cu(II)
(2) M = Zn(II)

^{13}C-N.m.r. spectroscopy of ^{13}C-enriched D-idose in deuterium oxide showed the presence of the α- and β-furanoses and pyranoses as well as the aldehydo-form and its hydrate. The proportions were found to be 13.5% α-furanose, 16.5% β-furanose, 35.9% α-pyranose, 33.4% β-pyranose, 0.5% aldehydo hydrate, and 0.1% free aldehyde.[13]

2. Acyclic systems

The differentiation of threo- and erythro-isomers of 1-substituted glycerol obtained by thermodynamically controlled isopropylidenation has been achieved by observation of $\Delta\delta$ values for the acetal methyl groups in ^{1}H n.m.r. spectra; for terminal isopropylidene $\Delta\delta$ is $\geqslant$ 0.05 p.p.m., since only one methyl group is shielded by the chairs, whereas for the α-threo isopropylidene group $\Delta\delta \leqslant 0.05$. The values of $\Delta\delta$ were obtained for twenty-eight alditol isopropylidene derivatives.[14] Observed coupling constants for protons in tetritol and

hexitol peracetates have been compared with those calculated by molecular mechanics and a generalized Karplus equation. It was concluded that these methods were useful in the determination of stereochemistry in such flexible fragments.[15] Stability constants of complexes of mannitol hexanitrate and tert-pentyl alcohol with pyridine and its derivatives were determined by n.m.r. methods.[16] ^{1}H-N.m.r. spectra of six heptitols in deuterium oxide have been determined at 400 MHz.[17] A 1,3-parallel interaction between C-2 and O-5 detected in a heptitol by X-ray analysis (see Chapter 22, ref. 26a) is also present in solution according to ^{1}H n.m.r., and on re-examination of other heptitols several showed similar interactions, leading to a reassessment of their conformations; contrary to accepted views, C//O interactions can be more favourable than O//O.[18]

3. Furanose systems

The mode of interaction of copper(II) and manganese(II) with D-ribose and D-arabinose has been studied by ^{13}C-n.m.r. spectroscopy. Specific line-broadening effects were used to determine the principal sites of chelation, which were found to be the cis-diol at C-1 and C-2 of α-D-ribofuranose with copper(II). In the other cases the results were not unambiguous.[19] Chemical shifts of methyl groups in di-O-isopropylidene furanoses in ^{1}H- and ^{13}C-n.m.r. spectra have been examined to find whether they reflect molecular conformation and site of ring fusion. No reasonable correlation was discovered, but through measurements of ^{13}C spin lattice relaxation times a number of noteworthy motional characteristics related to overall molecular tumbling, hydrogen bonding, and internal mobility were detected.[20]

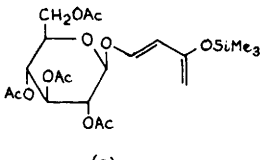
It has been shown from a study of the ^{1}H- and ^{13}C-n.m.r. spectra of eleven furanosyl 2'-deoxy-C-nucleosides with the β-D-erythro-, α-D-erythro-, and β-D-threo-configurations that the configuration may be deduced using a combination of coupling constant and chemical shift data.[21] Conformations deduced from n.m.r. parameters of the flexible mono-nucleotides 5'-adenosine monophosphate and 5'-guanosine monophosphate in aqueous solution have been critically reviewed.[22] ^{13}C-N.m.r. data on eighteen nucleosides has been analyzed. Signals due to C-2' and C-3' were examined, and it was shown that C-2' is always downfield relative to the C-3' signal.[23] Conformational assignments of 4-O-ethyl-2'-deoxythymidine from ^{1}H-n.m.r.

data have been correlated with those from an X-ray study.[24] Some observations on ^{13}C-n.m.r. assignments of the pentofuranose part of β-nucleosides showed that δ and carbon-hydrogen one-bond coupling constants can be used to assign sugar carbon atoms and the configuration of the 2'-hydroxy group, as well as the location of ester, methoxy or halogen substituents on the sugar ring. Some forty β-D-purine and pyrimidine nucleosides were examined.[25] Assignments of ribose ^{13}C-resonances of puromycin and its analogues have been made using 2D techniques.[26] N.m.r. studies on deoxy-sugars are mentioned in Chapter 12.

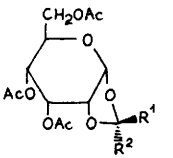
4. Pyranose systems

1,5-Anhydro-D-glucitol has been studied by 2D ^{1}H- and ^{13}C-n.m.r. spectroscopy and its conformation deduced.[27]

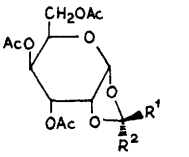
All isomers of tetra-O-acetyl-D-glucopyranose and the corresponding monobenzyl and monotrityl ethers have been synthesized and their ^{1}H- and ^{13}C-n.m.r. spectra completely assigned.[28] The exo-anomeric effect in the glucosyl diene (3), which determines its diastereofacial discrimination, has been probed by n.O.e. differences in ^{1}H-n.m.r. spectra.[29] Examination of the ^{1}H-n.m.r. spectra of



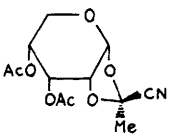
(3)



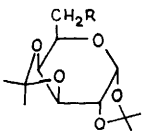
(4) $R^1 = H, R^2 = Me$
$R^1 = Me, R^2 = H$
$R^1 = CN, R^2 = Me$



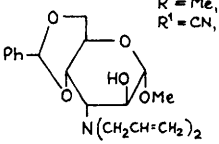
(5) $R^1 = OBu^t, R^2 = Me$
$R^1 = CN, R^2 = Me$
$R^1 = H, R^2 = Me$
$R^1 = Me, R^2 = H$



(6)



(7) R = OH, OMe, I



(8)

the 4-O-acetyl groups of 6-O-tritylaldohexopyranose derivatives of the gluco, manno, and galacto series shows that there are differences in their diamagnetic shieldings attributed to rotational isomerization about the C-5 - C-6 bond. The study was facilitated by use of deuterium labels in the acetyl groups, in methyl ether groups, and in the 6S position, which enable couplings between H-5, H-6, and H-6'

and the separate signals due to H-6(*R*) and H-6(*S*) to be identified.[30] The conformations of peracetylated 1,2-*O*-alkylidene-allo-, -gulo-, and ribo-pyranose derivatives, (4), (5) and (6) respectively, have been examined by ^{1}H-n.m.r. spectroscopy and shown to be skew in all cases.[31,32] The conformations of 1,2:3,4-di-*O*-isopropylidene-galactose derivatives (7) determined by ^{1}H-n.m.r. spectroscopy have been compared with *X*-ray crystal data and molecular mechanics calculations.[33]

A flexible twist-boat conformation has been assigned to methyl 4,6-*O*-benzylidene-3-deoxy-3-dialkylamino-α-D-altropyranoside (8) in $CDCl_3$ on the basis of ^{1}H-n.m.r. spectroscopy at 350 MHz. Evidence that[3] this is due to an intramolecular hydrogen bond between the nitrogen and the hydroxy group on C-2 was obtained when the $^4C_1$(D) conformation was adopted in the H-bond breaking solvent DMSO. In the absence of the benzylidene ring, the evidence suggests that the $^1C_4$(D) conformation is preferred.[34]

^{1}H.m.r. evidence indicates a 1:3 metal to sugar ratio in europium-(III) and dysprosium(III) complexes with sodium (methyl and benzyl α-D-galactopyranosid)uronate, which may be relevant to the gelation of polysaccharides in the presence of metal ions.[35]

5. Oligosaccharides and related compounds

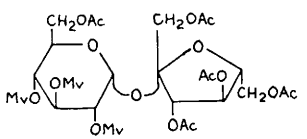
Inter-residue heteronuclear negative n.O.e. have been observed between hydrogen atoms and carbon atoms at the bridging points of oligosaccharides, and their use in oligosaccharide sequencing suggested.[36]

The 2D-n.m.r. spectroscopic technique has been applied to methyl β-xylobioside.[37] Heteronuclear RELAY 2D n.m.r. has been used to achieve ^{13}C-line assignments in methyl 2-(β-D-xylopyranosyl)-β-D-xylopyranoside pentakis(trimethylsilyl)ether.[38]

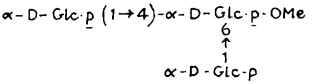
An investigation has been carried out into the scope and limitations of secondary isotope multiplet n.m.r. spectroscopy of partially labelled entities (SIMPLE) in its application to the glucodisaccharides α,α-trenalose, sophorose, kojibiose, laminaribiose, gentiobiose, and isomaltose. Each linkage gives rise to a unique pattern of ^{13}C isotopomers, which, in principle, may be used for complete assignment of the spectra and structural analysis. Assignments in aqueous solution were obtained using the differential isotope shift method in conjunction with SIMPLE, and the spectra were often simplified by the degeneracy caused by the presence of two glucose residues. In practice, nearly all signals could be assigned with

the remainder being choices between two possible assignments.[39] ^{13}C-N.m.r. spectra of some benzoylated derivatives of cellobiose, lactose, and maltose have been reported.[40] N.O.e. enhancement in methyl β-maltoside, resulting from irradiation of H-1' of the non-reducing glucose residue, was measured and calculated theoretically. Comparison of the data revealed a complicated conformational equilibrium in aqueous solution; the two most feasible conformations proposed either involve hydrophobic interactions between C-H bonds or suggest an extended conformation similar to that in maltose derivatives indicated by X-ray crystal analysis.[41] Structural assignments of 2-O-β-D-GlcpUA-D-Manp and 6-O-β-D-GlcpVA-D-Galp (fragments of apricot tree gum) have been made on the basis of ^{13}C-n.m.r. data.[42] Computer assisted analysis of ^{1}H-n.m.r. spectra of peracetylated galactose-containing oligosaccharides has been reported.[43]

Complete n.m.r. assignments for α-D-GalNAc-(1→3)-D-GalNAc and β-D-Gal-(1→4)-β-D-GlcNAc-(1→6)-D-GalNAc have been made using 2D correlation (COSY, RELAY-COSY, and F_1-decoupled) together with high resolution unidimensional n.m.r. spectroscopy at 500 MHz.[44] Inter-residue shielding and Δδ effects in 3-amino-3-deoxy-α-D-altropyranosyl 3-amino-3-deoxy-α-D-altropyranoside have been examined.[45] ^{13}C-N.m.r. spin-lattice relaxation times and n.O.e. enhancements measured under different conditions for sucrose in deuterium oxide have been used to determine the frequency dependence and amplitude of the rotational spectral density function, and hence the influence of the rotational components of vibrational modes. Local torsional and vibrational motions were also determined.[46] Complete assignment of the ^{1}H- and ^{13}C-n.m.r. spectra of sucrose octa-acetate has been achieved by concerted use of homo- and hetero-nuclear 2D n.m.r., including heteronuclear shift correlation via one bond and long-range couplings.[47] The positions of (+)-(3S)-methylvaleryl groups in the peracylated sucrose (9) have been confirmed by using long-range internuclear shift correlation 2D n.m.r. spectroscopy for the carbonyl carbon atoms and the acyl group protons with the ring protons.[48] Application of the SIMPLE n.m.r. method to



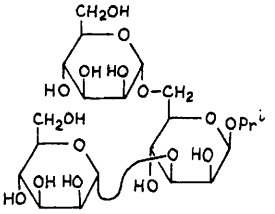
(9) Mv = $Bu^{s}CH_2CO$



(10)

O-3' derivatives of sucrose in DMSO-d_6 revealed the presence not only of the intramolecular hydrogen bond of the 1-hydroxy group of fructose to the 2-hydroxy group of glucose in 3,3',4',6'-tetra-O-acetylsucrose but also of an extensive hydrogen bond network in the glucose residue of 3',6'-di-O-benzoylsucrose.[49,50]

