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Carbohydrate Chemistry
Volume 16

Part 1

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Carbohydrate Chemistry

Volume 16
Part I

A Specialist Periodical Report

Carbohydrate Chemistry

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Mono-, Di-, and Tri-saccharides and Their Derivatives

A Review of the Literature Published during 1982

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Preface

This report covers the literature for 1982 available to us by February 1983.

It is still too early to be sure whether the change to the cheaper camera-ready format adopted for Volume 15 has had the anticipated effect on sales, although the few comments that have been received from individual consumers have been encouraging. Perhaps the critics are being silent! The same format has been adopted for this report, with a somewhat improved presentation of diagrams. We would like to stress that we are very keen to receive any comments that might serve to improve the coverage or presentation of this literature survey consistent with a reasonable economy of time, effort and expense of production.

I would like to thank Dr. R. Khan for his contribution to this report as one of the team of reporters, and also to thank Dr. P. Gardam and Mrs. H. Pape at the Royal Society of Chemistry for their encouragement and assistance. We are also indebted to Mrs. A. Beattie, Ms. W. F. James, Ms. S. J. Wharton and Mrs. J. Cox for producing the high-quality typescript for this report.

May 1984 Neil R. Williams

Contents

Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ad	adenin-9-yl
Bn	benzyl
Bz	benzoyl
c.d.	circular dichroism
DBU	1,5-diazobicyclo[5,4,0]undec-5-ene
DCC	dicyclohexylcarbodi-imide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
dpm	dipivaloylmethanato
e.s.r.	electron spin resonance
fod	2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato
g.l.c.	gas-liquid chromatography
HMPT	hexamethylphosphotriamide
i.r.	infrared
LAH	lithium aluminium hydride
MCPBA	*m*-chloroperbenzoic acid
Ms	methanesulphonyl
NBS	*N*-bromosuccinimide
n.m.r.	nuclear magnetic resonance
o.r.d.	optical rotatory dispersion
py	pyridine
RNA	ribonucleic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
TMS	trimethylsilyl
Ts	toluene *p*-sulphonyl
U	uracil-1-yl

1
Introduction

This report continues the format adopted in previous volumes. Some account has been taken of criticism regarding the unsatisfactory coverage of oligosaccharides in this series of annual reviews, so that the chapter on glycosides now contains a section devoted to oligosaccharides. In view of the expanding interest in the chemistry of oligosaccharides following the advent of versatile and efficient methods for their synthesis, it is intended in future issues to devote a separate chapter in Part I to chemical aspects of oligosaccharides, including syntheses, leaving more biochemical aspects, and in particular their isolation as characteristic components of polysaccharides and glycoconjugates, to be treated in Part II. It is inevitable that this group of carbohydrates falls between the principal areas of monosaccharides and polysaccharides covered in the two sections, and we would welcome suggestions on ways in which the coverage could be improved.

The papers mentioned in this report show that traditional areas of research have continued to be well supported, but there is clearly growing interest in glycoside and oligosaccharide synthesis, in the synthesis and modification of carbohydrate antibiotics and nucleoside analogues, and in the application of carbohydrates as chiral templates for the synthesis of a wide range of important natural products and their biologically active analogues. The chapter on amino-sugars reflects the very varied approaches now being used to prepare these important compounds, and here and elsewhere the report demonstrates that carbohydrates provide fertile ground for the application of new ideas and methods for synthesizing polyfunctional chiral compounds.

A monograph on advanced sugar chemistry has been published,[1] and reviews of general interest dealing with the synthesis of sugars from non-carbohydrate substrates[2] and the selective removal of protecting groups in carbohydrate chemistry[3] have appeared.

Recommendations for the abbreviations to be used when naming oligosaccharide chains have been published.[4]

References

1 R.S. Shallenberger, 'Advanced Sugar Chemistry', AVI Publ. Co., Westport, CT, U.S.A., 1982.

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3 A.H. Haines, Adv. Carbohydr. Chem. Biochem., 1982, 39, 13.

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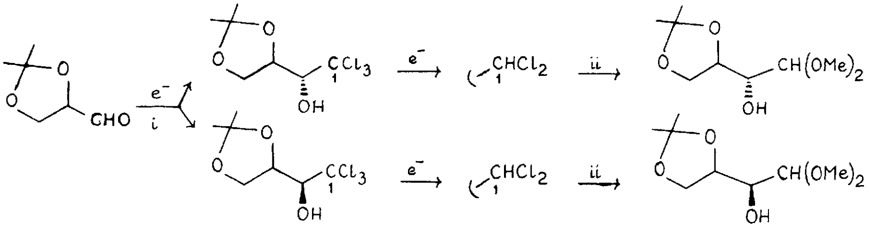
2
Free Sugars

The nomenclature of monosaccharides and related compounds has been reviewed.[1] Reviews have also appeared on the chemistry of maltose,[2] the chemistry and biochemistry of D- and L-fucose,[3] the morphology of sucrose crystals,[4] and the utilization of disaccharides by yeasts.[5] [U-^{14}C]Xylose, [U-^{14}C]glucose, and [U-^{14}C]sucrose have been used to demonstrate that sugars are the major carbon source for triterpene synthesis by the plant _Euphorbia lathysis_.[6]

1 Synthesis

The formose reaction continues to attract attention. Detailed product analysis has been carried out on the autocatalytic condensation of formaldehyde using capillary g.l.c.-mass spectrometry. In addition to the previously reported sugars, pent-2-uloses, hex-3-uloses, DL-apiose and other branched hexoses were found.[7] U.v. irradiation of formaldehyde on zeolites of types A and X has been shown to produce sugars.[8] A formose reaction carried out in the presence of hydroxyoxo compounds at high pH has been described. Equilibrium constants were evaluated in water and aqueous methanol solution saturated with calcium hydroxide or sodium hydroxide in a unimolecular ratio with formaldehyde and known accelerators, such as 2-hydroxyacetophenone, DL-glyceraldehyde, 1,3-dihydroxyacetone, D-glucose, D-fructose or 2,3-dihydroxypropiophenone. The initial rate of conversion was measured and shown to correspond with hydroxide ion-catalyzed aldol reactions at these pH values.[9] Quaternized poly{_p_-[2-(diethylamino)ethyl]styrene} gel has been shown to be a high efficiency catalyst for the formose reaction. Formaldehyde consumption was high when the catalyst had a high extent of quaternization or low degree of cross-linking.[10]

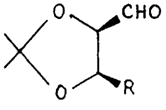
The synthesis of sugars from non-carbohydrate substrates has been reviewed.[11] Nucleophilic addition to 2,3-_O_-isopropylidene-D-glyceraldehyde has been used in syntheses of tetroses. Thus 2-deoxy-D-_glycero_-tetrose was prepared by reaction with nitromethane under basic conditions, followed by hydrolysis, acetylation, and hydrogenation.[12] The nucleophilic addition was brought about by electro-reduction in the reaction sequence leading to D-erythrose and D-threose (Scheme 1). Also obtained in a similar sequence were D- and L-erythulose.[13] Chiral induction in this type of reaction has been reviewed.[14]



Reagents: i, Cathodic reduction in $CHCl_3$-CCl_4 ; ii, MeOH-KOH

Scheme 1

Methanolic potassium carbonate has been used to cause epimerization at C-2 of 2,3-*O*-isopropylidene-aldehydes (1) giving a route to the difficultly prepared 2,3-*threo*-sugars, (2). The same reagent also will epimerize mixed thioxa-acetals as in Scheme 2.[15]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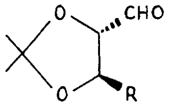
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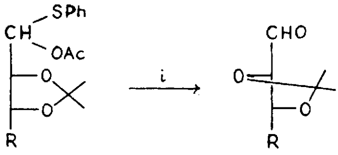
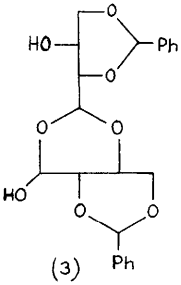


Reagents: i, MeOH-K_2CO_3

Scheme 2

D-Threose has been synthesized by periodate cleavage of 1,3-*O*-benzylidene-D-arabinitol and acid hydrolysis of the resulting dimer (3).[16] The synthesis of 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose, a useful building block for the preparation of L-sugars, by the Swern oxidation (DMSO-$(COCl)_2$) of the monobenzyl-2,3-

isopropylidene-L-threitol (4), has been reported.[17]



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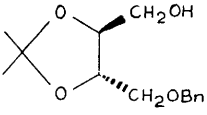
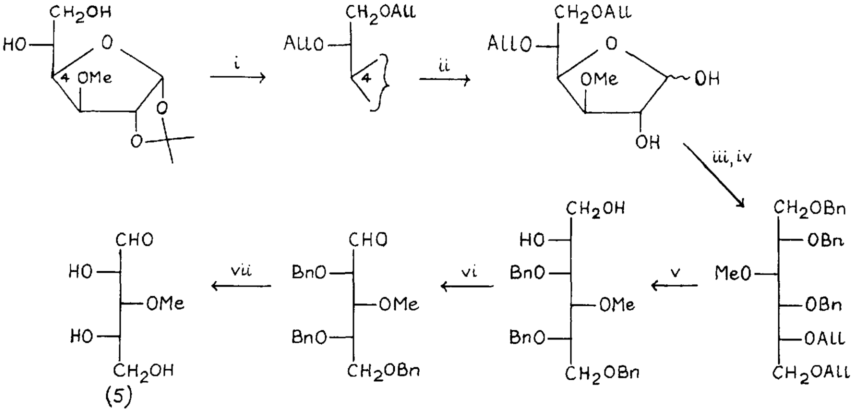


(4)

The sym-dimethyl ester derived from furan and dimethyl acetylenenedicarboxylate was efficiently hydrolysed by pig liver esterase to yield half esters with high optical purity. Precursors with the L-configuration were obtained by chemical transformation while chirality transfer through ester exchange led to precursors with the D-configuration; both products were used to synthesize the enantiomeric riboses.[18] 3-O-Methyl-L-xylose (5), (found in the lipopolysaccharides of Gram-negative bacteria) has been synthesized by the route shown in Scheme 3.[19]

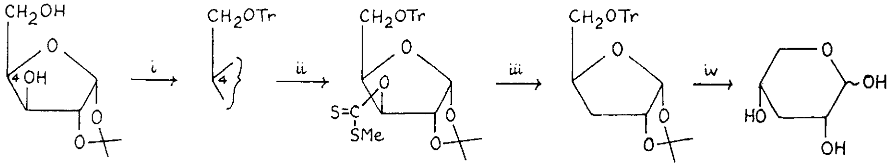


Reagents: i, $CH_2=CHCH_2Br-KOH$; ii, $H_2SO_4-H_2O$-EtOH-Dioxane ; iii, $NaBH_4$; iv, BnBr v, 10% Pd-C ; vi, IO_4^- ; vii, H_2-Pd-C

Scheme 3

A convenient synthesis of 3-deoxy-D-erythro-pentose (6) is depicted in Scheme 4.[20]

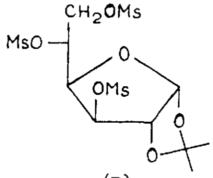
A synthesis leading to L-idose has been achieved by inversion at C-5 of the tri-mesylate (7) using a resin in the acetate form in acetic anhydride; the resulting diacetate (8) was de-esterified without further inversion by means of methanolic sodium methoxide.[21]



(6)

Reagents: i, TrCl-Py ; ii, CS_2-MeI-NaOH-DMSO ; iii, Bu_3SnH-PhMe ; iv, 80% HOAc

Scheme 4



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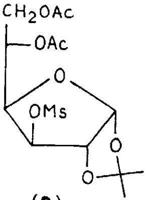
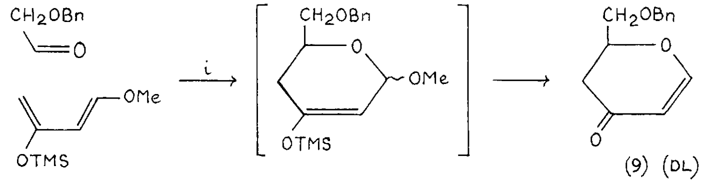


(8)