The structure of a saponin, including the sequence of its per-acetylated α-L-Ara(1→2)-β-D-Glc-(1→2)-α-L-Ara moiety, has been determined using ^{1}H-n.m.r. spectroscopy only, with normal unidimensional, 2D COSY, and 2D long-range COSY experiments being sufficient.[51] The n.m.r. parameters of the branch-point trisaccharide of amylopectin (10) have been assigned using 2D ^{1}H-n.m.r. spectroscopy at 500 MHz. Similar data was obtained for methyl β-D-maltoside and -isomaltoside.[52] Specifically deuterated derivatives of β-isopropyl mannotrioside (11) have been synthesized and used to demonstrate unequivocally a disputed inter-residue n.O.e. enhancement between H-5 on the α-mannose linked to the β-mannose at O-3 and the H-2 on the β-mannose.[53] A galactose trisaccharide (12) has been characterized by 2D J-resolved COSY ^{1}H-n.m.r. spectroscopy.[54]



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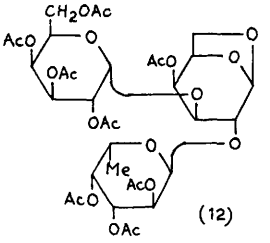


(12)

A tetrasaccharide unit from the saponins Camellidin-I and -II, β-D-Glc-(1→2)-β-D-Gal-(1→4)-[α-D-Gal-(1→2)]-β-D-GlcA, has been characterized without degradation by a combination of modern n.m.r. techniques.[55] The oligosaccharides obtained by endo-β-galactosidase treatment of keratan sulphate, which include di-, tri-, tetra-, and hexa-saccharides, have been characterized by 500 MHz ^{1}H-n.m.r. spectroscopy using COSY and spin-decoupling.[56] A conformational analysis of the branched pentasaccharide sequence (13)

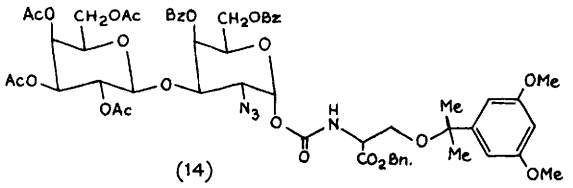
α-D-Man-p-(1→3)-[β-D-Glc-pNAc-(1→4)]-[α-D-Man-p-(1→6)]-β-D-Man-p-(1→4)-D-GlcNAc

(13)

in the core structure of bisected type of N-glycoproteins has been carried out by n.m.r. spectroscopy and GESA calculations.[57] ^{1}H-N.m.r. assignments for G_{m1}-oligosaccharide in deuterium oxide using

2D-SECSY techniques at 500 MHz have been made.[58]

The structure of a glycopeptide (14), obtained by a rearrangement during attempted glycosylation of N-Ddz serine benzyl ester, has been determined by the COLOC technique.[59] The structure determination of peracetylated glycosphingolipids by unidimensional and 2D ^{1}H-n.m.r. techniques at 360 and 500 MHz has been reported. The studies confirm that peracetylated oligosaccharides are particularly well suited for such techniques.[60] Pure absorption and RELAY experiments have been found to be particularly useful for establishing connectivities in poorly resolved regions of the spectra of glycolipids. The techniques were applied to an octasaccharide obtained from the spermatozoa of a bivalve which was shown to contain an internal fucopyranosyl residue, a terminal xylosyl residue, and 4-O-methylglucopyranosyluronic acid groups (see also Chapter 4).[61] Two-dimensional ^{1}H-n.m.r. spectroscopic studies on digitoxose[62] and neomycin B[63] have been reported.



(14)

6 N.m.r. of nuclei other than ^{1}H or ^{13}C

The complexes between borate and cyclohexane cis-1,2-diol, cis,cis-1,3,3-triol, myo- and epi-inositol have been investigated using ^{11}B-n.m.r. spectroscopy.[64] An aqueous solution of sucrose has been subjected to a ^{17}O-n.m.r. spectroscopic study in which spin-lattice and transverse relaxation times were determined. Solutions of concentrations from 0 - 70% and at temperatures between 305 and 370K were analyzed, and correlations of n.m.r. data with viscosity and concentration made to determine the number of associated water molecules. The results were consistent with a solvent shell of sixteen water molecules.[65]

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22
Other Physical Methods

1 I.r. Spectroscopy

I.r. and Raman spectra of α- and β-D-glucose and 5-C-deuterated derivatives have been measured on solid-state samples and predictive rules for C-H stretching modes proposed.[1] F.t.i.r. and ^{13}C-n.m.r. c.p.-m.a.s. ('solid state') spectroscopy and differential thermal analysis has been used to study the structure of sucrose in the amorphous state (i.e., non-crystalline material obtained from a quenched-melt or through freeze drying) and in 10-70% w/w aqueous solution. Evidence was obtained for disruption of hydrogen bonding involving the fructose unit.[2] Bands characteristic of the sugar and the base unit have been identified from comparative F.t.i.r. and laser-Raman spectroscopy of cytosine and cytidine [3] and of guanosine and guanine.[4]

2 Mass Spectrometry

Fast atom bombardment (FAB) m.s. of glucose and sucrose in the presence of various metal complexes have been studied. Potassium hexacyano ferrate(II) gave useful $[M+K]^+$ ions.[5] Components of the polyoxins, a fermentation-produced complex of nucleoside peptide antibiotics, have been identified by FAB m.s. following separation by h.p.l.c.[6] The FAB m.s. of the natural ribo- and deoxyribo-nucleosides and -nucleotides and some cytosine analogues have been investigated. The use of the negative ion mode reduced interference from positive counter-ions (e.g., Na^+) and permitted rapid sequence determination of simple di- and tri-nucleotides.[7]

Molecular secondary ion m.s. of the constituent pentasaccharide viridopentaoses of the antibiotic sporaviridin gave informative sugar sequence ions in addition to molecular ions.[8] A comparative study on the application of desorption c.i.-m.s. and secondary ion m.s. to aminoglycoside antibiotics has shown that such materials containing an aminoacyl group can be unequivocally characterized by

a combination of these techniques.[9]

The presence of molecular ions from field desorption (f.d.)-m.s. of glucose and sucrose is taken to indicate that these sugars are volatile, and a mechanism for ion formation is discussed.[10] It has been claimed, however, that molecular ions seen by others are not f.d., the ionization of sucrose, raffinose, and stachyose particularly under f.d. conditions being discussed.[11]

The g.c.-m.s. identification of aldoses and their O-methyl ethers, deoxy- and acylaminodeoxy-hexoses, in mixtures as their per-acetylated O-methyloxime derivatives, has been reported,[12] as have the m.s. of per-O-trimethylsilylated oxime derivatives of mono-saccharides and galacturonic acid [13] and seventeen peracetylated methyl acetamidodeoxy- and acetamidodideoxy-hexopyranosides.[14] A study of the m.s. of acylated glycosylamines, in particular N-nitrobenzoyl glucopyranosylamine acetates, has emphasized the influence of the nitro-group on fragmentation.[15] The e.i.-m.s. fragmentation of 2-methylthio(glyco)oxazoline derivatives of pentoses and hexoses has been studied using labelled compounds, evidence supporting the expected structures of these compounds being obtained.[16] G.c.-m.s. data has been reported on partially methylated and acetylated derivatives of 3-deoxy-octitols, and rules given for their fragmentation in e.i.-m.s., in connection with the analysis of KDO units and their stereoisomers.[17] In-beam e.i.-m.s. of nucleosides has given protonated molecular peaks more abundant than in conventional spectra.[18]

In the c.i.-m.s. of mono- and di-saccharides and cycloalkanediols using trimethylborate as reagent gas, the reagent reacts with 1,2-cis-diol moieties to give characteristic ions, allowing stereo-isomers to be distinguished.[19] Anomeric hexoside tetraacetates have been examined by e.i.- and c.i. (CH_4, i-C_4H_{10}, and NH_3)-m.s. While practically no fragmentation was observed with NH_3-c.i., minor differences in relative intensities of common ions between spectra of anomeric pairs were enhanced by CH_4- and i-C_4H_{10}-c.i., and in the absence of thermal decompositions the β-anomers show greater intensities of glycosyl ions.[20] The behaviour of ions generated in c.i.-m.s. of methyl (methyl O-methyl-α-D-mannopyrano-sid)uronates under severe or mild gas-phase protolysis depended upon the position of the methoxy-groups on the pyranose ring. Under severe conditions, the main fragmentation involved sequential loss of the C-1 and C-3 or C-4 substituents.[21] Negative ion c.i.-m.s. using a mixed CH_4-CH_2Cl_2 reagent gas has been exemplified with

nucleoside samples.[22]

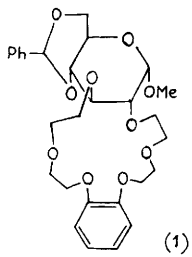
A combined h.p.l.c.-m.s. technique with thermospray ionization has been used for microscale structural studies on mono- and di-saccharides, methyl glycosides, and permethylated mono- to tetra-saccharides. The technique employs a reversed-phase column with aqueous ammonium formate as eluent, generates abundant $M+NH_4^+$ ions, and is suitable for monitoring sub-nanogram quantities, e.g., 0.5 pmol of methyl hexopyranosides.[23] Preliminary results have been reported on the application of this technique to glucose, maltose, and corn starch hydrolyzate components eluted from a reversed-phase column with water, with ammonium acetate added post-column as the c.i.-reagent.[24]

3 X-ray Crystallography

The x-ray analysis of a number of 3- and 4-O-trityl ether derivatives of pyranose 1,2-orthoesters and one methyl glycoside has confirmed the steric accessibility of the reaction centre in glycosylation reactions.[25] The crystal structure of a complex between galacturonic acid and tryptophan methyl ester [i.e., $(TyrOMe)_4.(\alpha\text{-GalA})(\beta\text{-GalA})(HCl)_3(H_2O)_2$] has been studied as a model for sugar-peptide interactions in biological systems. Hydrophobic bilayers of amino acid sandwich sugar monolayers containing strongly bound sugar dimers.[26] A crystal structure of D-glycero-L-allo-heptitol indicates the presence of a 1,3-parallel interaction between C-2 and O-5, an interaction hitherto considered unlikely;[26a] an n.m.r. study on this and related heptitols is covered in Chapter 21.

Specific crystal structures have been reported as follows: Free Sugars and Simple Derivatives Thereof.- Sodium α-D-gluco-pyranose 6-phosphate,[27] dipotassium β-D-fructofuranose 6-phosphate,[28] trisodium β-D-fructofuranose 1,6-diphosphate octahydrate,[29] 1,2,3,4,6,7-hexa-O-acetyl-L-glycero-β-D-manno-heptopyranose,[30] 1,2:3,4-di-O-isopropylidene-6-O-tosyl-α-D-gluco-pyranose,[31] 3,4,6-tri-O-acetyl-1,2-O-(S)-exo-ethylidene-α-D-allo-pyranose,[32] 3,4,6-tri-O-acetyl-1,2-O-(R)-(1-cyanoethylidene)-α-D-gluco- and galacto-pyranose,[33] 3,4-di-O-acetyl-1,2-O-(S)-(1-cyano-ethylidene)-α-D-ribopyranose,[34] 3-O-acetyl-1,2-O-[1-(exo-cyano)-ethylidene]-β-L-rhamnopyranose,[35] and the 3-O-acetyl-4-O-trityl- and 4-O-acetyl-3-O-trityl- derivatives of 1,2-O-[1-(exo-cyano)-ethylidene]-β-L-arabinopyranose.[36]

Glycosides and Derivatives Thereof.- Methyl β-L-arabinopyranoside,[37] isopropyl 1-thio-β-D-galactopyranoside,[38] methyl 2,3,4-tri-O-acetyl-β-D-xylopyranoside,[39] rhizolotine (a β-D-ribofuranosyloxy tetrahydropyrimidine derivative),[40] 3β-O-(2',3'-O-isopropylidene-α-L-rhamnopyranosyl)digitoxigenin,[41] methyl 2,6-di-O-methyl-3,4-O-thiocarbonyl-β-D-galactopyranoside and methyl 2-O-methyl-3,4-O-thiocarbonyl-β-L-arbinopyranoside,[42] and the 18-crown-6 compound (1) incorporating a methyl α-D-glucoside moiety.[43]



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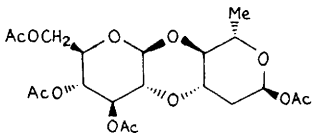


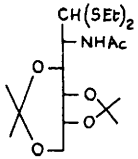
(2)

Di- and Tri-saccharides and Derivatives Thereof.- α-Laminaribiose (i.e., β-D-Glcp-(1 → 3)-α-D-Glcp) octaacetate,[44] galabiose (i.e., α-D-Galp-(1 → 4)-α+β-D-Galp),[45] 4-O-β-D-galactopyranosyl-α-D-mannopyranose,[46] the sweetener neohesperidin dihydrochalcone (a phenolic glycoside containing a α-L-Rhap-(1 → 2)-β-D-Glcp-moiety),[47] the trehalose derivative 6-O-mesyl-2,3,4-tri-O-methyl-α-D-glucopyranosyl 6-O-mesyl-2,3,4-tri-O-methyl-α-D-glucopyranoside and its β,β-anomer,[48] α-wilforibiose tetraacetate (2) (a derivative of a novel disaccharide isolated from hydrolysis of a natural glycoside),[49] 3,6-anhydro-4-O-β-D-galactopyranosyl-D-galactose dimethyl acetal hexaacetate (a derivative of the carrageenan fragment, carrabiose),[50] mannotriose (i.e., β-D-Manp-(1 → 4)-β-D-Manp-(1 → 4)-α-D-Manp. $3H_2O$),[51] and methyl α-maltotrioside tetrahydrate (with three α-(1 → 4)-linkages).[52]

Anhydro-sugars.- 2,3,5-Tri-O-acetyl-1,6-anhydro-α-D-galactofuranose [53] and methyl 2,6-anhydro-3-azido-4-O-benzoyl-3-deoxy-α-D-idopyranoside.[54]

Halogen-, Nitrogen-, and Sulphur-containing Compounds.- 3-Deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose,[55] 2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride,[56] 3,5-O-(R)-benzylidene-6-deoxy-6-iodo

-1,2-O-isopropylidene-α-D-glucofuranose,[57] 2-amino-2,6-dideoxy-α-D-glucopyranose 6-sulphonic acid,[58] 5-acetamido-5-deoxy-1,2:7,8-di-O-isopropylidene-3-O-methylthiomethyl-β-L-erythro-L-talo-octofuranose,[59] the 2-acetamido-3,6:4,5-di-O-isopropylidene-D-glucose derivative (3),[60] the D-xylosylamine derivative (4),[61] the 2-amino-2-deoxy-D-glycero-α-D-galacto-heptofuranosylamine derivative (5)[62] and its 2-amino-2-deoxy-α-L-galactofuranosylamine tri-O-acetate[63] and N-phenyl 2-amino-2-deoxy-D-glycero-α-D-talo-heptofuranosylamine tetra-O-acetate[64] analogues, the peracetylated derivatives of 1-deoxy-1-nitro-β-D-glucopyranose, 2-acetamido-1,2-dideoxy-1-nitro-α-D-glucopyranose, and 1-deoxy-1-nitro-β-D-galacto- and ribofuranose,[65] 1,2-dideoxy-1-nitro-D-arabino-hex-1-enopyranose,[66] and



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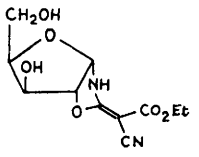
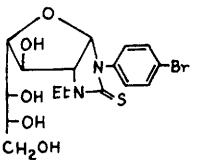


(4)



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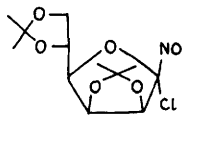
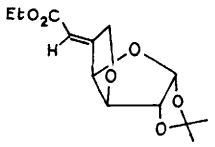


(6)

the chloronitroso compound (6).[67]

Unsaturated Compounds.- The 5-C-ethoxycarbonylmethylene-hexofuranurono-6,3-lactone (7).[68]



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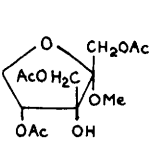

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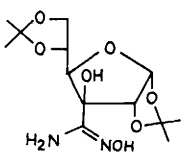

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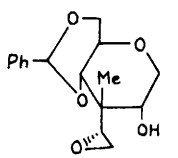

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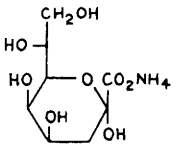

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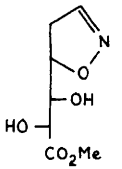

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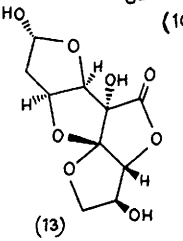
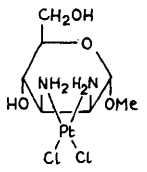


(13)

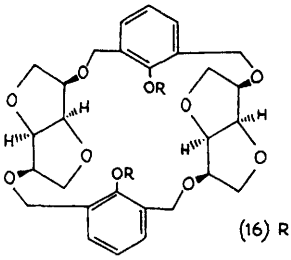
Branch-Chain Sugars.- The racemic 3-C-acetoxymethyl-α-erythropentuloside (8),[69] the α-hydroxyamidoxime (9),[70] and the gem-dialkylated anhydroalditol (10).[71]

Sugar Acid Derivatives.- n-Octyl D-gluconate (and a study of its thermal crystal-crystal transition and melting behaviour),[72] N-(n-octyl)-D-gluconamide,[73] N-(n-decyl)-D-ribonamide,[74] ammonium 3-deoxy-D-manno-octulosonate (11) (although some confusion over the anomeric configuration is evident in the report),[75] the racemic 2-deoxy-penturonic acid derivative (12),[76] methyl β-D-glucofuranosid-urono-6,3-lactone, its 2-O-acetyl-5-O-pivaloyl derivative, and 5-O-pivaloyl-β-D-glucofuranurono-6,3-lactone,[77] the tetraacetate of dehydroascorbic acid dimer,[78] and the adduct (13) from L-ascorbic acid and fumaric dialdehyde.[79]

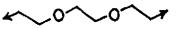
Inorganic Derivatives.- The platinum(II) complex (14) with a 2,3-diamino-2,3-dideoxy-α-D-mannoside.[80]



(14)



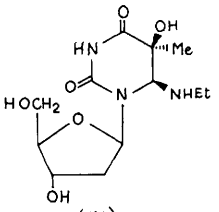
(15) R = Me

(16) R = 

Alditols and Derivatives Thereof.- 1,3:2,5:4,6-Tri-O-methylidene-D-mannitol,[81] 1-O-[bis(diethylamido)thionophosphate]-2,4:3,5-bis[O-(diethylamino)thionophosphate]ribitol,[82] 1-amino-1-deoxy-N-methyl-N-nonanoyl-D-glucitol,[83] 2,5-anhydro-L-iditol,[84] the crown ethers (15)[85] and (16)[86] incorporating two 1,4:3,6-dianhydro-D-mannitol units, an analogous crown ether containing a pyridine moiety,[87] DL-(1,3,5/2,4)-1,2,3,4-tetra-acetoxy-5-(acetoxymethyl)cyclohexane (i.e., pseudo-β-DL-glucopyranose pentaacetate),[88] and a 1:1 adduct of caffeine with potassium chlorogenate.[89]

Nucleosides, Nucleotides, and Derivatives.- 2',3',5'-Tri-O-acetyl-adenosine[90] and -guanosine,[91] 4-O-ethyl-thymidine,[92] N^6-methyl-2'-deoxyadenosine,[93] 5-methoxymethyl-2'-deoxy-uridine[94] and its β-D-threo-isomer,[95] 5-fluoroarabinosylcytosine,[96] the 2'-deoxynucleoside (17),[97] cis-thymidine 3',5'-cyclic methyl phosphonate[98] and the corresponding 3',5'-cyclic N,N-dimethylphosphoramidate,[99] a cobalt(II) complex with 2'-deoxyinosine 5'-monophosphate,[100] 2,2'-anhydro-1-β-D-arabinofuranosyl-6-methyluracil,[101] (6,2'-anhydro

-1-β-D-arabinofuranosyl)-6-ethyl-uracil,[102] (5'-O-acetyl-6,3'-anhydro-2'-deoxy-1-β-D-xylofuranosyl)-6-methyl-uracil,[103] methyl 2,3'-anhydro-1-β-D-fructofuranosylorotate (18),[104] the Bacillus megaterium produced antibiotic oxetanocin (19),[105] and neplanocin C (20).[106]



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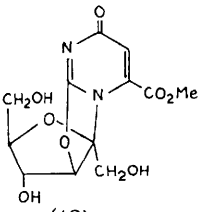

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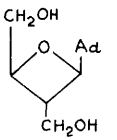

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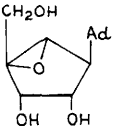

(20)

4 E.s.r. Spectroscopy

A review with 145 references on spin-labelled carbohydrates, including mono-, di-, and poly-saccharides, glycoproteins and nucleosides, has appeared.[107]

Glycosyl radicals produced by reaction of various alkylated and acylated glycosyl derivatives (1-Br, -SePh, or -C(O)Bu^t) with tin(II) derivatives have been examined by e.s.r. Preferred conformations were assigned and rationalized. Pyranosyl radicals were concluded to exist as almost planar π-type alkoxyalkyl radicals.[108] Carbohydrate radicals at C-2, C-3, and C-4 of pyranosyl compounds were similarly generated by dehalogenation, and shown to have the same conformations as the parent compounds.[109]

Aldonolactones have been shown to react with hydroxyl radical preferentially at C-2, but other reactions take place.[110] The nature of the stable free radicals in X-irradiated single crystals of sucrose has been re-examined using ENDOR spectroscopy complemented by X- and Q-band e.s.r. measurements. At least two radicals have been detected and assigned, one definitely a structure of type $RCO\dot{C}HCH_2OH$ resulting from opening of the glucose and fructose rings.[111] Oxidation of L-ascorbic acid by a nitroxide radical has been studied kinetically by e.s.r., an oxidation intermediate being observed.[112]

5 Polarimetry, Circular Dichroism, and Related Studies

The c.d. spectra of five 1,5-anhydroalditols and their 2-deoxy- and

2,3-dideoxy-analogues (as models for glucose and galactose) have been studied in aqueous solution. Difference spectra revealed the contributions of certain functional groups.[113] An o.r.d. and c.d. technique has been developed to determine the absolute configuration of the diacyl-*sn*-glycero moiety and the anomeric form of the D-carbohydrate moiety in monoglucosyldiacyl-*sn*-glycerols. A sample isolated from *Acholeplasma laidwil* was found to be 1,2-dioleoyl-3-*O*-α-D-glucopyranosyl-*sn*-glycerol.[114] The signs of two extrema (of opposite signs) in the 219-245 nm range in the c.d. spectra of the diethyldithioacetal derivatives of 14 carbohydrates, including 2,6-diamino-2,6-dideoxy-D-glucose and D-ribose, were correlated with the absolute configuration at C-2. Solvent dependence of the observed c.d. curves was ascribed to solvent-induced conformational changes on the basis of n.m.r. evidence.[115]

It has been shown that C-H stretching vibrational circular dichroism for sugars in aqueous solution can be understood in terms of vibrationally generated ring currents due to intramolecular association, *i.e.*, cooperative hydrogen bonding rings, or alkyl-π or alkyl-lone pair interactions. Spectra for D-glucose (and its 1-d_1, 2-d_1, and 6,6-d_2 labelled modifications), D-mannose, D-gulose, D-xylose and L-sorbose were recorded.[116]

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23
Separatory and Analytical Methods

1 Chromatographic Methods

General.- Reviews have appeared on the chromatography of mono- and di-saccharides, covering p.c., t.l.c., g.c., and h.p.l.c.,[1] and on profiling carbohydrates, glycoproteins and glycolipids in body fluids and tissues, covering t.l.c., g.c., h.p.l.c., and electrophoresis.[22]

Gas-Liquid Chromatography.- Unless otherwise stated, all analyses were performed on capillary g.c. columns.