The racemic enone (9), synthesized as shown in Scheme 5, has been used in a number of sugar syntheses (Scheme 6). A similar reaction sequence was used to synthesize DL-talose (Scheme 7).[22] Aspects of the application of the Diels-Alder reaction using heterodienophiles to the synthesis of D-talose are discussed inter alia in a review of this topic.[23] The chelates formed from β-hydroxyketones and boron tributyl in the presence of oxygen are reduced by sodium borohydride to give meso-1,3-diols. Thus condensation of the dimethoxyacetal of propan-2-onal with 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde gave the β-hydroxyketone (10) which was reduced via the boron chelate to give the diol (11). Hydrolysis with 0.25M sulphuric acid gave 3-deoxy-DL-ribo-hexose.[24] 2-O-Methyl-D-rhamnose, a component of the lipopolysaccharide of Bacterium faecalis alcaligenes, has been synthesized by standard methods.[25]

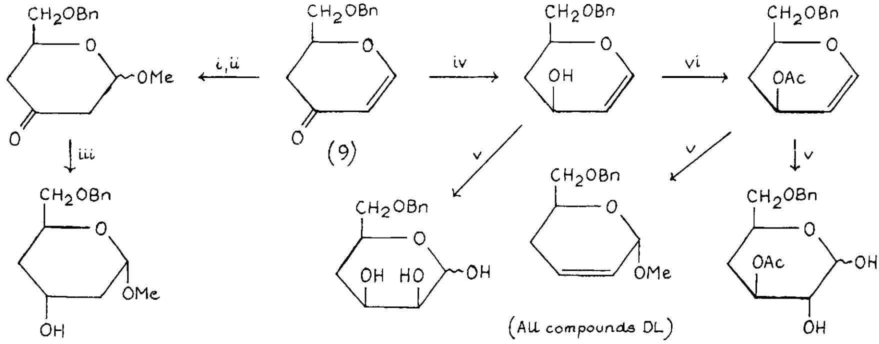
Carrying out the Kiliani reaction using $H^{13}CN$ on the dialdose derivative (12) followed by hydrolysis to the labelled alduronic acid, reduction to the alcohol and hydrolysis with trifluoroacetic acid gave a 2:1 mixture of [6-^{13}C]D-glucose and [6-^{13}C]1,6-anhydro-β-L-idopyranose.[26] [6-^{13}C]-D-Glucose has also been prepared by the route shown in Scheme 8. The same paper describes syntheses of 2-amino-2-deoxy-D-[1-^{13}C]glucose hydrochloride and

2-[^{15}N]amino-2-deoxy-D-glucose hydrochloride by means of the Kuhn reaction with labelled hydrogen cyanide and labelled benzylamine respectively.[27]



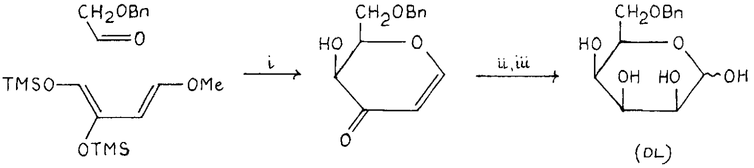
Reagent: i, $ZnCl_2$

Scheme 5



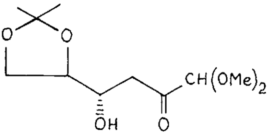
Reagents: i, $MeOH-H^+$; ii, H_2O-H^+; iii, L-Selectride; iv, DIBAL; v, $MoO_4-H_2O_2$, vi, Ac_2O-Py

Scheme 6



Reagents: i, $ZnCl_2$; ii, DIBAL; iii, $MoO_4-H_2O_2$

Scheme 7



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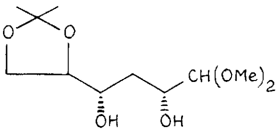

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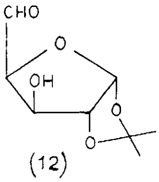
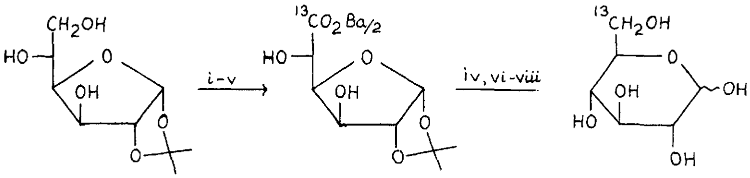


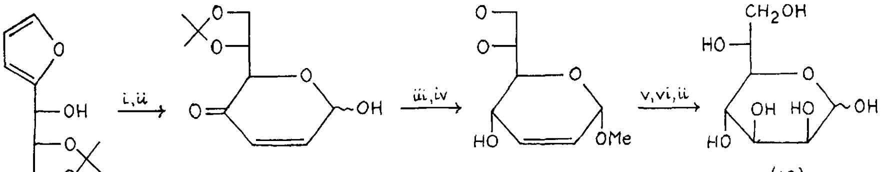
(12)

Condensation of D-mannose with nitromethane gave a mixture of 1-nitro-1-deoxy-D-*glycero*-D-*galacto*-heptitol and its D-*talo*-isomer, which was separated and the former reduced and acetylated to give 1-acetamido-1-deoxy-D-*glycero*-D-*galacto*-heptitol, oxidation of which, using *Acetobacter suboxydans*, gave 7-acetamido-7-deoxy-α-L-*galacto*-heptulopyranose.[28] D-*glycero*-D-*manno*-Heptose (13) has been synthesized using the Achmatowicz approach shown in Scheme 9.[29]



Reagents: i, $NaIO_4$; ii, $K^{13}CN$-HOAc; iii, Na_2CO_3, iv, H^+(Resin); v, $Ba(OH)_2$; vi, Δ(PhMe); vii, $LiAlH_4$; viii, H_3O^+

Scheme 8



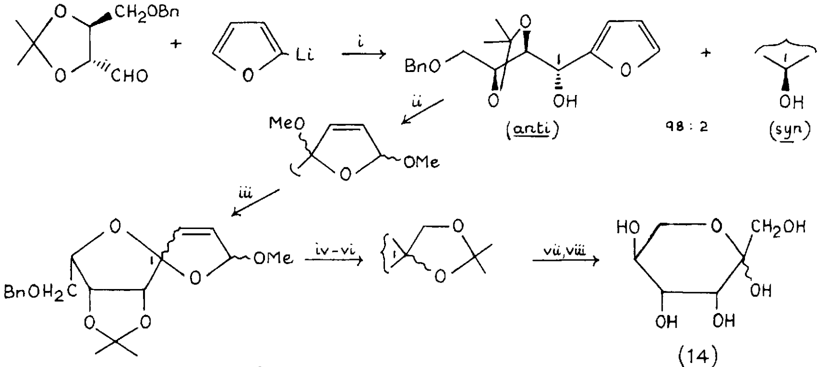
(13)

Reagents: i, Br_2-MeOH; ii, H_3O^+; iii, MeI-Ag_2O; iv, $NaBH_4$; v, OsO_4-Morpholine N-oxide; vi, NaOMe-MeOH

Scheme 9

L-Glyceraldehyde, readily prepared in high optical purity from L-galactono-(1-4)-lactone, was condensed with dihydroxyacetone to yield, after treatment with acetone-sulphuric acid, 2,3:4,5-di-*O*-isopropylidene-L-fructopyranose.[30] Attempts to apply the thermolysis of sucrose in DMSO to the synthesis of D-fructose derivatives gave irreproducible results; this was found to be due to the presence of an acid impurity in the solvent in variable, trace amounts. The kinetics of the acid-catalyzed reaction in DMSO, DMF and water were studied.[31] An extension of the work reported earlier in this chapter (ref. 17) allowing the synthesis of L-tagatose (14) from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose has been published (Scheme 10).[32]

Some by-products from the previously reported reaction of ketoses with ethyl acetoacetate have been examined in order to determine the mechanism of the reaction.[33]



Reagents: i, ZnBr$_2$-THF (-78°); ii, Br$_2$-MeOH; iii, Me$_2$C(OMe)$_2$-H$^+$; iv, O$_3$; v, NaBH$_4$; vi, Me$_2$CO-H$^+$; vii, H$_2$-Pd/C; viii, H$^+$

Scheme 10

A study of the formation of oligosaccharides on thermal degradation of lactose has shown that the pyrolysis proceeds <u>via</u> simultaneous aldose-ketose isomerization and condensation of initially-formed monosaccharides without involving any cleavage of the carbohydrate carbon skeleton.[34]

A new cation exchange resin, obtained by grafting sulphonic acid groups onto porous silica, has been shown to possess catalytic activity comparable to that of polystyrene sulphonic acid for the hydrolysis of oligosaccharides.[35]

2 Physical measurements

It has been demonstrated that, for D-glucose, D-mannose, D-fructose, and D-ribose, the use of ordinary, partially relaxed, pulse Fourier transform ^{13}C-n.m.r. provides tautomeric compositions with an accuracy comparable to those obtained by more sophisticated n.m.r. techniques.[36] On the basis of the ^{13}C-n.m.r. of honey, the predominant form of free fructose is β-D-fructopyranose and not the β-D-fructofuranose as is unequivocally stated in most undergraduate biochemistry texts.[37] ^{13}C-N.m.r. spectroscopy has been used to monitor the metabolic fate of [U-^{13}C]glucose <u>in vivo</u>.[38]

The molecular rotations, $[M]_D$, of derivatives of α-D-glucopyranose, α-D-galactopyranose, and α-D-xylopyranose having different substituents at the anomeric carbon atom are shown to be linearly related to the bond refractions, ΣR_D by the expression: $[M]_D = m\Sigma R_D + I$, where m, I are constants.[39] The mutarotation of D-glucose has been studied in the presence of electrolytes. With added copper(II) perchlorate in the pH range 3.5 - 4.4, the rates rise markedly. Details of the process are discussed and a reaction model is proposed involving an oriented set of hydration molecules which act as an enhanced electrophile in the aldehyde-forming step.[40] The proton- and solvent-catalyzed rate constants for the interconversions of the pyranose, furanose and open-chain forms of D-fructose have been measured and the activation and thermodynamic parameters calculated.[41] Kinetics of the mutarotation of 2,3,4,6-tetra-*O*-methyl-D-glucose in benzene at 30° using styrene - 2-pyridone as a co-polymer catalyst have been compared with those using the corresponding monomer; it was shown that pseudo-dilution with polymer chains is effective only in relatively dilute solutions and that the polymer chains rather facilitate the association in concentrated solutions.[42]

A review, in Russian, on the nature of primary free radicals in carbohydrates has been published.[43] γ-Irradiation of oxygen-free, nitrous oxide - saturated aqueous solutions of D-fructose 1-phosphate and 6-phosphate produced many products; among those identified were hexos-2-uloses, 6-deoxy-2,5-hexodiuloses, tetruloses, and 3-deoxytetruloses.[44] Lyoluminescence spectra of D-glucose, lactose, and L-arabinose and the effects of pH, and substances altering the lifetime of singlet oxygen, on the spectral intensity have been analyzed. Excited dimers of singlet oxygen were found to be responsible for the chemiluminescence at 630 nm.[45] Sensitized D-glucose has been studied in lyoluminescence experiments for its possible use in radiation dosimetry. The response of glucose was compared with some other commonly used carbohydrates. D-Glucose crystallized with lumenol was found to be a better lyoluminescent dosimetric material than any other sugar.[46] A study of *X*-irradiated single crystals of α-D-glucopyranose at 77K has shown that the dominant radical is a C-6 primary hydroxyalkyl which reorients slightly on warming to 200K, and converts to a C-2 primary hydroxyalkyl radical on warming to about 300K. Annealing a sample at room temperature for 16h gave several free-radical products, one identified as a C-2 secondary hydroxyalkyl radical.[47]

A series of 4-*O*-glycosyl-fructoses has been examined by deuterium-induced differential isotope-shift (d.i.s.) ^{13}C-n.m.r. experiments in aqueous solution. For the compounds studied, (lactulose, cellobiulose, and maltulose) the results of the equilibrium composition were 60:30:10:2 for the β-pyranose, α-furanose, β-furanose and open-chain forms of the fructose unit respectively. At higher temperatures, the percentage of furanose and open-chain forms increased. An anomolously high d.i.s. value for C-4 in 4-O-α-D-glycopyranosyl-glycopyranoses has a predictive value for the anomeric configuration.[48] Unidirectional rate-constants for interconversions of the furanose and open-chain forms of D-threose and D-erythrose have been obtained by ^{1}H and ^{13}C saturation-transfer n.m.r. spectroscopy using the [1-^{13}C]sugars. The technique involves saturation of H-1 or C-1 of the aldehydo-form and observing the saturation transfer to the α- and β-furanoses and the hydrate.[49]

Examination of the rate of deuterium for hydrogen exchange in the Raney nickel - deuterium oxide procedure (see Vol. 11, p. 132; Vol. 12, p. 13) and its stereochemical features has led to a theory based on the approach to catalyst surfaces of various configurational isomers.[50] The kinetics of oxygen exchange at the anomeric carbon atom of D-glucose and D-erythrose, by means of the ^{18}O isotope effect which causes a δ-shift in ^{13}C n.m.r., have been measured. The pseudo-first order rate constant for both the α- and β-pyranoses of D-glucose was found to be 9.5×10^{-5} s^{-1}. The advantages of the technique are the simplicity of the data and that all forms can be studied simultaneously.[51]

Computerized curve-fitting applied to thermogravimetric data on sugars has shown that the absence of an anomeric hydroxy group increases their thermal stability, and this is taken to indicate that this group is involved in initiating decomposition. Other conclusions were that a free secondary hydroxy group at C-4 is more reactive than the primary one at C-6, that five-membered rings are less stable than six-membered rings, and that oligomers and polymers start decomposing at higher temperatures, with a fair correlation to molecular weight.[52] Heat flow calorimetry has also been applied to the thermal decomposition of sugars.[53] The excess enthalpies of aqueous solutions of nine polyols have been determined.[54]

The wall friction of lactose and sucrose powders have been investigated in connection with the preparation of pharmaceutical tablets.[55]

Formation of mechano-radicals by ball-milling of sugars, and the crystal structure of di-D-fructose anhydride are mentioned in Chapter 21.

3 Isomerizations

An improved synthesis of D-psicose from base-catalysed isomerization of D-fructose using calcium ion cation-exchange resin chromatography has been reported.[56]

The kinetics of base-catalysed isomerizations of D-glucose and D-fructose,[57] and of maltose,[58] each in aqueous ethanol, have been determined. A revised free-energy diagram for biofunctionally-catalysed epimerization of 2,3,4,6-tetra-O-methyl-α-D-glucose(TMG) by 2-pyridinone in benzene has been obtained using microcalorimetry, polarimetry, and ^{13}C-n.m.r. Thermodynamic parameters for complexation of the α- and β-forms with 2-pyridinone were determined. A high yield synthesis of α-TMG was also given.[59]

Continuing earlier studies on the alkaline isomerization of sugars (see Vol. 10, p. 9; Vol. 13, p. 11), Kucar's group have shown that 4-deoxyaldoses in alkaline medium using DCC as transforming agent yield mainly 4-deoxy-hexos-2-uloses together with some of the corresponding C-3 epimeric hexosulose.[60]

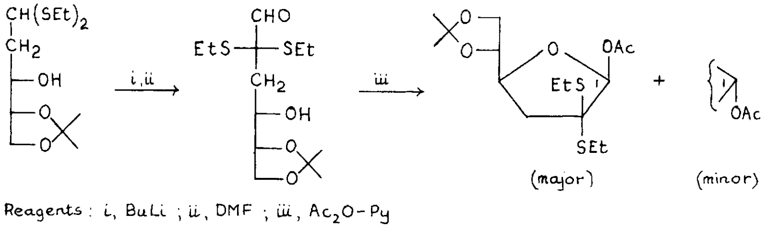
4 Oxidation

The kinetics of the oxidation of L-arabinose[61] and D-glucose[62] by potassium permanganate in aqueous phosphoric acid solution have been measured. The reduction rates of potassium dichromate by D-glucose at pH 8 and 9 have been shown to be identical and higher than that at pH 2 - 7. Reduction was complete in 75 min.[63] Indication that HgI_3^- is the true oxidant in Nessler's reagent has come from a study of its reaction with D-fructose, in which it was found that the rate is proportional to the concentrations of fructose and hydroxide ion, independent of the concentration of mercury(II), and inversely proportional to iodide ion.[64] Complex formation between vanadium(V) and L-rhamnose is suggested by the kinetic results from the reaction carried out in aqueous sulphuric acid.[65] The kinetics of oxidation of L-rhamnose by thallium(III) in aqueous perchloric acid show that the reaction is first order in the oxidant and the sugar and that the rate is decreased with increasing acidity. The reaction is strongly inhibited by added acetate or chloride ions.[66] The same oxidant has been studied with aldoses; the first step involves C-1 - C-2 cleavage of the aldehydo-form of the sugar, thus D-glucose gives D-arabinose and formic acid. In excess of oxidant, the final product is carbon dioxide.[67] A general mechanism for the oxidation of aldoses by manganese(III) sulphate has been proposed.[68] The products of periodate-oxidation of sorbose under various conditions have been examined; many reaction pathways are present.[69]

Evidence that a formic ester is an early intermediate in the periodate oxidation of D-ribose 5-phosphate has been presented.[70] The oxidation of pentitols and hexitols by bromine in the presence of calcium carbonate to yield alduloses, and the indirect anodic oxidation of D-glucitol and D-mannitol are detailed in Chapter 17.

5 Other reactions

1-C-Formylation of 2-deoxy-D-arabinose via its diethyldithioacetal anion has been carried out (Scheme 11).[71]



Scheme 11

An improved method for converting sugars to furfural derivatives using hydrochloric acid, a catalytic amount of surfactant, and mixed solvent systems of water with organic media has been described. A second method using hydrochloric acid and magnesium halides was also investigated. Pentoses gave furfural, hexoses and disaccharides yielded 5-chloromethyl-2-furaldehyde, and rhamnose was converted to 5-methyl-2-furaldehyde.[72]

The only species present in an aqueous solution of D-fructose absorbing and undergoing photolysis at 254 nm is the open-chain form. Its primary fragmentation involves carbon-carbon bond cleavage α to the carbonyl group. Products are formed from the subsequent disproportionation and combination reactions or from dehydration reactions of the radical produced by loss of carbon monoxide from the hydroxyalkyl acyl radicals. A different reaction proceeds in the presence of oxygen, due to the latter producing peroxyl radicals from the primary radicals.[73]

Addition of furfural inhibits the reaction of aldoses with ampicillin due to the formation of a Schiffs base which cannot attack the β-lactam carbonyl group.[74]

The degradation of α-D-glucose at 419K initiated by irradiation at doses of 2-10 Mrad proceeds by a chain mechanism to yield carbonyl compounds.[75] A study of the effect of nitrates, phosphites, chlorides, and sulphates of polyvalent cations on the rate of degradation of D-glucose by sulphur dioxide solution (simulating the pulping process of wood) has shown that they all cause increases. Salts of monovalent ions do not have this effect.[76]

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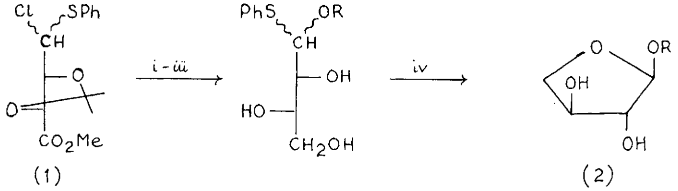
3

Glycosides and Oligosaccharides

Following Dr. Laurens Anderson's suggestion[1] the title of this Chapter is expanded; many compounds containing more than one sugar unit are referred to.

1 O-Glycosides and Oligosaccharides

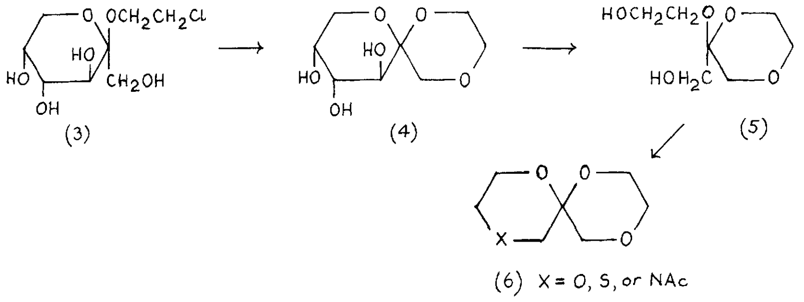
1.1 Synthesis of Monosaccharide Glycosides.- Compound (1), prepared from tartaric acid, offers a useful general means of obtaining α-L-threofuranosides (2) (Scheme 1). Simple glycosides were produced with *ca*. 6:1 selectivities, but this increased to 10:1 for the formation of threose-containing disaccharides.[2] Direct glycosylation of D-erythrose with allyl or benzyl alcohol gave the α- and β-furanosides in the ratio 1:10; these were isolated as ester derivatives.[3]



Reagents: i, ROH-$SnCl_2$-$AgClO_4$; ii, $LiAlH_4$; iii, H^+ ; iv, $Pd(OAc)_2$

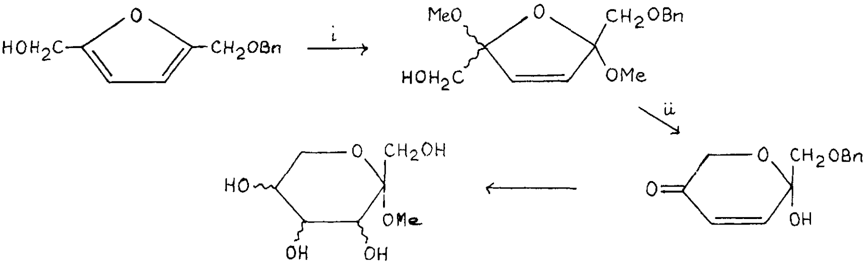
Scheme 1

The syntheses of the methyl D-fructofuranosides from 1,3,4,6-tetra-*O*-benzoyl-D-fructose have been developed, and hence a large range of derivatives with amino, azido, bromo, chloro, deoxy and acetylthio groups at C-1 and C-6 were prepared; ^{13}C n.m.r. spectra were recorded.[4] In related work several alkyl β-D-fructopyranosides were synthesized, and ^{13}C n.m.r. data for these and the related α- and β-furanosides were reported.[5] Fischer glycosidation of D-fructose with 2-chloroethanol affords in high yield the crystalline glycoside (3) which with base gives the spiroanhydride (4). Following periodate oxidation this was converted via the diol (5) into the novel, chiral spirobi-1,4-dioxans (6) (Scheme 2).[6] A



Scheme 2

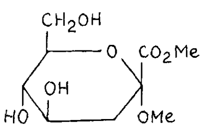
synthesis of racemic methyl ketohexosides with the α-sorbose, α-tagatose, and the α-psicose configurations is outlined in Scheme 3.[7]



Reagents : i, Br_2-MeOH ; ii, H^+

Scheme 3

Acidified methanolic treatment of 3-deoxy-D-*arabino*-2-heptulosonic acid gave the methyl ester methyl glycoside (7) which was characterized by X-ray analysis,[8] and benzaldehyde dimethyl acetal with methanol catalysed by *p*-toluenesulphonic acid gave the glycoside acetal (8) from D-mannose directly. In analogous fashion compound (9) was made from 2-acetamido-2-deoxy-D-glucose.[9]



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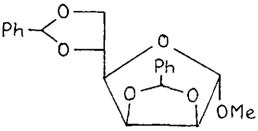

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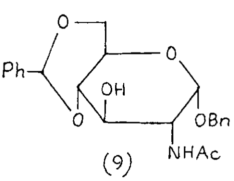
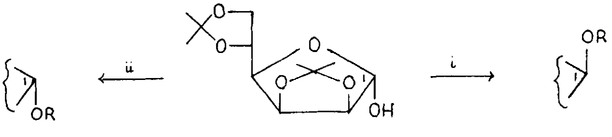


(9)

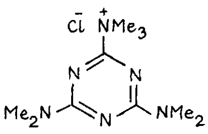
Several syntheses have involved the direct substitution of anomeric hydroxy groups. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucose condensed with alcohols in the presence of methanesulphonic acid, cobalt dibromide and tetraethylammonium perchlorate gave predominantly α-glycosides, secondary alcohols giving 80% yields and α,β-ratios *ca*. 3:1.[10]