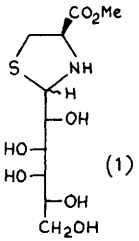
The preparation and identification by g.c.-m.s. of partially methylated and acetylated 3-deoxy-octitols from mono- and oligo-saccharide derivatives of KDO (3-deoxy-D-manno-2-octulosonic acid) has been detailed.[3] Hakamori methylation of 2-acetamido-2-deoxy-D-glucitol has been shown to generate mainly the 2-(N-methyl-acetamido)-penta-O-methyl-derivative, but also to cause C-methylation to give a small amount of the corresponding 2-(N-methyl-propionamido)-analogue.[4] For the simultaneous analysis of amino and neutral sugars as their alditol acetate derivatives on a packed column, the conventional preparation of derivatives was modified to include the conversion of aminoalditols to N,N-dimethylaminoalditols by reductive amination ($NaBH_3CN$-HCHO).[5] Reduction of sugar O-methyloxime derivatives (with $NaBH_3CN$) yielded deoxy(methoxyamino)-alditols which were suitable after trimethylsilylation or acetylation for g.c. analysis.[6] Permethylated deoxy(N-methyl-N-methoxyamino)alditol glycosides were obtained from reducing disaccharides in the same way, but including a final Hakamori methylation step. They were shown to be suitable for selective assays using a nitrogen-phosphorus detector (with $\sim$5 x greater response than an f.i.d. detector) and to have characteristic e.i.-m.s. fragmentation patterns.[7]

The identification of permethylated sugar acids and sugar phosphates by g.c.-m.s. has been assisted by transesterification with sodium ethoxide. Methyl ester groups were thus changed to

ethyl ester groups, and the number of negatively charged groups identified by comparison of the m.s. data. D-Glucose 6-phosphate, for example, was converted to penta-O-methyl-D-glucitol 6-(dimethyl -phosphate) and thence into the diethylphosphate derivative.[8] KDO units in polysaccharides have been determined following methanolysis and trifluoroacetylation, methanolysis conditions being optimized to provide primarily a single methyl ketopyranoside methyl ester.[9]

Anomeric pairs of peracetylated alkyl and aryl glycosides have been separated by g.c. on a packed column.[10]

The absolute configuration of rhamnose, fucose, xylose, mannose, galactose and glucose, released from a complex polysaccharide and isolated by cellulose column fractionation, have been determined by g.c.-m.s. of their acetylated (-)-2-octyl glycoside derivatives.[11] In a new approach, enantiomeric pairs of nine aldoses have been separated after reaction with L-cysteine methyl ester to generate diastereoisomeric methyl 2-(polyhydroxyalkyl)thiazolidine-(4R)-carboxylates, e.g., the D-galactose derivative (1), and pertrimethylsilylation. Each enantiomer gave a single peak, compared to the four observed for the (-)-2-octyl glycosides.[12]



(1)

Pertrimethylsilylation-g.c.-m.s. has been used to determine free and lipid-bound alditols, cyclitols, and monosaccharides present in nerves of uraemic and non-uraemic patients [13] and nucleosides released enzymically from DNA damaged in their base moieties by free radical reactions, especially with •OH radicals.[14] Nine polyhydroxyalkaloids, e.g., 1,5-dideoxy-1,5-imino-alditols, have been separated on packed columns as their trimethylsilylated derivatives.[15]

The oxime derivatives prepared from galactose, glucose, and mannose, by treatment with a premixed reagent [NH_2OH-Me_3Si•imidazole or NH_2OH-$(Me_3Si)_2NH$-CF_3CO_2H], chromatographed as well separated single peaks on a packed column, whereas stepwise derivatization led to unresolved peaks.[16] Mixtures of 2-acetamido-2-deoxy-D-glucose and -galactose and their corresponding alditols, produced during

the analysis of the N-linked oligosaccharides of glycoproteins cleaved by alkaline borohydride, have been separated on a packed column by conversion of the free sugars to O-methyloxime derivatives prior to acetylation or trimethylsilylation.[17] The relative retention of related sugar O-methyloxime derivatives was also detailed. Products from the radiolysis of aqueous D-fructose solutions, which include D-arabino-hexos-2-ulose as the major component, have been analyzed as their trimethylsilylated O-benzyloxime derivatives.[18]

Thin Layer Chromatography.- The preparative separation of glucose oligomers (DP 1-7) from corn starch hydrolyzate on a centrifugally accelerated silica gel t.l.c. apparatus (a Chromatotron) was used to demonstrate the improved separating ability of plates dried at 70°C while being continuously rotated for use with highly polar solvents (in this case EtOAc-MeOH-H_2O, 104:72:26).[19] Ten branched cyclodextrins, i.e., mono- to tri-glycosylated, have been examined on primary amine bonded silica t.l.c. plates.[20] A method for the complete separation of amino-sugars in polysaccharide hydrolyzates by t.l.c. on silica plates (using MeCN-AcOH-EtOH-H_2O, 13:1:2:4) has been described.[21]

High Pressure Liquid Chromatography.- Reviews on the analysis of sugars by h.p.l.c., in which packings and detection techniques are discussed (258 refs.),[22] and on the advantages and limitations of several separation and detection techniques for sugars, including adsorption, partition, and ion-exchange chromatography (36 refs.),[23] have been published.

Post-column derivatization of reducing sugars with ethylenediamine in a weakly alkaline medium at 150°C generates compounds detectable down to ca. 1 pmol by electrochemical oxidation. This procedure was recommended over an earlier reaction involving 2-cyanoacetamide (Vol.18, p.240) because the response varied less with sugar structure.[24] Electrically neutral carbohydrates can be detected by conductivity by using a boric acid solution as an h.p.l.c. eluent to form borate complexes. Detection limits were in the 10^{-5} M range, and applications in food analysis were described.[25] Mono- to oligo-saccharides, after separation by ion-exchange h.p.l.c. using an alkaline eluent, have been detected by oxidation at a nickel(III) oxide electrode, with a ∿20 ppb detection limit for monosaccharides and ∿100 ppb for oligosaccharides.[26] A

combined h.p.l.c.-thermospray m.s. technique for microscale (e.g., subnanogram) structural studies of mono- and di-saccharides, methyl glycosides, and permethyl ethers of mono- to tetra-saccharides used aqueous ammonium formate as eluent for reversed-phase h.p.l.c.[27] Microbore h.p.l.c. (1 mm i.d. column with primary amine bonded silica packing), with a moving wire flame ionization detector, has been demonstrated with the separation and detection of xylose, glucose, sucrose, maltose, and lactose, with detection limits of ∿1-400 ng.[28]

The separation of common mono- and di-saccharides by h.p.l.c. on vinylpyridinium polymers bearing N-H, N-methyl or N-butyl moieties and a variety of counterions has been investigated. Best results were attained with the N-methylated polymer in the phosphate form, some useful separations being reported.[29] A commercial Ag^+-form cation-exchange resin column (polystyrene based, 6% cross-linked) has been shown to be suitable for the analysis of mono- and di-saccharides. Residual sulphonic acid groups on the column partially hydrolyze sucrose oligosaccharides at temperatures >25°C, but this was overcome by using a Pb^{2+}-modified column prepared by regeneration using a small percentage of $PbNO_3$ in aqueous $AgNO_3$. An improved analysis of sugars in food was achieved using series connected Ag^+/Pb^{2+}- followed by Pb^{2+}-form columns of different percentage cross-linking, but certain co-elution problems were still encountered.[30] The α- and β-anomers of glucose, xylose, galactose, mannose, arabinose, maltose, and cellobiose have been separated on a Ca^{2+}-form exchange resin column with water as eluent at 1.5°C, the anomers bearing a 1,2-cis-diol unit being retarded due to complex formation.[31] A procedure for the quantitative estimation of glucose, fructose, and sucrose in beet extracts by h.p.l.c. has been reported.[32]

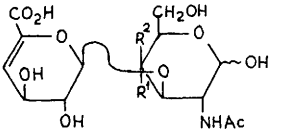
D- and L-Cymarose, which co-occur in certain natural glycosides, have been resolved following sequential methanolysis and O-carbamoylation (with 3,5-dinitrophenylisocyanate), on a Sumipax OA-1000 column (presumably with a chiral phase), although only the pyranoside enantiomers, which were minor constituents of the product mixture, were resolved.[33] Peracetylated alkyl and aryl glycoside anomers have been separated by normal-phase or preferably reversed-phase h.p.l.c.[10] Saponins, synthetic glycosides including isomeric methyl xylosides, arabinosides and some disaccharides, and steviol glycosides have been analyzed on a polyvinylalcohol-based ion-exchange column with $-\overset{+}{N}HEt_2$ as the basic group and borate in

aqueous acetonitrile (pH 8-8.5) as eluent at 75°C.[34] The retention of cardiac glycosides on reversed-phase h.p.l.c. has been described by the additive contributions of the steroid and sugar units.[35] Teniposide, a semisynthetic 4,6-*O*-(2-thienylidene)-β-D-gluco-pyranoside of a podophyllotoxin derivative, has been assayed in human serum by reversed-phase h.p.l.c. with electrochemical detection.[36]

Useful separations of oligosaccharides have been achieved using reversed-phase h.p.l.c. Malto-oligosaccharides were separated up to DP 9 with water as eluent, better resolution being attained at lower temperatures (down to 5°C). Retention was significantly influenced by silica pore size and alkyl chain length, decreasing in the order $C_{18}>C_8>C_6$. Some commercial columns performed better than others, but all gave separate peaks for anomers even up to 55°C. Separations of di-D-fructose dianhydrides were also reported.[37] The performance of five commercial reversed-phase columns, four silica- and one polystyrene-based, for the separation of malto-, cello-, isomalto-, and cyclo-dextrins up to DP 8 has been evaluated.[38] The separation of ten mono- to tri-glycosylated cyclodextrins has been examined on reversed-phase, primary amine-bonded silica, and polyvinylalcohol-based columns.[20] A Pb^{2+}-form polystyrene-based ion-exchange column has been used to separate mono- and oligo-saccharides (up to DP 4) from enzymically degraded xylan, arabinan, galactan and cellulose.[39] A combination of gel chromatography and reversed-phase h.p.l.c. has been used to map the reduced oligosaccharides released from mucus glycoproteins.[40] Isomeric mono- to tetra-sialylated oligosaccharides (up to DP ∿21) from the hydrazinolysis of α_1-acid glycoprotein have been separated according to charge by semipreparative h.p.l.c. on a quaternary ammonium-bonded silica column and independent fractionation of the resulting four groups on primary amine-bonded silica with a KH_2PO_4 buffered eluent containing an amine modifier.[41]

Free *N*-acetylneuraminic acid in urine has been determined on a cation exchange column with an acidic eluent in connection with monitoring for sialuria, a group of diseases characterized by elevated excretion of this amino-sugar.[42] *N*-Acetyl- and *N*-glycolyl-neuraminic acids released from serum and urine samples by hydrolysis have been determined down to ∿12 pg, permitting the analysis of 5 µl samples, by reversed-phase h.p.l.c. after derivatization with 1,2-diamino-4,5-dimethoxybenzene (a reagent for α-keto-acids), and fluorimetric detection.[43] The unsaturated non-sulphated

disaccharides (2) and (3), which, having glucosamine and galactosamine at the reducing end, can be released enzymically from hyaluronic acid and chondroitin, respectively, were efficiently separated on a Na^+-form polystyrene-based sulphonic acid ion-exchange column.[44]



(2) R^1=OH, R^2=H
(3) R^1=H, R^2=OH

D-arabino-Hexos-2-ulose and other products from the radiolysis of aqueous D-fructose solutions have been analyzed as their O-benzyloxime derivatives on a silica column.[18] N-(1-Deoxy-hexitol-1-yl) amino acids, produced by sequential acid hydrolysis and borohydride reduction of 'glycated' proteins, have been chromatographed on a cation-exchange column, and detected using a periodate reaction.[45]

Inositol bis- and tris-phosphates and other sugar phosphates have been separated on an anion-exchange column and subjected to post-column hydrolysis by immobilized alkaline phosphatase with detection of the liberated inorganic phosphate to <1 nmol using a molybdate reagent.[46]

In connection with a study of the oxidation of glucosyl phosphate over a platinum catalyst, glucose, glucuronic acid, gluconic acid, glucaric acid, α-D-glucopyranosyl phosphate and α-D-glucopyranuronic acid 1-phosphate have been analyzed by ion-moderated partition chromatography, using an H^+-form cation-exchange resin and an acidic eluent (aq. CF_3CO_2H) in which the phosphate moieties are fully protonated. Glucosyl phosphate, D-glucose 6-phosphate and D-fructose 6-phosphate were not separated by this system.[47] A very similar system has been used to analyze sugar acids and their lactones under conditions where they do not equilibrate. The method was used to monitor the base hydrolysis of an aldonolactone, to determine the equilibrium position for a uronic acid and its lactone, and to study the conversion of an aldonic acid into its various lactone forms.[48] Reversed-phase h.p.l.c. coupled to a post-column enzyme reactor containing immobilized β-glucuronidase and subsequent electrochemical detection has been evaluated using glucuronide conjugates of benzazepine drugs.[49] Derivatization of glucuronides with 4-bromomethyl-7-methoxycoumarin yields ester derivatives suitable for reversed-phase separation with u.v.-

detection down to ∿10 pmol, as demonstrated with menthol glucuronide.[50]

The 1-alkylthio-2-alkyl-isoindole derivatives formed from the components of the aminoglycoside antibiotic complex gentamicin on reaction with o-phthalaldehyde-mercaptoacetic acid have been shown to be unstable in the acidic conditions required for their elution from a reversed-phase column. Procedures were elaborated to minimize this problem.[51] The analysis on a silica column of neomycin sulphate as its per-N-(2-naphthalenesulphonyl)-derivative, shown by FAB-m.s. to be substituted on all 6 primary amine groups, was compared to alternative h.p.l.c., g.c. and microbiological analyses.[52] An improved ion-pair reversed-phase analysis for the components of tylosin, a macrolide antibiotic complex with varied glycosidic moieties, has been reported.[53] Ion-pair reversed-phase analyses have also been reported for the antiherpes drugs (E)-5-(2-bromovinyl)-2'-deoxyuridine [54] and 5-fluoro-2'-deoxycytidine, 5-trifluoromethyl-2'-deoxycytidine, and their related antimetabolites.[55] Reversed-phase analyses for the antineoplatic agents cytarabine (1-β-D-arabinofuranosylcytosine), 5-azacytidine and their degradation products,[56] and for the polyoxins, a group of nucleoside peptide antifungal agents,[57] have been reported.

A number of papers on the reversed-phase h.p.l.c. analysis of nucleosides, nucleotides and their constituent bases have appeared. Different mechanisms have been indicated for the retention of guanine, hypoxanthine, and their nucleosides and nucleotides at low and high temperatures.[58] Because purine nucleotides are poorly retained on the reversed-phase columns used to separate the bases and nucleosides, a column switching technique was used to transfer the early eluted nucleotides onto a weak anion-exchange column for analysis.[59] A silica-bound phenylboronic acid column was used to concentrate ribonucleosides in physiological fluids, the nucleosides being eluted directly onto an h.p.l.c. column for analysis by changing from an alkaline to an acidic eluent.[60] Other analyses were of adenosine, inosine and hypoxanthine in human placenta,[61] of picomole quantities of 'modified' nucleosides which mostly stem from transfer RNA breakdown, in sera and urine of cancer patients,[62] and of pyrimidine nucleosides, bases, and related compounds in serum following derivatization (N-alkylation in the base) with 4-bromomethyl-7-methoxycoumarin and using fluorimetric detection (to 50-150 pg of nucleoside).[63] Different ion-pair reagents, tetrabutylammonium phosphate or C_5-C_8 alkylsulphonic acids, have been

applied to the reversed-phase analysis of certain biochemically relevant nucleosides, nucleotides and bases.[64]

Column Chromatography.- The diffusion coefficients of glucose in a gel type and a macroreticular type anion-exchange resin have been determined, and diffusion of carbohydrates in such resins has been discussed.[65] A re-working of previously published data on the effect of increasing on-column sugar concentrations on the bonding of glucose and fructose to Ca^{2+}-form cation-exchange resins (Vol.18, p.244, ref.74) has revealed a much less pronounced effect than originally suggested.[66]

The preparative gel chromatography of oligosaccharides containing uronic acid moieties from graded hydrolysis of Rhizobium exo-polysaccharides using a volatile buffer (aq. HCO_2H-MeCN) as eluent has been detailed, the effect of eluent pH being noted.[67] A uronic acid specific carbazole-sulphuric acid reagent has been described for use in a post-column detector system in the gel chromatography of proteoglycans.[68]

An amino acid analyzer has been used to monitor the Maillard reaction of model deoxyfructosyl-lysines and related 'glycated' natural proteins.[69]

Paper and Partition Chromatography.- Good but slow separations of isomeric pentitols and hexitols have been obtained on O-(carboxymethyl)cellulose paper in the calcium, barium or preferably the lanthanum form.[70]

Centrifugal partition chromatography, which operates on a similar basis to droplet counter-current chromatography but with centrifugally driven droplets, has been applied to the preparative separation of hydrolyzable tannins, e.g., polygalloyl glucoses.[71]

2 Electrophoresis

A recently developed thin-layer electrophoresis system which employs silanized silica gel with a 1-octanol surface coating as support, and aqueous borate as buffer, has been examined for the separation of mono-, oligo-, and poly-saccharides as well as phenolic compounds and other degradation products from the hydrolythermolysis of biomass. As expected, mobility depended upon the ability to complex with borate. Chemically aggressive reagents could be used to detect the components on this support.[72] Isotachophoretic analysis

of hyaluronate oligosaccharides (up to DP 4) released by enzymic hydrolysis, which have a β-D-glucopyranuronosyl(1 → 3)-2-acetamido-2-deoxy-β-D-glucopyranosyl(1 → 4) repeating unit, has been reported.[73]

3 Other Analytical Methods

Removal of boric acid from solutions of carbohydrates with a boron-selective resin (IRA-743) which has 1-deoxy-1-methylamino-D-glucitol residues covalently linked through nitrogen to a polystyrene matrix has been examined.[74] Highly sensitive assays for glucose (e.g., in serum) have employed immobilized glucose oxidase to generate hydrogen peroxide, which is detected electrochemically.[75,76] Sucrose in sucro-glyceride, a commercial surfactant prepared by reaction of sucrose with glycerides, has been assayed by separation of sucrose from the product (using BuOH-H_2O) and colorimetry using an anthrone-sulphuric acid reagent, the result being verified by t.l.c.[77] A uronic acid specific assay is referred to in the section on Column Chromatography.

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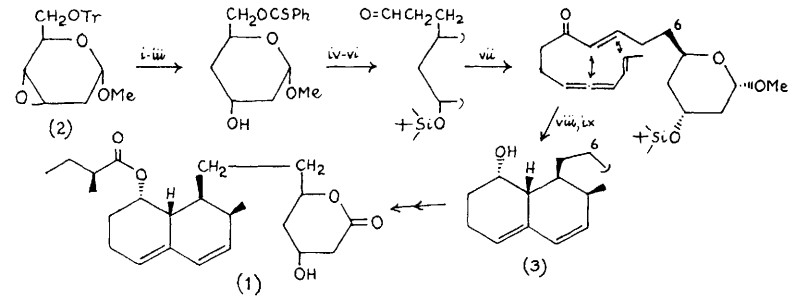
24
Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

A review has been given of the use of (R)- and (S)-2,3-O-isopropylideneglyceraldehyde as chiral precursors to compounds of many different types,[1] and a new convenient large-scale route to the less accessible (S)-isomer has been described, proceeding from L-ascorbic acid via L-gulonolactone.[2]

1 Carbocyclic compounds

A review on the synthesis of mevinic acids such as compactin (1) includes several routes starting from carbohydrates.[3] In a new convergent synthesis of (+)-compactin (1), the known epoxide (2) was manipulated as outlined in Scheme 1; in the key intramolecular Diels-Alder reaction, the desired isomer (3) was produced along with the diastereomer of opposite configuration in the hexahydronaphthalene system.[4]

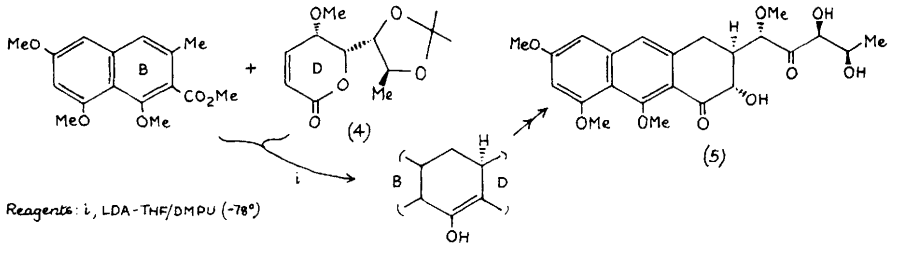


Reagents: i, LAH; ii, Li-NH_3(l); iii, Ph_2OCSCl-Py; iv, CH_2=$CHCH_2SnBu_3$ (hν); v, Bu^tMe_2SiCl; vi, O_3-Me_2S; vii, Wittig reagent; viii, PhMe (140°); ix, $LiBH(Bu^s)_3$

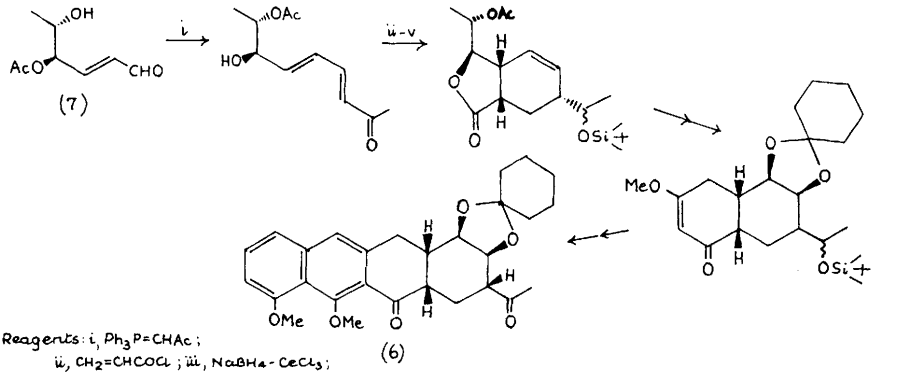
Scheme 1

A Michael reaction-Claisen condensation involving the previously reported intermediate (4) derived from galactose (see Vol. 18, p.256) was a key stage in the first stereoselective synthesis of olivin trimethyl ether (5) (Scheme 2),[5] whilst an intramolecular Diels-Alder reaction established the correct stereochemistry during a synthesis (Scheme 3) of a compound (6)

with the nucleus of the aglycone of (+)-pillaramycinone; the starting material (7) was prepared from diacetyl-L-rhamnal.[6]