Oxyanions at the anomeric centre have been used with alcohol triflates to produce α- and β-D-mannofuranosides (Scheme 4), and likewise, α- and β-D-mannopyranosides were prepared using 2,3,4-tri-*O*-benzyl-D-mannose.[11] Direct treatment of D-glucose with the salt (10) in aqueous base gave the β-glycoside (11),[12] and the naturally occurring glycoside (12) and its epimer were made by condensation between 2,3,4,6-tetra-(1-ethoxyethyl)-D-glucose and the appropriate phenol in the presence of diethyl azodicarboxylate and triphenylphosphine.[13] Acid-catalysed *trans*-acetalation of 2-bromoacetaldehyde dimethyl acetal with 2,3,4,6-tetra-*O*-acetyl-D-glucose gave the α-diastereoisomers (13 and isomer) which were separated chromatographically.[14]



Reagents: i, NaH - ROTf ; ii, NaH-ROTf - Crown Ether

Scheme 4



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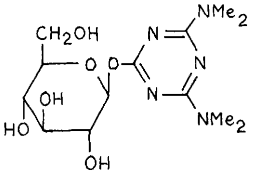

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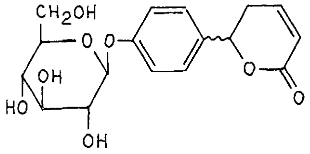

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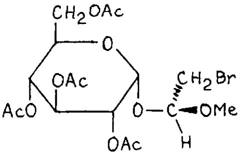
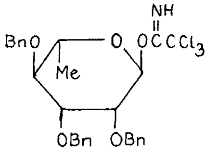


(13)



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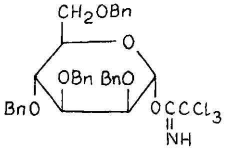
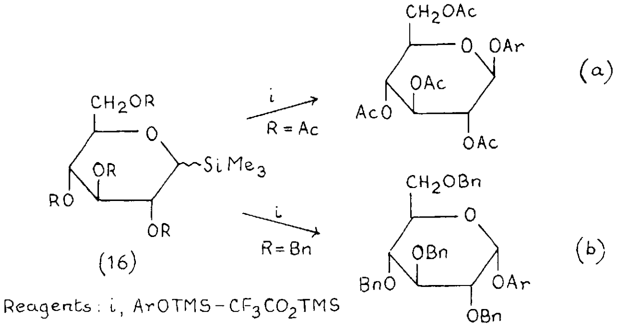


(15)

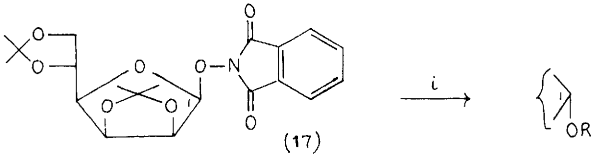
Various derivatives of C-1 hydroxy compounds have been used in glycoside syntheses: a D-glucuronic acid 1-methanesulphonate gave mono- and di-glucuronisides of bilirubin,[15] 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose gave *O*-β-D-ribofuranosides of various pharmacologically active aglycones (*e.g.*, corynanthine and tropanol[16] and L-dopa and α-methyl L-dopa[204]), and trichloroacetimidates have been used in the L-rhamnose and D-mannose series. Compounds (14) and (15), treated with alcohols (including sugar derivatives) in the presence of p-toluenesulphonic acid and molecular sieves, gave anomerically mixed products with simple alcohols but mainly disaccharides with retained configuration i.e. α-compounds with sugars.[17] A potentially useful stereoselective synthesis of aryl β- D-glucopyranosides (α:β <1:10) involves the reaction illustrated in Scheme 5a. When the tetrabenzylated starting material was used, however, the α-anomers predominated (α:β ≈3:1) (Scheme 5b).[18]



Reagents: i, ArOTMS-CF_3CO_2TMS

Scheme 5

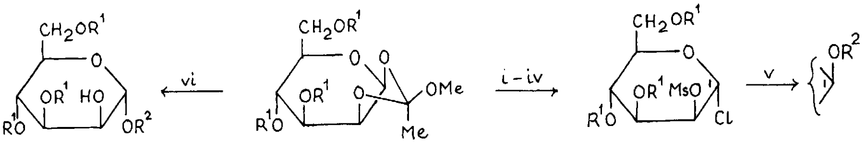
The α-anomer of compound (16, R = Ac) can be obtained in high yield and with 96% selectivity by treatment of the mixed anomers with catalytic trimethylsilyl trifluoromethanesulphonate.[19] Compound (17), obtained by condensation of the free sugar with N-hydroxyphthalimide using diethyl azodicarboxylate and triphenylphosphine, on reaction with alcohols in the presence of tin(IV) chloride, gives the α-linked products specifically (Scheme 6).[20]



Reagents: i, ROH-$SnCl_4$

Scheme 6

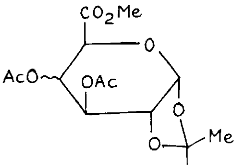
Various syntheses have been effected using glycosylating agents within which the anomeric carbon atom is a component of two rings. 1,2-Orthoesters are the best known members of this class and have been used to prepare 2-O-α-D-mannopyranosylmyoinositol.[21] Procedures for preparing α- or β-D-mannopyranosides are outlined in Scheme 7.[22] The preparations of the D-gluco- and D-galacto-1,2-O-cyanoethylidene uronic acid derivatives (18), useful for the pre-



Reagents: i, H^+; ii MeO^-; iii, HCl; iv MsCl; v, $R^2OH-CF_3SO_3Ag$; vi, R^2OH-H^+

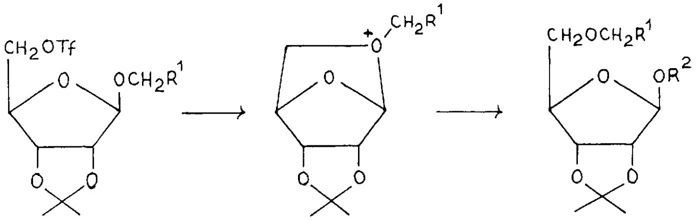
$R^1 = CH_2{=}CHCH_2-$

Scheme 7



(18)

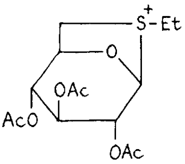
paration of β-linked glycosides and disaccharides, have been reported.[23] Reaction intermediates (19) come into this category of glycosylating agent and can be made and used (with simple or complex alcohols) as indicated in Scheme 8, the initial aglycone



(19)

Scheme 8

having migrated to C-5.[24] An interesting analogous species is the crystalline salt (20) which can be made by ethylation of the thio-anhydro compound and which, with oxygen nucleophiles, gives the β-glycosides (21). With azide, the orthoester analogue (22) is



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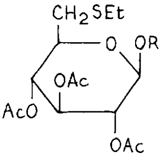

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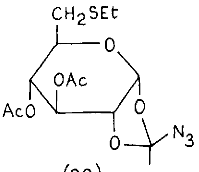

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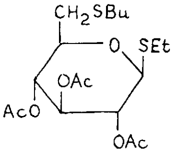
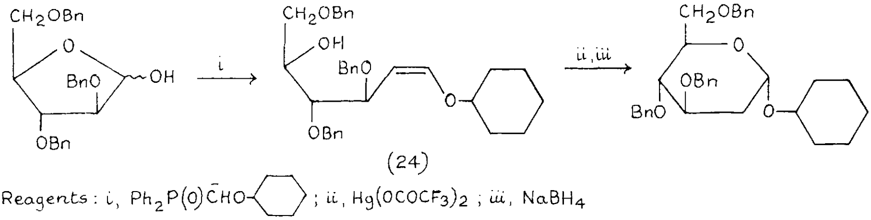


(23)

mainly produced, whereas thiols afford the 6-substituted products e.g., (23).[25]

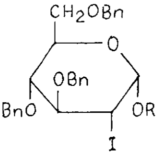
Unsaturated sugar derivatives continue to be used in glycoside syntheses. Scheme 9 illustrates an interesting approach to the stereo-controlled synthesis of 2-deoxy-α-D-*arabino*-hexopyranosides from 2,3,5-tri-*O*-benzyl-D-arabinose by way of the Wittig-derived alkene (24). Alternatively, when the (Z)-alkene was treated with phenylselenyl chloride followed by reductive deselenation the β-glycoside was the main product. Similar treatment of (E)-isomer again gave the α-anomer predominantly.[26] The same authors then extended this approach using a series of (Z)-vinyl ethers analogous to compound (24) (including disaccharide derivatives) with *N*-iodosuccinimide which resulted in very high yields of products which were almost exclusively the α-D-*gluco*-compounds (25). In this case the (E)-alkenes again gave mainly the α-compounds, but also the β-D-*manno*-isomers (ratio 7:3). The former procedure was used to prepare the glycolipid (26) *via* the glycerol glycoside (27).[27]



(24)

Reagents: i, $Ph_2P(O)\bar{C}HO$–; ii, $Hg(OCOCF_3)_2$; iii, $NaBH_4$

Scheme 9



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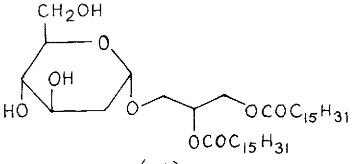

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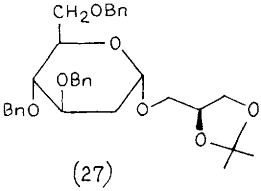
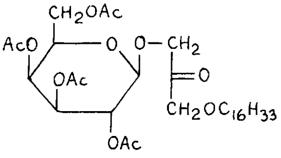


(27)

Access to compound (26) is also obtainable by the addition of 1,2-*O*-isopropylideneglycerol to tri-*O*-acetyl-D-glucal in the presence of *N*-bromosuccinimide.[28] Benzyl alcohol used in this approach affords access to benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside and -β-D-glucopyranoside from which various 2- and 3-amino- and 2,3-diamino-products have been made by standard procedures.[29] The glycal→2,3-unsaturated glycoside reaction has been used to prepare a 2,3,6-trideoxy-α-L-*erythro*-hexose cardenolide glycoside.[30] See Chapters 12 and 18 for other examples. Reference is made to the use of hex-3-enopyranosides in the synthesis of aminosugar glycosides in Chapter 8.

Many examples of the use of glycosyl halides as glycosylating agents continue to appear. The use of tetra-O-pivaloyl-α-D-glucopyranosyl bromide with silver salts is recommended for the preparation of β-D-glucopyranosides since, for steric reasons, the formation of 1,2-orthoesters is suppressed.[31] Aryl 1,2-trans-glycosides are obtainable in 70-90% yield by use of acetylated glycopyranosyl bromides with silver imidazolate and zinc chloride.[32] An improved route to phenyl α-L-arabinofuranoside uses commercially available 2,3,5-tri-O-benzyl-β-L-arabinose which is converted to the 1-p-nitrobenzoate and thence to the glycosyl chloride which was treated with phenol in the presence of molecular sieve. Chromatographic separation gave the α-glycoside in about 80% yield (10% β).[33]

Several reports have been devoted to the preparation of glycerol glycosides. Tetra-O-acetyl-α-D-glucopyranosyl, -mannopyranosyl and -galactopyranosyl bromides have been used to produce 3-O-glycopyranosyl-1,2-di-O-tetradecyl-sn-glycerol (α- and β-anomers);[34] related work led to 3-O-manno-oligosyl-1,2-di-O-tetradecyl-sn-glycerols.[35] Control of the stereochemistry at C-2 of the glycerol components of such compounds has been attempted by use of ketones such as (28) which was made by Collins oxidation of the corresponding alcohol produced by glycosylation of 2-O-benzyl-1-O-hexadecylglycerol. On L-Selectride reduction compound (28) gave the product with the R-configuration (71% diastereoisomer excess) whereas, under the same conditions, the β-D-gluco- and α-D-manno-analogues gave mainly the R- and S-products (58 and 3% diastereoisomer excess) respectively.[36] Fluoresence-labelled glucosyl glycerides with the label (dansyl group) at C-2 of the glycerol or O-6 of the D-glucose have been prepared by standard methods,[37] and racemic glycerol derivatives have been resolved by glycosylation of 1,2-O-protected compounds, separation of the diastereoisomers, and deglycosylation.[38]