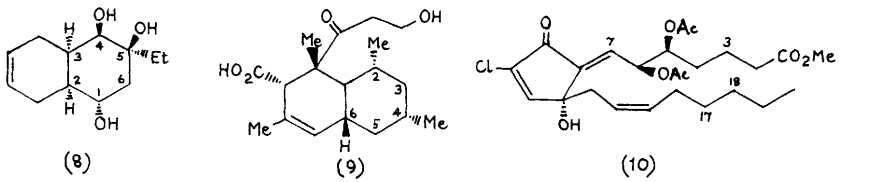


Scheme 2



Scheme 3

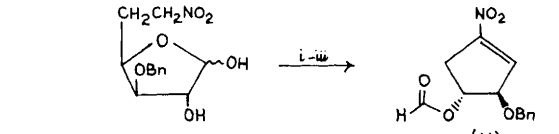
Diels-Alder reaction between a glucose-derived enone and butadiene, followed by Ferrier rearrangement, gave (8) (glucose numbering shown), which corresponds to the AB-ring stereochemistry of β-rhodomycinone.[7]



The bicyclic system of the mycotoxin diplodiatoxin (9) was established by intramolecular Diels-Alder reaction, with the precursor derived in optically pure form from glucose (sugar numbers shown).[8]

In a synthesis of the chlorinated prostanoid punaglandin 4

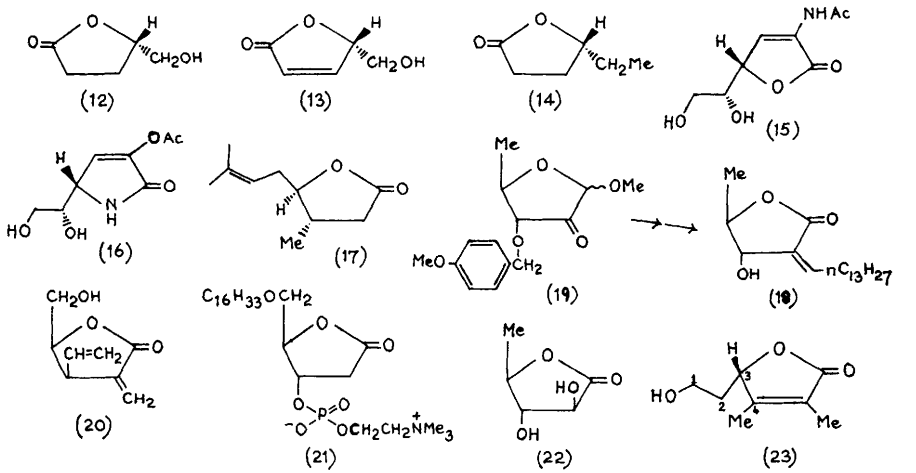
(10), the side-chain stereochemistry was derived from 2-deoxy-D-ribose, C-3 to C-7 corresponding with C-1 to C-5 of the sugar; the 17,18-cis-dehydro compound, punaglandin 3, was also prepared.[9] A potential prostaglandin synthon (11) was prepared, ultimately from glucose, as outlined in Scheme 4,[10] and a full account has been given of the route to a prostacyclin synthon referred to last year (Vol. 19, p.254).[11]



Scheme 4

2 γ- and δ-lactones

The simple chiral building block (12) has been been prepared from D-mannitol, via (R)-isopropylidene glyceraldehyde, using a Wadsworth-Emmons reaction; the unsaturated synthon (13) was also prepared by a variant on the route.[12] Using (12) prepared in a different way, the pheromone (R)-γ-hexanolide (14) was synthesized.[13] An alternative route from isopropylidene glyceraldehyde to (13) has also been reported.[14]

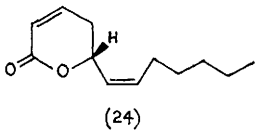


The structure and absolute configuration of the marine metabolite leptosphaerin (15) were confirmed by synthesis from

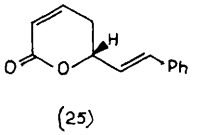
(R)-isopropylidene glyceraldehyde;[15] the alternative structure (16), which could not be excluded on spectroscopic data, was also prepared and shown not to be the natural product.[16] The pheromone (+)-eldanolide (17) has been synthesized from ribonolactone, using cuprate chemistry to introduce the extra carbon atoms.[17]

Litsenolides C_1 (18) and C_2, the E-isomer, have been prepared from glucose by a sequence involving a Wittig reaction of Ketone (19),[18] and the α-methylene-γ-butyrolactone (20) is accessible from isopropylidene-D-glyceraldehyde, using a Claisen rearrangement to establish the vinyl group.[19] Conformationally restricted analogues of the platelet-aggregating factor, such as (21), have been synthesized from 2-deoxyribose; similar tetrahydrofuran analogues were also prepared.[20] The hydroxylated butyrolactone (22) was prepared by oxidative cleavage of the double bond in 3,4-di-O-acetyl-6-deoxy-D-glucal,[21] and the butenolide (23) has been synthesized from 2-deoxy-D-ribose in a multistep sequence (sugar numbering shown).[22]

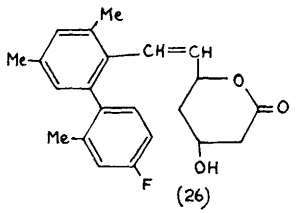
Argentilactone (24) and goniothalamin (25) have been prepared from glucose in multistep sequences; the chiral centre of the lactones corresponds to C-2 of glucose.[23] The HMG-CoA reductase inhibitor (26) has been reported;[24] papers on compactin are mentioned in Section 1.



(24)



(25)

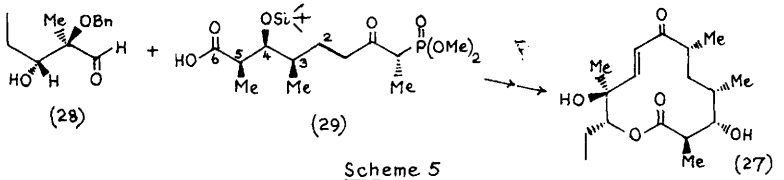


(26)

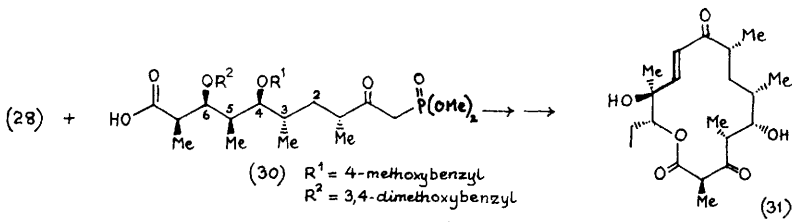
3 Macrolides and their constituent segments

A review on the total synthesis of macrolide antibiotics includes discussion of chiral routes to the aglycones from carbohydrates.[25]

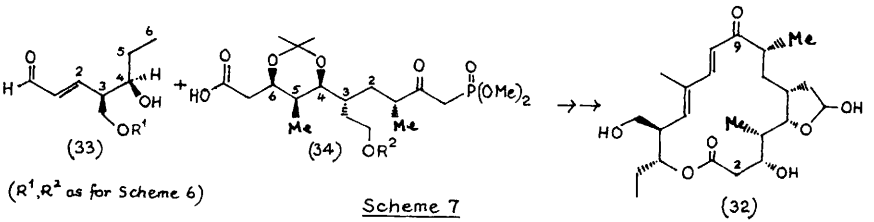
Methynolide (27), the aglycone of methymycin, has been prepared from the hydroxy-aldehyde (28) and the acid (29) by esterification followed by intramolecular Wadsworth-Emmons reaction (Scheme 5);[26] a similar sequence involving (28) and (30) led to pikronolide (31), the aglycone of pikromycin (Scheme 6).[27] The same group have used a similar approach to form tylonolide (32) from the building blocks (33) and (34) (Scheme 7).[28] In the last two sequences,[27,28] the selective removal of the 3,4-dimethoxybenzyl protecting group



Scheme 5



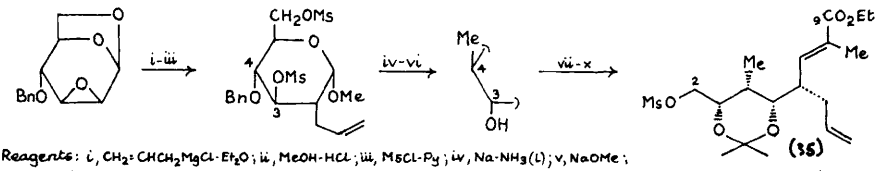
Scheme 6



Scheme 7

with DDQ was essential in the later stages. All the building blocks in Schemes 5-7 were prepared from D-glucose, the sugar numbering being indicated.

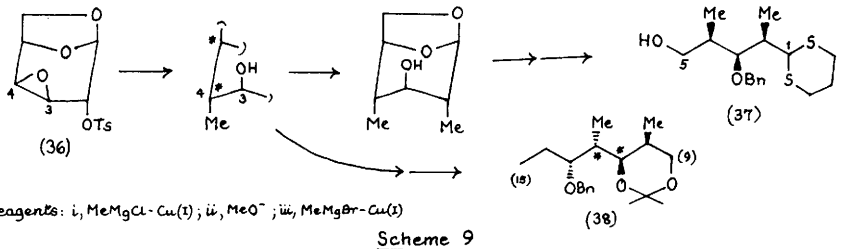
The aglycone of rosaramycin is identical in its 'eastern half' with tylonolide (32). An intermediate (35) representing C-2 to C-9 of (32) has been prepared as outlined in Scheme 8,[29] the starting material shown being a known compound easily accessible from laevoglucosan. Fraser-Reid has used his concept of 'pyranosidic homologation' to synthesize intermediates which also correspond to the 'eastern half' of rosaramycin.[30]



Reagents: i, $CH_2{:}CHCH_2MgCl{\cdot}Et_2O$; ii, MeOH-HCl; iii, MsCl-Py; iv, Na-NH_3(l); v, NaOMe; vi, MeMgCl-CuBr; vii, $HS(CH_2)_3SH$-$BF_3{\cdot}Et_2O$; viii, $Me_2C(OMe)_2$-TsOH; ix, MeI-$CaCO_3$-MeCN/H_2O; x, $Ph_3P{=}C(Me)CO_2Et$

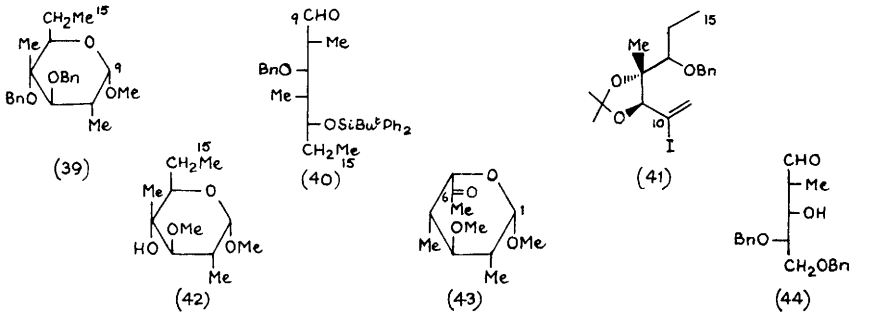
Scheme 8

Further routes to segments of aglycones of the erythromycin group have appeared. The laevoglucosan-derived epoxytosylate (36) was converted into C(1)- C(5) and C(9)- C(15) fragments (37) and (38) of 6-deoxyerythronolide B, as outlined in Scheme 9;[31] similar chemistry was also used to prepare the C(9)- C(15) fragment (39)



Scheme 9

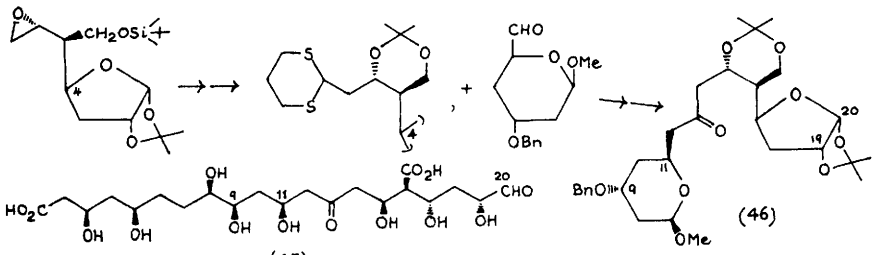
of erythronolide A[32] and a C(9)- C(15) segment (40) of erythronolide B.[33] The C(10)- C(15) segment (41) of erythronolide A has been synthesized from D-ribose,[34] and, in conjunction with other fragments (see Vol. 16, p.151), used for the total synthesis of the aglycone.[35] A C(9)- C(15) segment (42) of erythronolide A



and a C(1)- C(6) segment (43) were both synthesized from glucose via a common intermediate,[36] and the potential macrolide/ionophore synthon (44) has been reported.[37]

A number of glucose-derived compounds have been reported which are stereochemically appropriate for the polyhydroxylic array (45) present in the polyene macrolide amphotericin,[38] and two such units have been linked together about a pivotal carbonyl group to give a compound (46) (Scheme 10) which corresponds to the right hand side of (45).[39]

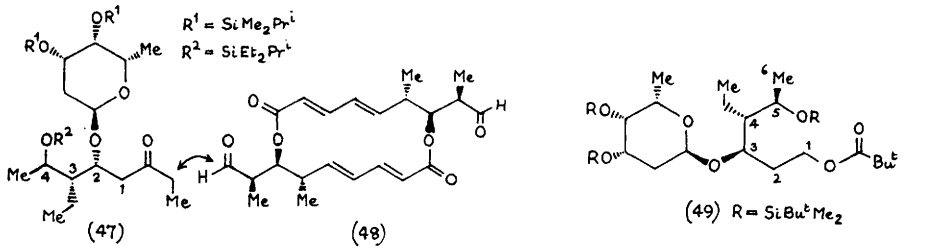
The total synthesis of the 16-membered macrodiolide elaiophilin has been accomplished by a route which involved as a key step the reaction of a boron enolate of (47), derived from glucose (numbers



(45) (46)

Scheme 10

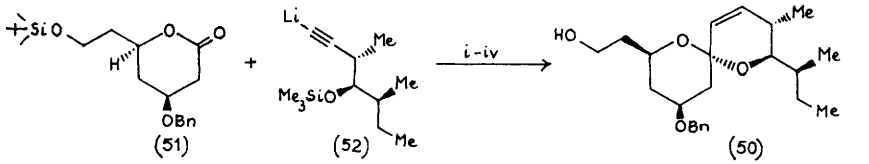
shown), with the dialdehyde (48), produced by Wittig extension of an earlier reported intermediate (Vol.15, p.253-4). In the aldol condensation, other syn-aldol products were also produced.[40] The 'disaccharide' side-chain unit of elaiophilin has also been prepared by other workers in the form of (49) (glucose numbers); the ethyl group was introduced by a copper-catalysed Grignard opening of epoxide (36).[41]



(47) (48) (49) R = $SiBu^tMe_2$

4 Other Oxygen Heterocycles

A synthesis of avermectin B_{1a} has been achieved[42] using the previously reported (S.Hanessian, A. Ugolini, and M. Therein, J. Org. Chem., 1983, 48, 4427) spiroketal unit (50), prepared from the glucose-derived lactone (51) as outlined in Scheme 11; the unit (52) can be derived from glucose, but is best prepared from

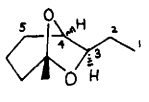


(51) (52) (50)

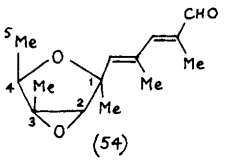
Reagents: i, Mix in Et_2O, -78°, then PPTS; ii, H_2-Pd/$BaSO_4$-C; iii, $BF_3 \cdot Et_2O$; iv, Bu_4NF-THF

Scheme 11

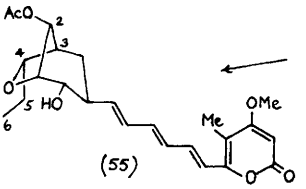
L-isoleucine. A full account has been given[43] of the synthesis of the spiroketal antibiotic A23187 (calcimycin) from glucose (see Vol. 18, p.250-1). Full details have also been reported for the synthesis of a glucose-derived fragment, mentioned last year (Vol. 19, p.256), corresponding to C(9)- C(14) of okadaic acid,[44] and the total synthesis of the complete structure of this marine toxin has been accomplished by linking together sugar-derived building blocks mentioned in earlier volumes.[45]



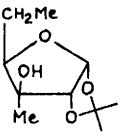
(53)



(54)



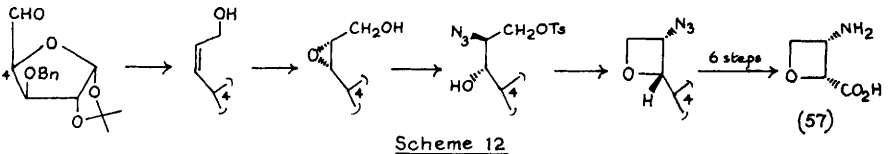
(55)



(56)

A further sugar-based synthesis of the pheromone (+) exo-brevicomin (53) has been carried out, starting from D-xylose (sugar carbons numbered).[46] The degradation product (54) of the neurotoxin verrucosidin has been prepared from D-glucose (numbers indicated); this synthesis confirms the absolute stereochemistry of the natural product and provides a promising synthetic intermediate.[47] A further synthesis of pseudomonic acid C from carbohydrate precursors has been reported,[48] and aurovertin B (55), an inhibitor of ATP synthesis, has been synthesized from D-glucose via the intermediate (56), this synthesis serving to determine unambiguously the absolute configuration of the natural product.[49]

The interesting antibiotic and herbicide oxetin (57) has been prepared from glucose via the multi-step route outlined in Scheme 12. Other stereoisomers of oxetin were also obtained from reaction intermediates, since neither the Wittig reaction nor epoxidation were stereospecific.[50]

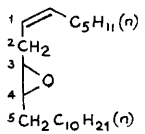


(57)

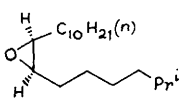
Scheme 12

A number of papers deal with chiral synthesis of epoxides. The pheromone of the ruby tiger moth (58) has been prepared in 10 steps from D-xylose diethyldithioacetal (sugar carbons numbered);[51] a full account has been given[52] of glucose-based routes to both enantiomers of the gypsy moth pheromone disparlure

(see Vol. 19, p.256), and the bioactive (7R, 8S)-isomer (59) has been prepared from D-ribose.[53] The fatty acid metabolite (-)-vernolic acid (60) has been obtained from 2-deoxy-D-glucose (sugar



(58)



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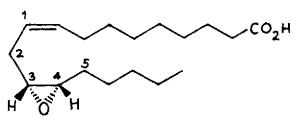
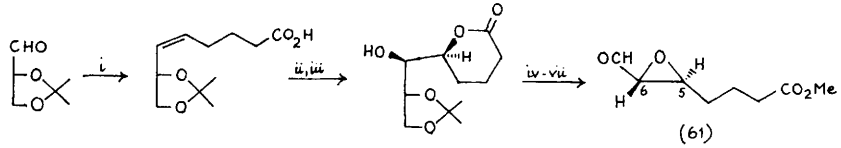


(60)

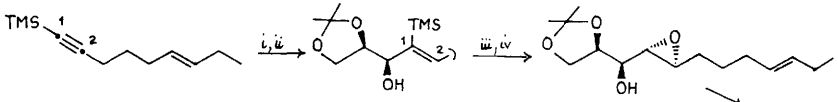
carbons numbered).[54] The important building block (61) of leukotriene A4 has been prepared in two ways from isopropylidene D-glyceraldehyde. In one approach (Scheme 13) hydroxylation according to the Kishi rule is used to establish the stereochemistry of the epoxide,[55] whilst in the other (Scheme 14) a



(61)

Reagents: i, Wittig reagent; ii, OsO_4-NMMO; iii, DCC-DMAP; iv, MsCl-Py; v, OMe^-; vi, AcOH-H_2O; vii, $NaIO_4$

Scheme 13



(61)

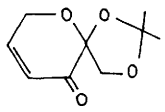
Reagents: i, Bu^iMgBr-$(Cp)_2TiCl_2$, then CuI-Me_2S; ii, Isopropylidene D-glyceraldehyde; iii, Bu^tO_2H-$VO(acac)_2$; iv, Bu^tOH-Bu_4NF

Scheme 14

highly stereoselective addition of a vinyl copper reagent is the key step.[56] The (5S, 6R)- and (5R, 6R)-isomers of (61) have also been prepared from D-xylose.[57]

The spirocyclodihydropyranone (62) and its 3,4-dehydro-5-keto-isomer have been prepared from D-fructose and suggested as potentially useful chiral synthons.[58] The compound (63), prepared by a ring-contraction reaction, has been advocated as a chiral isoprene synthon.[59] The chiral diol (64) can be prepared by the hydrogenolysis of tri-O-acetyl-D-glucal or its allylic rearrangement product,[60] whilst diol (65) has been prepared by dehydration of 2-deoxy-D-aldohexoses, the chiral centre corresponding to C(5) of the sugar.[61]

Papers dealing with sesbanimide are mentioned in the next section.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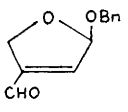
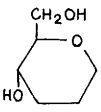
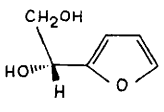
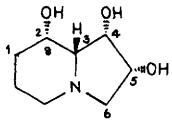

(63)

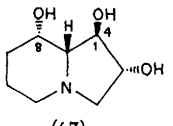

(64)


(65)

5 Nitrogen and Sulphur Heterocycles

(-)-8-Epi-swainsonine (66) has been prepared by a cyclization between N(3) and C(6) of a 3-amino-3-deoxy-D-glucose derivative (glucose numbers exocyclic), and (-)-1,8-di-epi-swainsonine (67) was accessible by including an inversion of configuration at C(4) of the sugar.[62,63] By a somewhat similar sequence starting from a 3-azido-3-deoxy-D-altropyranoside, itself prepared from glucose, (-)-8a-epi-swainsonine (68) was available; this was an α-mannosidase inhibitor, but not such a powerful one as swainsonine itself.[64]


(66)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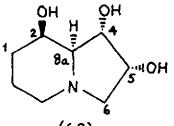
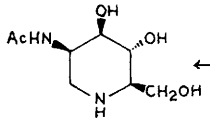
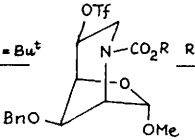
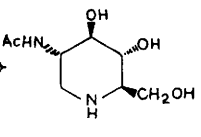

(68)


(71)


(69)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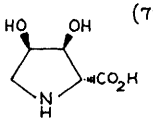
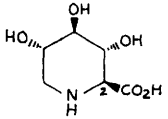
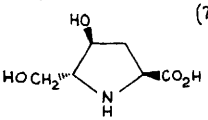
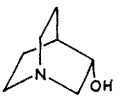

(72)


(73)

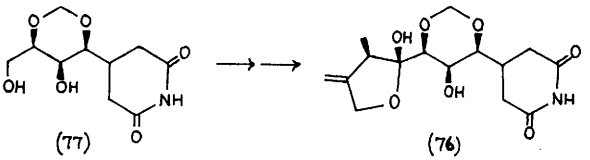

(74)


(75)