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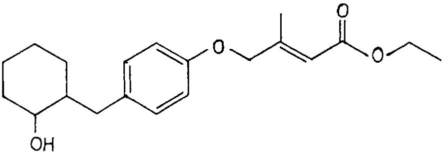
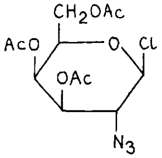


(29)

Koenigs-Knorr reactions have been used to prepare glycosides of natural products or otherwise of interest in biology as follows: various cardiac glycosides (using Fetizon's reagent)[39] including 2,6-dideoxyhexopyranosides,[40] a terpene D-glucoside,[41] triterpene α-L-arabinopyranosides[42] and a β-D-glucopyranosyl derivative of compound (29) with juvenile hormone activity.[43]

Several amino-sugar glycosides have been prepared using glycosyl halides. The azido-derivative (30) has been bonded to serine and serine derivatives to produce glycopeptide haptens with T_N specificity[44] and, in related work, to a Schiff-base protected ethanolamine to afford compounds based on glycoside (31) and carrying D-galactosyl units at O-3 or O-4 which are antigenically active compounds.[45] Reaction of the corresponding α-glycosyl bromide with alcohols in acetone containing mercury(II) cyanide and bromide and tetrabutylammonium bromide gave the acetal glycosides (32).[46] The 3-azidohexopyranosyl derivative (33), an analogue of carminomycin, was produced (α:β 3:1) by use of the 4-*O*-*p*-nitrobenzoylglycosyl chloride,[47] and the diaminohexosyloxycinnamate part (34) of glycocinnamoylspermidines has been made by use of compound (35) and the analogous 4-tosylate.[48,49]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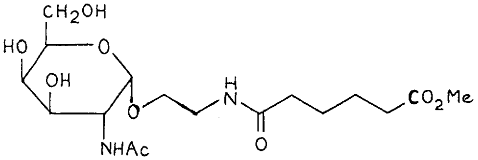
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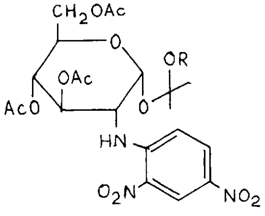
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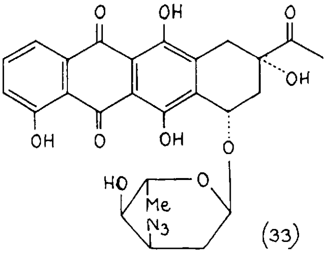
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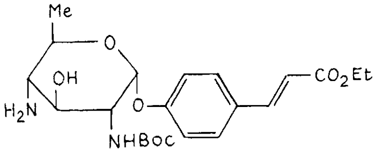
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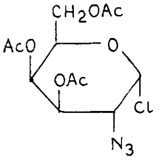
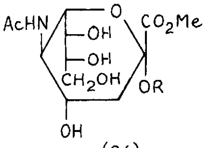

(35)

Several β-D-glucuronides have been synthesized by use of an esterified glycopyranosyl bromide. These include the glycosides of mandelamide (the product was also dehydrated to give the mandelonitrile glucuronide),[50] 4-hydroxyestrogen,[51] tetrahydrocortisol and tetrahydrocortisone,[52] 2-hydroxyestradiol monomethyl ethers,[53] and bile acids and their conjugates.[54]

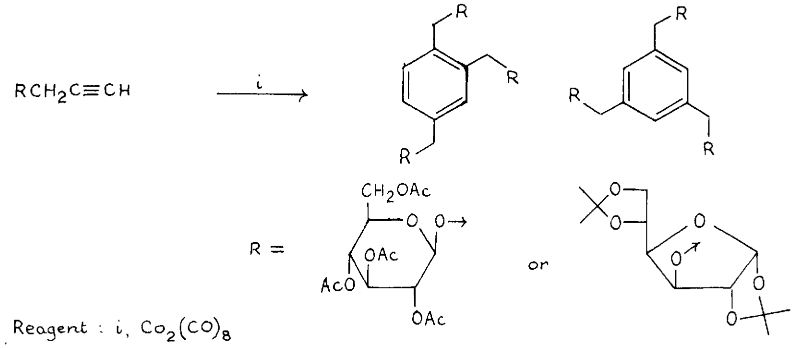
Alkyl α-glycosides of N-acetyl-D-neuraminic acid (36) have been synthesized using primary and secondary alcohols together with the acetylated glycosyl chloride methyl ester.[55] Whereas attempted condensation of this chloride with a coumarin led to elimination, use of a crystalline tetrabutylammonium salt of 7-hydroxy-4-methylcoumarin gave the α-glycoside satisfactorily.[56]



(36)

Enzymic methods can be successful in cases where the Koenigs-Knorr procedure is not; a series of benzo[a]pyrene glucuronides have been prepared using UDP-D-glucuronic acid and an appropriate transferase.[57] A β-D-glucosidase from Stachybotrys atra causes transfer of xylosyl residues from aryl β-D-xylopyranosides to phenols so that new aryl glycosides are produced. Analogous transfer does not occur from aryl β-D-glucopyranosides to phenols, but anilines do act as acceptors.[58]

Modification of accessible glycosides can be used as an important strategy, and 2-bromoethyl glycosides treated with various thiols have afforded products with "spacer arms" appropriate for attachment to macromolecules for use in biological work.[59] An interest-



Scheme 10

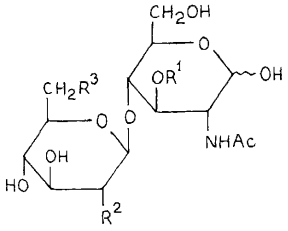
ing set of "aryl cluster glycosides" have been synthesized (Scheme 10) as possible triggers for phytoalexin activity in plants (they were not active).[60]

1.2 Synthesis of Disaccharides and their Derivatives.- Provisional recommendations have been made for abbreviations to be used for the representation of oligosaccharide chains.[61] In the following, compounds are classified according to their non-reducing components but on several occasions it has proved beyond the scope of this treatment to refer to every disaccharide synthesized.

Methods of synthesis of α-linked D-glucose disaccharides continue to attract attention and tetra-O-benzyl-α-D-glucopyranosyl chloride used in the presence of silver imidazolate and mercury(II) chloride gave, with 1,2:3,4-di-O-isopropylidene-α-D-galactose and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, products containing more than 50% of the α-linked disaccharides.[62] Considerably better α,β-ratios (ca. 6:1) were obtained using tetra-O-benzyl-α-D-glucopyranose together with trimethylsilyl bromide, cobalt bromide, tetrabutyl ammonium bromide and a molecular sieve,[63] and a related "one pot" procedure involving this benzyl ether uses p-nitrobenzenesulphonyl chloride, silver trifluoromethanesulphonate, N,N-dimethylacetamide and triethylamine. α-Products predominated and were, in some cases, formed almost exclusively.[64] Use of tetra-O-acetyl-α-D-glucopyranosyl bromide with silver imidazolate and zinc chloride affords good means of obtaining β-linked disaccharides, the yields (as in several of the above cases) being ca. 90% and 40% in the cases of primary and secondary sugar alcohols, respectively.[65] Treatment of benzyl exo-3,4-O-benzylidene-β-L-arabinopyranoside with tetra-O-acetylglucosyl bromide gave the expected product of condensation but, in addition, the isomer with the alternative configuration at the benzylidene acetal centre was produced.[66]

Various D-glucose-containing disaccharide derivatives have been prepared mainly for biochemical work. These include the 2-(p-aminophenyl)ethyl glycosides of the α- and β- (1 → 2) and (1 → 3) linked D-glucobioses,[67] the 2(R)- and 2(S)-hydroxypropyl glycosides of α-cellobiose (prepared from glycerol glycosides),[68] 3-O-β-gentiobiosylglycerol distearate[69] and the disaccharide dipeptide (37) as well as the di-amino analogues (38) and (39) and related compounds.[70]

Several other disacharides produced by use of a 2-amino-2-deoxy-D-glucosylating agent have been reported. Improvements in the



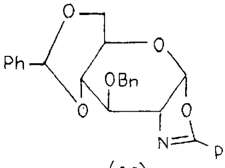
(37) $R^1 = X, R^2 = R^3 = OH$

(38) $R^1 = X, R^2 = NHAc, R^3 = OH$

(39) $R^1 = X, R^2 = OH, R^3 = NHAc$

$X = CH(Me)CO$-L-Ala-D-isoGln

oxazoline procedure include use of compound (40) together with 2,6-dimethylpyridinium p-toluenesulphonate;[71] the more common glycosylating agent (41) has been used to prepare the D-ribitol derivative (42) which is the antigenic determinant of



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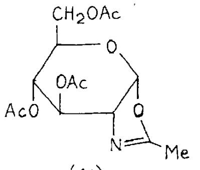
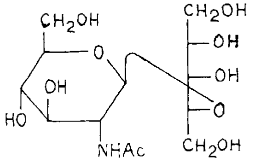
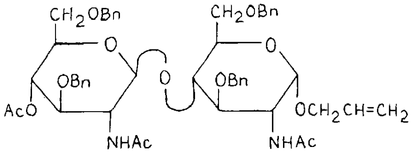


(41)



(42)

Staphylococcus aureus.[72] Immunoadjuvent activities of compounds produced by the oxazoline method which have peptide bonded muramic acid linked to O-6 of 2-acetamido-2-deoxy-D-glucose variously substituted on the amino group have been reported.[72a] N-Phthalimido protected glycosylating agents continue to be used and have led to syntheses of the chitobiose derivative (43),[73] 8-methoxycarbonyloctanyl 6-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-acetamido-2-deoxy-α-D-galactopyranoside[74] and p-nitrophenyl 3-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-α-L-rhamnopyranoside.[75] Use of the 2,4-dinitroanilino compound (44) has led to glycosylation of methyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside (α- and β-anomers produced) and 1,3,4,6-tetra-O-benzyl-D-fructose (to give an α,β-linked non-reducing disaccharide).[76]



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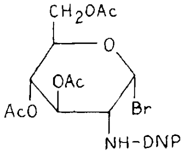
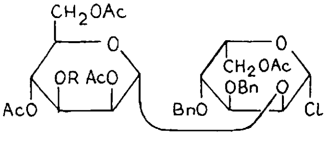


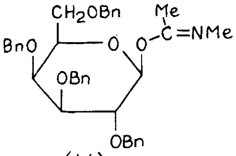
(44)

In the area of D-mannopyranosyl disaccharides, 2,3:4,6-di-O-cyclohexylidene-α-D-mannopyranosyl chloride in the presence of silver imidazolate and mercury(II) chloride leads to moderate yields.

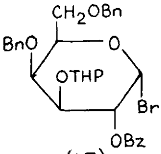
of β-linked disaccharides even with sterically hindered alcohols.[77] Methyl 3-*O*-(α-D-mannopyranosyl)-α-D-glucopyranoside has been prepared by standard methods[78] and the 2-O-α-D-mannopyranosyl-L-gulose derivative (45) has been used in the total synthesis of the complex antibiotic bleomycin.[79]



(45) R = $-CON(Ac)CO_2Bu^t$



(46)

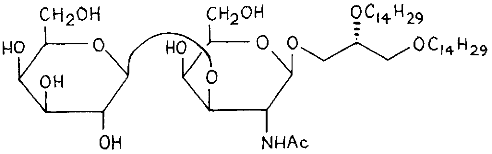


(47)

Considerable effort has gone into the synthesis of D-galactopyranosyl disaccharides and their derivatives. Full details have appeared on the use of the imidate (46) in the synthesis of α-linked compounds;[80] tetra-*O*-benzyl-α-D-galactopyranosyl chloride in the presence of silver imidazolate and mercury(II) chloride also gives α-products mainly.[62] Good yields of β-linked products, on the other hand, arise from use of tetra-*O*-acetyl-α-D-galactopyranosyl bromide with silver imidazolate and zinc chloride,[65] and glycosylating agents with different substituents at O-2 and O-3 (*e.g.*, 47) have been made as suitable precursors of β-D-galactopyranosyl residues of oligosaccharides which require these units to carry other sugars at O-2 or O-3.[81]

Several reports on the preparation of D-galactobioses have appeared: the four isomers of methyl *O*-β-D-galactopyranosyl-β-D-galactopyranose have been made by Koenigs-Knorr procedures, and α,β-mixtures were obtained in parallel work using a 1,2-orthoester derivative.[82] *p*-Nitrophenyl 2-*O*-α- and 2-*O*-β-D-galactopyranosyl-β-D-galactopyranosides,[83] the 3-linked isomers[84] and 6-*O*-β-D-galactopyranosyl-D-glucose and -D-galactose were prepared specifically, the latter compounds being required for coupling to proteins.[85] Condensation between tetra-*O*-acetyl-α-D-galactopyranosyl bromide and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside gave the 1,2- and 1,3-α-linked disaccharide products together with several trisaccharides.[86] A set of differently linked galactobioses were obtained by partial hydrolysis of D-galactose-containing polysaccharides which contained pyruvic acid acetals. For the purposes of this work the 2-*O*- and 4-*O*-β-D-galactopyranosyl-D-galactoses were synthesized.[87] The disaccharide units of agar and κ-carrageenan, *i.e.*, 3,6-anhydro-4-*O*-β-D-galactopyranosyl-L- and -D-galactose, have been isolated following acid hydrolysis and studied by ^{13}C n.m.r. spectroscopy.[88]

Their significance in biochemical situations has led to the preparation of several disaccharides comprising D-galactose bonded glycosidically to amino-sugars. Several groups have obtained lactosamine derivatives, the sugar itself being synthesized from hexa-*O*-acetyllactal by the nitrosyl chloride addition method. β-Glycosides are obtainable also by this approach[89] and *N*-acetyllactosamine linked α- to L-serine and L-threonine have been synthesized by use of a 2-azido-β-D-glycosyl chloride.[90] The β-*p*-trifluoroacetamidophenyl glycoside has been made by galactosylation of an aryl glucoside derivative,[91] and *N*-acetyllactosamine itself have been made on a 80 mmol scale by a cyclic, enzymic process involving the use of D-glucose 6-phosphate, 2-acetamido-2-deoxy-D-glucose and phosphoenolpyruvate.[92] A general method of making 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosides has been reported,[93] and the 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-α-D-galactopyranosides of L-serine and L-threonine have been produced by two different strategies.[94,95] The closely related glycerol glycoside (48) has been synthesized by a procedure based on galactosylation of an appropriately protected glycerol glucoside derivative.[96]



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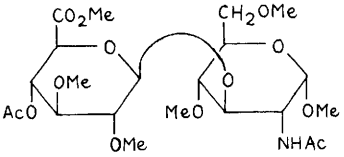


(49)

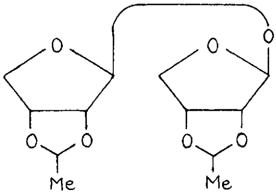
Representatives of the reverse type of disaccharides - *i.e.*, those with 2-amino-2-deoxy-α-D-galactose in the non-reducing position can be made, for example, by use of the trichloroacetimidate of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-galactopyranose.[97]

In the area of uronic acid-containing disaccharides, the fully substituted derivative (49) has been isolated in 70% yield from methylated hyaluronic acid by methanolysis and acetylation,[98] and methyl 4-*O*-(methyl α-D-galactopyranosyluronate)-β-D-galactopyranoside hexaacetate has been obtained by derivatization of an aldobiouronic acid produced by partial hydrolysis of a plant polysaccharide.[99] Disaccharides comprising *N*-acetyl-D-neuraminic acid bonded 6-*O*-α- to D-galactose[100] and 6-*O*-β- to 2-acetamido-2-deoxy-D-glucose have been prepared,[101] and disaccharide nucleosides having this acid α-bonded to O-5 of ribonucleosides are mentioned in

Chapter 19.

The first derivatives of β-D-erythrofuranosyl β-D-erythrofuranoside (*e.g.*, 50) have been isolated following the periodate oxidation and acetaldehyde treatment of starch.[102]

2,3-Di-*O*-acetyl-4-*O*-benzyl-D-xylosyl bromide has been used in an iterative synthesis of the methyl β-glycosides of (1 → 4) linked β-D-*xylo*oligosaccharides of chain lengths 2-6. ^{13}C N.m.r. spectra of the products were reported and interpreted.[103] The same glycosylating reagent condensed with 1,2,3-tri-*O*-acetyl-β-D-xylopyranose gave access to the analogous oligoxyloses (DP 2-5). α-Linked products were also reported, and again ^{13}C n.m.r. data were provided.[104] The diaminoxylobiose derivative (51) has been prepared using a 2-azido glycosylating agent as a key intermediate for the total synthesis of glycocinnamoylspermidines.[49]



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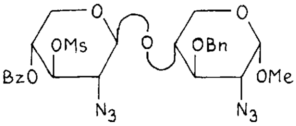
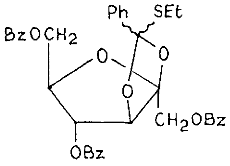


(51)

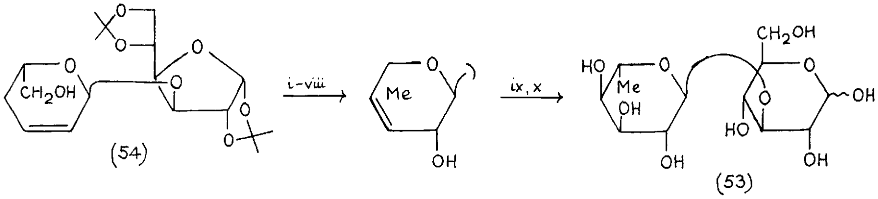


(52)

The D-fructofuranose thio-orthoester (52) has been found effective as a means of access to α-D-fructofuranosides; condensation with 1,2,3,4-tetra-*O*-acetyl-6-*O*-triphenylmethyl-β-D-glucose and deprotection gave 6-*O*-α-D-fructofuranosyl-D-glucose.[105] A fructosylxylose and a difructosylxylose were formed by the action of a fungal fructosyl transferase on sucrose in the presence of D-xylose as acceptor.[106]

The synthesis of β-linked L-rhamnopyranosides can be effected by use of 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnosyl bromide as was exemplified by the preparation of methyl 4-*O*-(β-L-rhamnopyranosyl)-α-L-rhamnopyranoside and its 2- and 3-linked isomers.[107] 3,4-Di-*O*-benzyl-2-*O*-methanesulphonyl-1-*O*-trifluoromethanesulphonyl-α-L-rhamnose has also been used for this purpose, giving methyl 2-*O*-(β-L-rhamnopyranosyl)-α-D-glucopyranoside in high yield (α,β-ratio 1:5) but being less specific when applied in the 2-*O*-glycosylation of mannopyranosyl derivatives.[108] Use of tri-*O*-acetyl-L-rhamnopyranosyl bromide in the presence of mercury(II) cyanide gives mainly α-linked products and, in this way, 2-*O*-α-, 3-*O*-α-, 3-*O*-β- and 4-*O*-α-L-rhamnopyranosyl-D-galactose have been synthesized.[109,110]

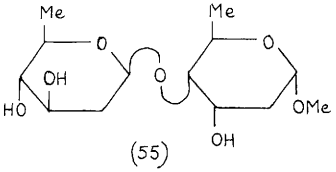
An ingenious synthesis of 3-O-α-L-fucopyranosyl-D-glucose (53) utilizes the unsaturated compound (54) which was made by cycloaddition procedures (Scheme 11). In similar fashion 3-O-(2-acetamido-2-deoxy-α-D-galacto- and talo-pyranosyl)-D-glucoses were synthesized from a 2,3-unsaturated-4-deoxyglycosylglucose derivative.[111] Phenyl 2-acetamido-2-deoxy-4-O-(α-L-fucopyranosyl)-β-D-glucopyranoside[112] and the 6-linked disaccharide (as its p-nitrophenyl[112] and p-trifluoroacetamidophenyl[91] glycosides) have been prepared for biochemical work.

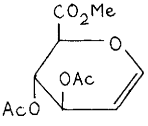


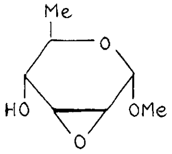
Reagents: i, TsCl-Py ; ii, NaI ; iii Bu_3SnH ; iv, H_2O_2-PhCN, v, TMSI ; vi, DBU ; vii, DMSO-DCC ; viii, $LiAlH_4$; ix, OsO_4 ; x, H^+

Scheme 11

The β-(1 → 4) linked dideoxysugar disaccharides (55) was obtained by use of the uronic acid glycal derivative (56) and the epoxide (57) in the presence of N-iodosuccinimide; α-linked and 1,3-linked compounds related to the disaccharide (55) were also produced in the course of this work.[113] A per-O-acetylated N-trifluoroacetylated disaccharide derivative and tin(IV) chloride catalysis was used in the preparation of the anthracycline analogue (58).[114]

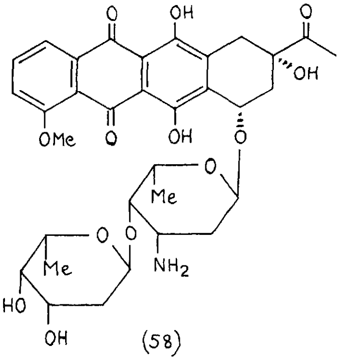

(55)


(56)


(57)

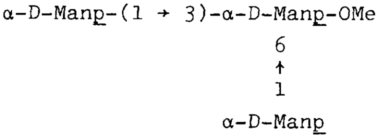
1.3 Synthesis of Trisaccharides.- The considerable developments recently reported on the chemical synthesis of complex oligosaccharides (particularly those of biological importance) have been expertly reviewed,[115] and provisional recommendations for the abbreviated representation of oligosaccharide chains have been made[61] and will be used henceforth in this Chapter.

In the area of neutral unbranched trisaccharides, β-D-Xylp-



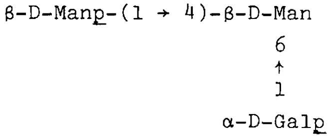
(58)

(1 → 4)-β-D-Xyl*p*-(1 → 4)-D-Xyl[116] and β-D-Man*p*-(1 → 4)-α-L-Rha*p*-(1 → 3)-D-Gal,[117] the repeating unit of the O-antigenic polysaccharide of *Salmonella newington*, have been synthesized and Koenigs-Knorr procedures applied to derivatives of the latter have led to hexa- and nona-saccharides. A dehydration glycosylation method has been used to give 16 linear trisaccharides with different disaccharides bonded to benzyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside.[117a] The following branched compounds have also been reported: (58A),[117b] (59), [and the related (60)],[118] (61), (62),[119] (63), which is the trisaccharide unit of the core of Salmonella



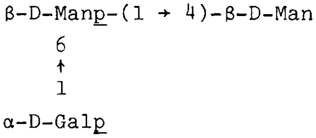
$$\begin{array}{ll} \alpha\text{-D-Man}p\text{-}(1 \rightarrow 3)\text{-} & \alpha\text{-D-Man}p\text{-OMe} \\ & \quad 6 \\ & \quad \uparrow \\ & \quad 1 \\ & \alpha\text{-D-Man}p \end{array}$$

(58A)



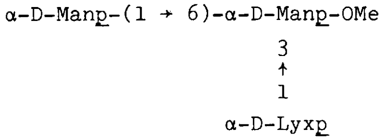
$$\begin{array}{ll} \beta\text{-D-Man}p\text{-}(1 \rightarrow 4)\text{-} & \beta\text{-D-Man} \\ & \quad 6 \\ & \quad \uparrow \\ & \quad 1 \\ & \alpha\text{-D-Gal}p \end{array}$$

(59)



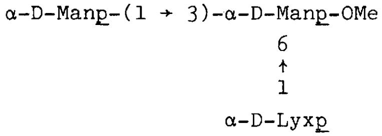
$$\begin{array}{ll} \beta\text{-D-Man}p\text{-}(1 \rightarrow 4)\text{-}\beta\text{-D-Man} \\ \quad 6 \\ \quad \uparrow \\ \quad 1 \\ \alpha\text{-D-Gal}p \end{array}$$

(60)