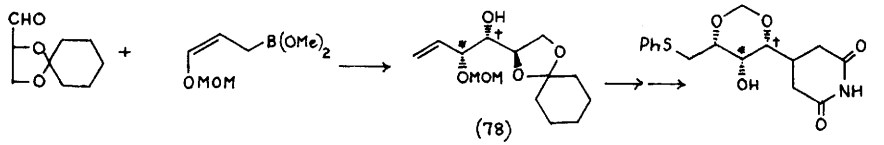
When the triflate (69; R=Bn) was treated with azide ion, inversion of configuration occurred to give a product which was converted to the β-N-acetylglucosaminidase inhibitor (70), whilst (69; R=t-Bu) reacted with azide to give predominantly the product of retention of configuration, and thus ultimately (71).[65] The aminoacid (2R, 3S, 4R)-dihydroxyproline (72) has been prepared from D-ribonolactone by a sequence which also involved an unexpected replacement of triflate by azide with retention.[66] The naturally occurring trihydroxypipecolic acid (73), its (2R)-

isomer, (2S, 4S, 5S)-dihydroxypipecolic acid, and bulgecinine (74) have all been prepared from 1,2-O-isopropylidene-D-glucuronolactone by introduction of nitrogen at C(5) and subsequent cyclization.[67] Two alternative routes have been devised for the preparation of S-quinuclidinol (75) from D-glucose.[68,69]

The potent antitumour agent (+)-sesbanimide A (76), approaches to which have been discussed in the two previous volumes, has finally been synthesized by further manipulation of the intermediate (77), derived from D-xylose, reported last year.[70] The enantiomer of (77), available from D-sorbitol (see Vol. 18, p.252), has been used simultaneously by two groups to produce the unnatural (-)-enantiomer of sesbanimide A;[71,72] prior to these syntheses the absolute configuration of the natural product had remained unknown. An alternative approach to the AB ring system



(77) (76)

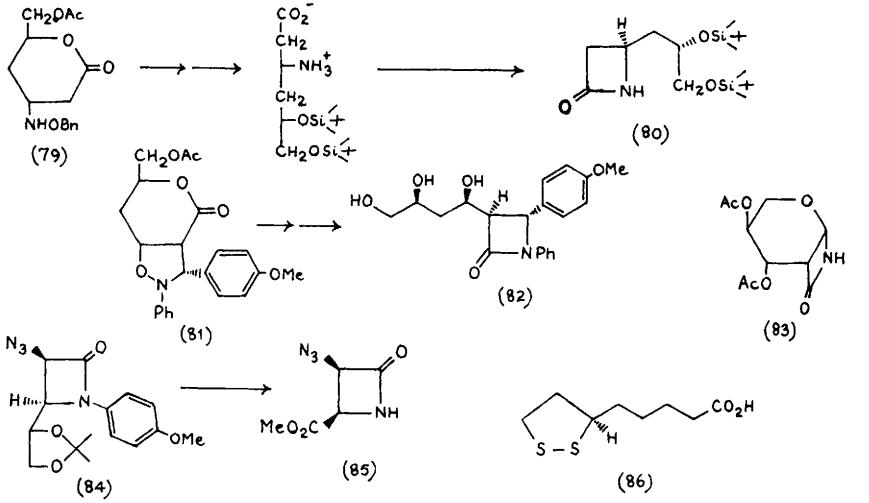


(78)

of sesbanimide (in the enantiomeric series) uses the reaction of an allyl boronate with cyclohexylidene D-glyceraldehyde to generate (78) in a key step.[73] A further route has been reported from D-xylose to the O,O,N-tribenzyl derivative of (77).[74]

Chiral routes to β-lactams from sugars have attracted attention. Michael addition of O-benzyl hydroxylamine to an enone gave (79), which was transformed via the β-aminoacid to β-lactam (80).[75] Alternatively cycloaddition of a nitrone to the same enone gave stereoselectively the adduct (81), which could be converted to (82).[76] Reaction of di-O-acetyl L-xylal with trichloroethyl isocyanate, followed by treatment with Florisil, gave the [2+2] cycloadduct (83), but in low yield; the diastereomer at C(1) and C(2) and a [4+2] cycloadduct were also formed.[77]

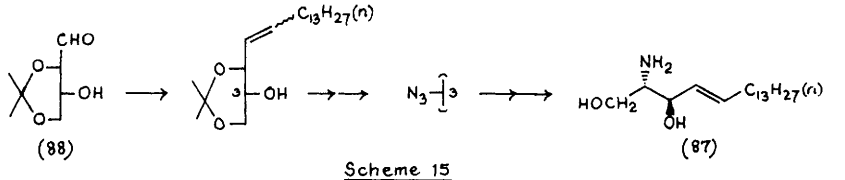
Ketene-imine cyclization, involving an imine of D-glyceraldehyde acetonide, gave rise diastereospecifically to the β-lactam (84), which was converted in several steps to the N-unsubstituted compound (85).[78]



An enantiospecific synthesis of (R)-(+)-lipoic acid (86) from glucose has been presented; the chiral centre in (86) corresponds with C(4) of glucose, with inversion of configuration.[79]

6 Acyclic Compounds

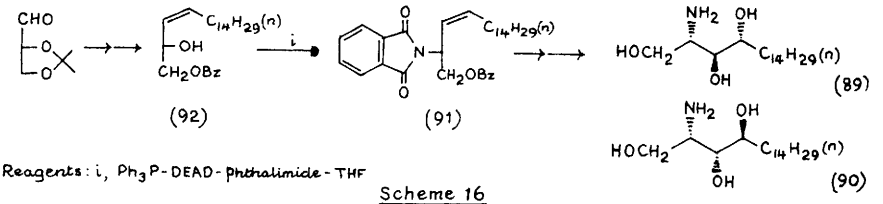
Two groups have independently reported very similar routes (Scheme 15) to D-erythro-sphingosine (87) and related compounds from 2,4-O-isopropylidene-D-threose (88) or the corresponding benzylidene acetal; these materials are easily accessible by periodate degradation of 3,5-O-isopropylidene-D-xylose or 4,6-O-benzylidene/isopropylidene-D-galactose.[80-82] Use of the benzylidene acetal gave a better yield of trans-product in the Wittig reaction.[80]



Scheme 15

Alternatively, di-isopropylidene-glucose has been used to prepare 4(E)- and 4(Z)-D-erythro-ceramide in 10 steps, C(1)-C(4) of sphingosine (87) being derived from C(2) to C(5) of glucose, with

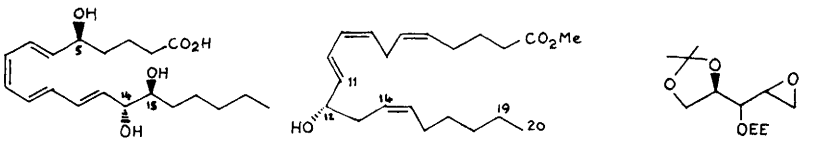
inversion at the nitrogen-bearing centre.[83] The phytosphingosines (89) and (90), of which the D-ribo-isomer (89) and its C_{20} homologue are widely distributed in plant sphingolipids, have been prepared from isopropylidene-D-glyceraldehyde as outlined in Scheme 16; hydroxylation of intermediate (91) gave a 2:1 ratio of the precursors of (89) and (90) respectively, and the enantiomers of (89) and (90) were obtained by Mitsunobu inversion of (92) with benzoate, and then similar reactions.[84]



Reagents: i, Ph_3P-DEAD-phthalimide-THF

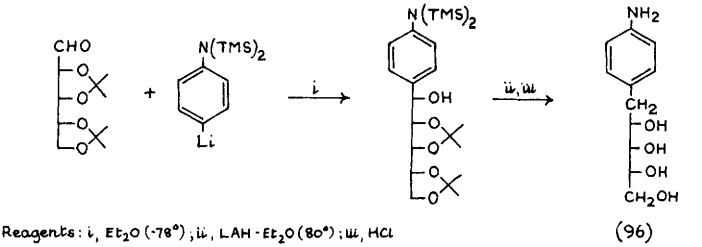
Scheme 16

A synthesis of (+)-leukotriene B_4 from D-mannitol has been completed by extension of earlier work (Vol.19, p.263) on the synthesis of chiral α-hydroxyaldehydes,[85] and two optically active propargylic alcohols, which are useful intermediates for LTB_4 synthesis, have been prepared from D-xylose.[86] In work concerned with the structural assignment of lipoxin B, a series of four isomers of 5,14,15-trihydroxyeicosatetraenoic acid was synthesized from 2-deoxy-D-ribose. One of these was the (5S, 14R, 15S)-8-cis-isomer (93); natural lipoxin B was found by this research group[87] to be a mixture of (93) and the two all-trans isomers discussed last year, and which other workers have reported as the sole constituents of lipoxin B. The methyl ester of 12(S)-hydroxyeicosatetraenoic acid (94) and all three products of its



further hydroxylation at C(19) or C(20) have been prepared from glucose, with C(2)- C(5) of glucose giving rise to C(14)- C(11) of (94).[88] All four stereoisomers of structure (95) have been prepared from D-glyceraldehyde acetonide and converted, by nucleophilic opening of the epoxide and subsequent manipulation, into a series of α-hydroxy- and α,β-dihydroxyaldehydes of use in the synthesis of lipoxygenase metabolites.[89]

The degradation product (96) of the coenzyme methanopterin has been synthesized as outlined in Scheme 17; various other configurations of the tetraol were also prepared in a similar way and shown to differ from the degradation product.[90]

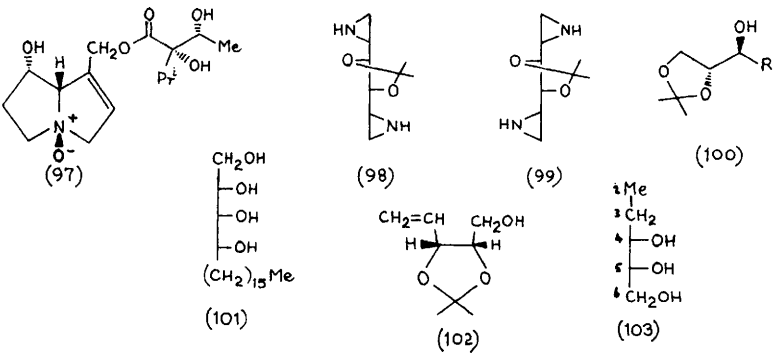


Scheme 17

(-)-Indicine-N-oxide (97), the enantiomer of the natural antitumour agent, has been prepared by linking the previously reported chiral pyrrolizidine (see Vol. 19, p.260) with a chiral carboxylic acid derived from D-arabinose.[91]

An improved procedure has been reported for the synthesis of a C(19)- C(29) fragment of rifamycin W (see Vol. 16, p.270).[92]

The diaziridines (98) and (99) have been prepared from D-mannitol, and, by organometallic opening of the aziridine rings



followed by central oxidative cleavage, these could be converted to chiral α-aminoacids.[93] Adducts of type (100), produced diastereoselectively from D-glyceraldehyde acetonide, can be converted, by Mitsunobu inversion with phthalimide, hydrolysis, and oxidative cleavage, into D-α-aminoacids or (R)-α-phthalimido aldehydes.[94]

By employing Wittig reactions on 5-aldehydo-pentosides, chiral

long-chain 1,2,3,4-tetraols of D-ribo-(101), D- and L-lyxo-, and D-xylo-configurations were obtained; these are related to natural products found in some plants, and to phytosphingosine.[95]

The chiral synthon (102) has been prepared by zinc-copper cleavage of 5-bromo-5-deoxy-2,3-O-isopropylideneribonolactone, followed by reduction; it could also be made from divinyl carbinol by Sharpless' kinetic resolution procedure.[96] The chiral triol (103) has been obtained from D-glucose (numbers shown) via a dithioacetal of 2-deoxy-D-ribose, and the enantiomer of (103) was also prepared from L-arabinose.[97] 2-Deoxy-D-ribose served as a precursor for the chiral synthons (S)-2-benzyloxybutanal and (S)-3-benzyloxy-2-pentanone.[98]

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