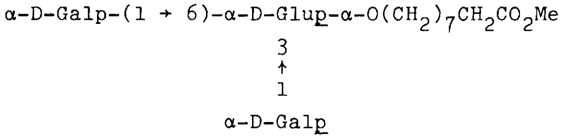
$$\begin{array}{ll} \alpha\text{-D-Man}p\text{-}(1 \rightarrow 6)\text{-} & \alpha\text{-D-Man}p\text{-OMe} \\ & \quad 3 \\ & \quad \uparrow \\ & \quad 1 \\ & \alpha\text{-D-Lyx}p \end{array}$$

(61)



$$\begin{array}{ll} \alpha\text{-D-Man}p\text{-}(1 \rightarrow 3)\text{-} & \alpha\text{-D-Man}p\text{-OMe} \\ & \quad 6 \\ & \quad \uparrow \\ & \quad 1 \\ & \alpha\text{-D-Lyx}p \end{array}$$

(62)



$$\begin{array}{ll} \alpha\text{-D-Gal}p\text{-}(1 \rightarrow 6)\text{-} & \alpha\text{-D-Glu}p\text{-}\alpha\text{-O}(CH_2)_7CH_2CO_2Me \\ & \quad 3 \\ & \quad \uparrow \\ & \quad 1 \\ & \alpha\text{-D-Gal}p \end{array}$$

(63)

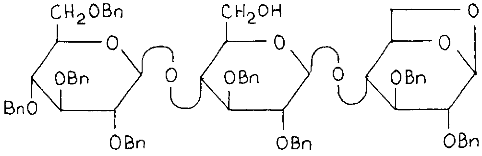
lipopolysaccharides,[120] as well as the dideoxyhexose-containing trisaccharide glycosides 8-methoxycarbonyloctyl 3,6-di-*O*-(3,6-dideoxy-α-L-*xylo*-hexopyranosyl)-α-D-glucopyranoside[120] and 8-methoxycarbonyloctyl 3-*O*-(3,6-dideoxy-α-D-*arabino*- and α-D-*ribo*-hexopyranosyl)-2-*O*-α-D-galactopyranosyl-α-D-mannopyranoside,[121] all of which are related to bacterial polysaccharide antigens.

Biological studies have required the preparation of several aminosugar-containing trisaccharides: β-D-Gal*p*-(1 → 3)-β-D-Glc*p*NAc-(1 → 6)-D-Gal together with the analogous (1 → 3) (1 → 3), (1 → 4) (1 → 6), and (1 → 4)(1 → 3) compounds and their 8-methoxycarbonyloctyl β-glycosides,[122] β-D-Gal*p*-(1 → 4)-β-D-Glc*p*NAc-(1 → 6)-α-D-GalNAc as its related glycoside,[74] β-D-Gal*p*-(1 → 4)-β-D-GlcNAc*p*-derivatives of 7-deoxy-L- and -D-*glycero*-D-*galacto*-heptopyranose, *i.e.*, the D-galactose trisaccharides having *C*-methyl groups specifically introduced at the reducing moieties, which were made to assist with the assessment of the preferred conformations about the (1 → 6)-linkage of the trisaccharide as it is accepted at the binding site of anti-I Ma monoclonal antibody.[123] 6-Deoxyhexose-containing compounds of this class to have been produced are: α-L-Rha*p*-(1 → 3)-α-L-Rha*p*-(1 → 3)-2-acetamido-2,6-dideoxy-β-D-glucopyranosyl 8-methoxycarbonyloctanol (α- and β-glycosides),[124] α-L-Fuc*p*-(1 → 2)-β-D-Gal*p*-(1 → 4)-β-D-GlcNAc, β-D-Gal*p*-(1 → 4)[α-L-Fuc*p*-(1 → 3)]-β-D-GlcNAc as their 8-methoxycarbonyloctyl glycosides[125] and α-L-Fuc*p*-(1 → 2)-β-D-Gal*p*-(1 → 3)-D-GlcNAc.[126]

The *N*-acetylneuraminic acid-containing trisaccharide α-D-Neu5Ac-

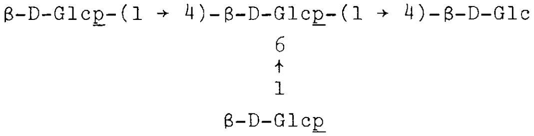
(2 → 6)-β-D-Galp-(1 → 4)-D-GlcNAc, which is present as a terminal group in many glycoproteins, has been synthesized,[127] and the related α-D-Neu5Ac-(2 → 3)-β-D-Galp-(1 → 4)-D-Glc containing an O-acetyl group at position 4 of the acid unit is the main oligosaccharide of the milk of the Australian chidna.[128] An aminosugar-containing trisaccharide component of anthracycline antibiotics is noted in Chapter 18.

1.4 Synthesis of Tetra- and Higher Saccharides.- Cellotetraose has been synthesized using the trichloroacetamidate method; the adopted procedures involved the use of the trisaccharide derivative (64)



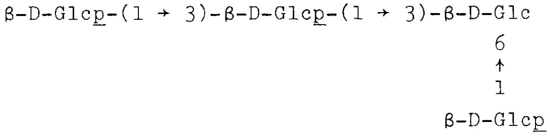
(64)

from which the branched glucotetraose (65) was also produced.[129] Other homotetrasaccharides to have been reported are the other glucotetraose (66),[130] the D-mannose compounds (67) (the corresponding hexaose was also prepared)[131] and (68),[119] and the D-galactose tetramer (69).[132] Fructosyl transferase from asparagus catalyses



$$\beta\text{-D-Glc}p\text{-}(1 \rightarrow 4)\text{-}\underset{\substack{6\\ \uparrow\\ 1\\ \beta\text{-D-Glc}p}}{\beta\text{-D-Glc}p}\text{-}(1 \rightarrow 4)\text{-}\beta\text{-D-Glc}$$

(65)

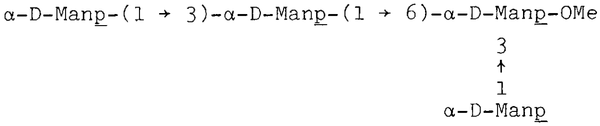


$$\beta\text{-D-Glc}p\text{-}(1 \rightarrow 3)\text{-}\beta\text{-D-Glc}p\text{-}(1 \rightarrow 3)\text{-}\underset{\substack{6\\ \uparrow\\ 1\\ \beta\text{-D-Glc}p}}{\beta\text{-D-Glc}}$$

(66)

α-D-Manp-(1 → 2)-α-D-Manp-(1 → 2)-α-D-Manp-(1 → 2)-α-D-Man

(67)



$$\alpha\text{-D-Man}p\text{-}(1 \rightarrow 3)\text{-}\alpha\text{-D-Man}p\text{-}(1 \rightarrow 6)\text{-}\underset{\substack{3\\ \uparrow\\ 1\\ \alpha\text{-D-Man}p}}{\alpha\text{-D-Man}p}\text{-OMe}$$

(68)

β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-(1→6)-β-D-Gal*p*-OPr (69)

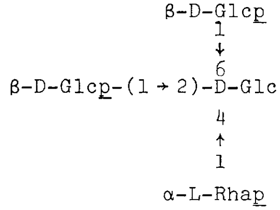
the transfer of β-D-fructofuranose from 1',6-di-*O*-β-D-fructofuranosylsucrose to sucrose and gives the isomeric tetrasaccharide kestose.[133] The biological repeating units of Salmonella A, B, and D antigenic polysaccharides have been made as their *p*-trifluoroacetamidophenyl glycosides (70)-(72) from a common trisaccharide derivative,[134] and the unusual trisubstituted D-glucose compound (73) has been made by dehydrative glycosylation.[134a]

R-(1→3)-α-D-Man*p*-(1→4)-α-L-Rha*p*-(1→3)-α-D-Gal*p*-$OC_6H_4NHCOCF_3$(*p*)

R = 3,6-dideoxy-α-D-*ribo*-hexopyranosyl (70)

R = 3,6-dideoxy-α-D-*xylo*-hexopyranosyl (71)

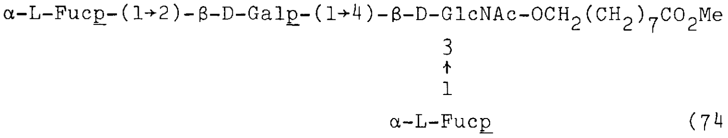
R = 3,6-dideoxy-α-D-*arabino*-hexopyranosyl (72)



$$\begin{array}{r} \beta\text{-D-Glc}p \\ 1\quad \\ \downarrow\quad \\ 6\quad \\ \beta\text{-D-Glc}p\text{-}(1\rightarrow 2)\text{-D-Glc} \\ 4\quad \\ \uparrow\quad \\ 1\quad \\ \alpha\text{-L-Rha}p \end{array}$$

(73)

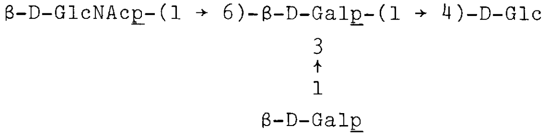
The aminosugar-containing tetrasaccharides (74)-(77) have been synthesized; they are, respectively, a blood group antigenic determinant,[125] "P-antigen globoside",[135] a tammar wallaby milk constituent,[136] and a core unit of some glycoproteins.[137]



$$\begin{array}{l} \alpha\text{-L-Fuc}p\text{-}(1\rightarrow 2)\text{-}\beta\text{-D-Gal}p\text{-}(1\rightarrow 4)\text{-}\beta\text{-D-GlcNAc-OCH}_2\text{(CH}_2)_7\text{CO}_2\text{Me} \\ \hspace{20em} 3 \\ \hspace{20em} \uparrow \\ \hspace{20em} 1 \\ \hspace{18em} \alpha\text{-L-Fuc}p \end{array}$$

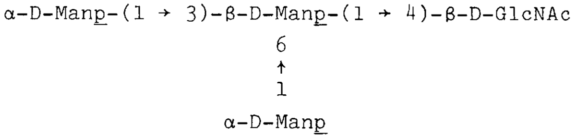
(74)

β-D-GalNAc*p*-(1 → 3)-α-D-Gal*p*-(1 → 4)-β-D-Gal*p*-(1 → 4)-D-Glc (75)



$$\begin{array}{l} \beta\text{-D-GlcNAc}p\text{-}(1\rightarrow 6)\text{-}\beta\text{-D-Gal}p\text{-}(1\rightarrow 4)\text{-D-Glc} \\ \hspace{12em} 3 \\ \hspace{12em} \uparrow \\ \hspace{12em} 1 \\ \hspace{10em} \beta\text{-D-Gal}p \end{array}$$

(76)



$$\begin{array}{l} \alpha\text{-D-Man}p\text{-}(1 \rightarrow 3)\text{-}\beta\text{-D-Man}p\text{-}(1 \rightarrow 4)\text{-}\beta\text{-D-GlcNAc} \\ \qquad\qquad\qquad\qquad\qquad\qquad 6 \\ \qquad\qquad\qquad\qquad\qquad\qquad \uparrow \\ \qquad\qquad\qquad\qquad\qquad\qquad 1 \\ \qquad\qquad\qquad\qquad\qquad\quad \alpha\text{-D-Man}p \end{array}$$

(77)

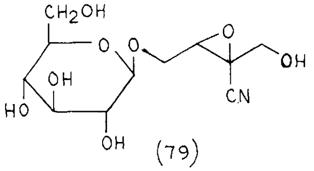
Two reports have appeared on the preparation of the pentasaccharide (78) of the Forssman antigen.[138,139]

α-D-GalNAc*p*-(1→3)-β-D-GalNAc*p*-(1→3)-α-D-Gal*p*-(1→4)-
β-D-Gal*p*-(1→4)-D-Glc (78)

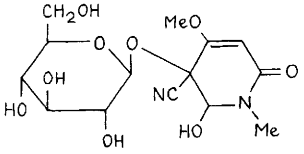
A specific mannohexaose is mentioned in reference 131, and a further hexasaccharide and a nonasaccharide have been produced by the di- and tri-merization of β-D-Man*p*-(1 → 4)-α-L-Rha*p*-(1 → 3)-D-Gal.[117]

1.5 *O*-Glycosides Isolated from Natural Products.- Again a highly selective policy has had to be adopted in this section; many reported simple and complex glycosides have been omitted.

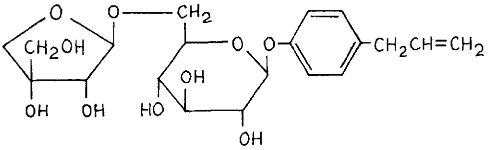
The first monoglucoside of a simple aliphatic dihydric alcohol (2-methylpropane 1,2-diol) has been isolated from a plant[140] as have unusual glucosides of *m*- and *p*-methoxybenzyl alcohol.[141] The new cyanogenic glucosides (79)[142] and (80)[143] have been reported. D-Allose has again been found as a component of plant glycosides[144] occurring as a 2-*O*-β-D-allopyranosyl-D-glucopyranosyl unit of a flavonoid compound.[145] Furcatin, a further plant product, is the apiose-containing disaccharide glycoside (81).[146]



(79)



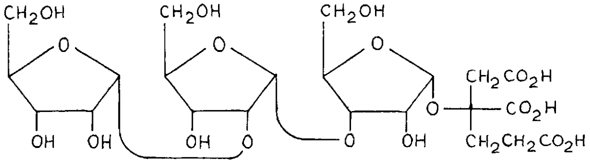
(80)



(81)

A range of starfish steroidal glycosides have been surveyed,[147] and one such compound has been shown to contain the unusual disaccharide unit 2-O-(2-O-methyl-β-D-xylopyranosyl)-α-L-arabinofuranose.[148]

A streptomyces dextransucrase specific inhibitor is the unusual trisaccharide glycoside (82),[149] and the trisaccharide α-D-Manp-(1 → 3)-β-D-Manp-(1 → 4)-GlcNAc has been characterized by ^{13}C n.m.r. methods following its isolation from urine of a patient with mannosidosis.[150]



(82)

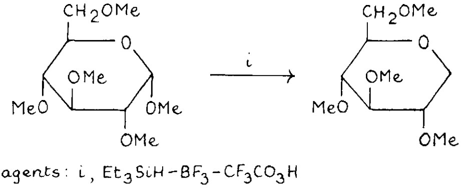
1.6 Reactions and Properties of Glycosides and Oligosaccharides.- The chemistry of sucrose has been reviewed[151] and Bock and Lemieux have carried out an important study of the conformation and flexibility of the compound using ^{1}H and ^{13}C n.m.r. as well as molecular modelling methods.[152] The hydrolysis of sucrose catalysed by anthraquinone 2-sulphonic acid adsorbed on a non-ionic stationary phase has been examined,[153] and products of its treatment with ethylene oxide are efficient phase-transfer catalysts.[154]

The physico-chemical properties of β-lactose have been reviewed following an improvement in its method of preparation.[155]

Rates of acid-catalysed hydrolysis of 19 glyco-furanosides and -pyranosides have been measured at pressures up to 1.5 Kbar; volumes of activation for the reactions showed parallel trends to their entropies of activation.[156] Titanium(IV) chloride catalyses the anomerization of methyl tetra-O-benzyl-β-D-glucopyranoside at room temperature and disaccharide derivatives can be anomerized similarly.[157]

At high temperatures and for extended times alkali treatment of methyl α-L-arabinofuranoside gives small conversion to the β-pyranoside following, it is proposed, attack at C-1 by O-2 and ring opening.[158]

Prop-1-enyl glycosides are cleaved to give the free sugars with iodine and aqueous THF, whereas in dry THF 1,2-trans-related glycosides of 2-acetamido-2-deoxy sugars afford oxazolines. Both reactions are markedly better than corresponding methods which employ mercury(II) salts.[159] Glycosides are cleaved on treatment with aqueous thiols containing small amounts of iodine, the plant β-D-glucopyranoside darutoside affording 70% of aglycone in 10 h at room temperature by this procedure.[160] A further novel method of cleaving glycosidic linkages uses triethylsilicon hydride, boron trifluoride and trifluoroacetic acid (Scheme 12). It can be used



Scheme 12

with furanosides, and can indicate the position of linkage and ring size of sugar units in polysaccharides. In addition it has preparative value, 1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol being obtainable almost quantitatively from the corresponding methyl β-glycoside.[161] Another way of releasing aglycones from glycosides (exemplified with a steroidal compound) involves periodate oxidation, conversion of the resulting dialdehyde to a bishydrazone with 1,1-dimethylhydrazine, and alkaline cleavage.[162]

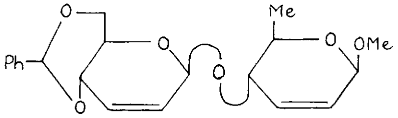
Photolysis of aqueous solutions of methyl α-D-glucopyranoside and hydrogen peroxide gave free radicals, six of which were identified by an e.s.r. method as follows: $-\dot{C}_6HOH$ (formed by hydrogen abstraction from C-6), $>\dot{C}_2-OH$, $O_5-\dot{C}H_2$, $>\dot{C}_3-OH$, $>\dot{C}_1-H$ and $>\dot{C}_5-CH_2OH$.[163] Oxidation of this glycoside with Fenton's reagent is described in Chapter 15.

The ability of chromium trioxide to oxidize glycoside peracetates with equatorial aglycones selectively has been used as the basis of a method for determining the nature of linkages in oligosaccharides. Less selectivity is found with permethylated derivatives.[164]

Prolonged treatment with Raney nickel in water causes methyl α-L-arabinopyranoside to be converted appreciably into methyl β-D-xylopyranoside and methyl α-L-lyxopyranoside. Similar epimerizations were found with other glycosides.[165]

The sections on oligosaccharide synthesis contain many references to substitution reactions of di- and higher saccharides. In addition, several derivatives of methyl β-cellobioside have been reported, notably the 4',6'-O-benzylidene acetal, the separate 6-

tosylates, 3,6-anhydro-derivatives and both 5,6-enes and the doubly unsaturated compound (83).[166]



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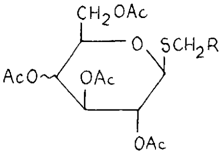
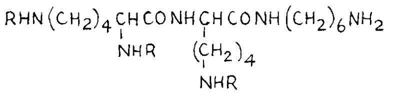


(84) R = CHO

(85) R = CH_2CHO

2 S-Glycosides

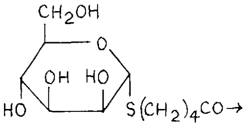
A one-pot synthesis of a series of 1,2-trans-related methyl 1-thioglycopyranoside peracetates involves acetobromination followed by treatment with the methanethiolate anion. Since this latter step causes some de-esterification, the products were reacetylated.[167] Fusion of penta-O-acetyl-β-D-glucopyranose or its 2-amino analogue with aryl thiols in the presence of zinc chloride affords the β-glycosidic products,[168] and p-nitrobenzenethiolate bound to resins can be used with acetylated glycosyl halides to make p-nitrophenyl 1-thioglycosides.[169] More specifically, the 2-oxoethyl and 3-oxypropyl 1-thio-β-D-glucopyranosides and -galactopyranosides (84), (85) were made by reaction of the 2,3,4,6-tetra-O-acetyl-1-thioaldoses with 2-bromoacetaldehyde and acrolein, respectively. The products, after deacetylation and reductive amination, could be



$$RHN(CH_2)_4\underset{\substack{|\\ NHR}}{CH}CONH\underset{\substack{|\\ (CH_2)_4\\ |\\ NHR}}{CH}CONH(CH_2)_6NH_2$$

(86)

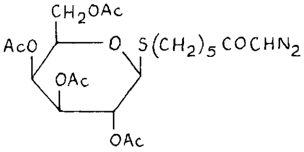
R =



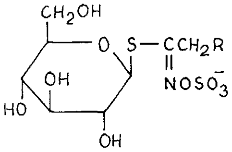
coupled to proteins.[170] Compound (86), coupled via the amino-group to the 6"-position of raffinose, has been produced as a specific tissue marker,[171] and the 1-thiogalactoside (87) has been synthesized for photoaffinity labelling studies.[172]

Heptyl 1-thio-α-D-mannopyranoside forms a liquid crystal between 65°C, at which temperature the hydrocarbon portions of the crystal 'melt', and 151°C, when the associations between the hydrophilic parts break down. The crystal structure was reported.[173]

Pericyclic elimination has been ruled out as the biosynthetic means of obtaining sinigrin (88) from the thiomethyl precursor (89),[174] and the enzymic hydrolysis of the former to give 1-cyano-



(87)

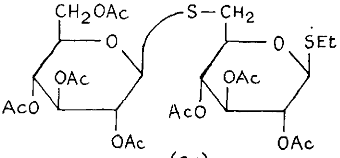


(88) $R = -CH{=}CH_2$

(89) $R = -(CH_2)_2SMe$

2,3-epithiopropane has been examined.[175]

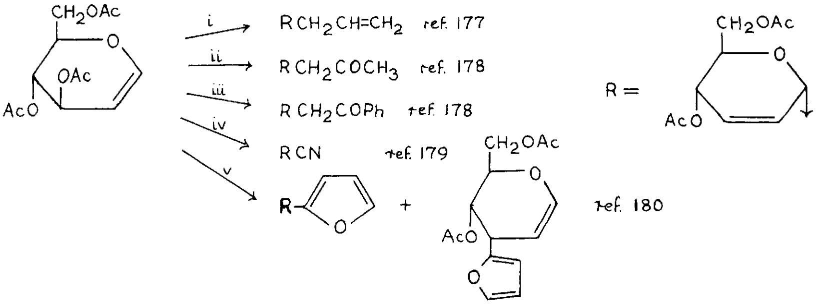
On treatment with nucleophiles, the cyclic sulphonium salt (20) can react in three different ways, sulphur compounds giving ethyl 1-thioglycoside derivatives with the nucleophile bonded to C-6. In this way the dithiodisaccharide (90) has been produced.[25] The 1,4-α-sulphur-linked D-glucobiose was synthesized by nucleophilic displacement on D-galactose 4-trifluoromethanesulphonates by 1-thio α-D-glucose.[176]



(90)

3 C-Glycosides

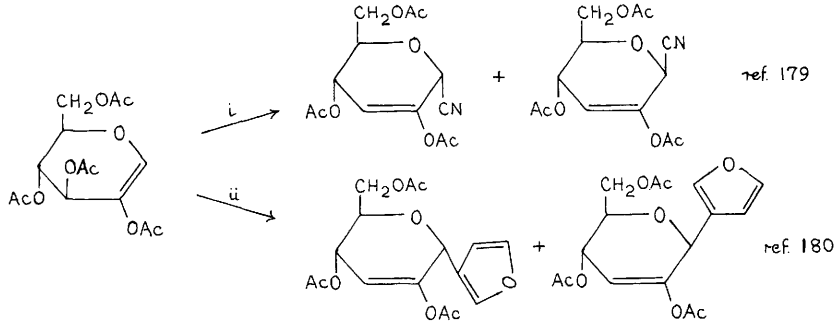
C-Glycosides have been of interest as building units in natural product synthesis, and unsaturated sugars have proved to be important precursors (see also Chapter 12). Glycals and hydroxyglycals react with several nucleophilic carbon reagents to give 2,3-



Reagents: i, $CH_2{=}CHCH_2SiMe_3-TiCl_4$; ii, $CH_2{=}\underset{OAc}{C}Me-BF_3$; $CH_2{=}\underset{OTMS}{C}Ph - BF_3$; iv, $Me_3SiCN-BF_3$; v, Furan - BF_3

Scheme 13

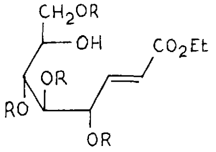
unsaturated C-glycosides (Scheme 13),[177-180] but in the case of the reaction with furan (and thiophene) 3-substituted glycals were also found.[180] α-C-Glycosides predominated, but were usually accompanied by some of the β-anomer. Analogous reactions of 2-hydroxyglycal esters are noted in Scheme 14; in these cases the stereoselectivity of the products was poor.[179,180]



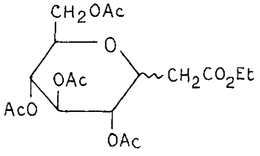
Reagents: i, $Me_3SiCN-BF_3$; ii, Furan-BF_3

Scheme 14

Several important developments have taken place in the synthesis of C-glycosides by way of alkenes derived by chain extensions from the carbonyl groups of aldose derivatives. The interesting observation has been made that the alkene (91), obtained by Wittig reaction of tetra-O-benzyl-D-glucopyranose, does not cyclize with

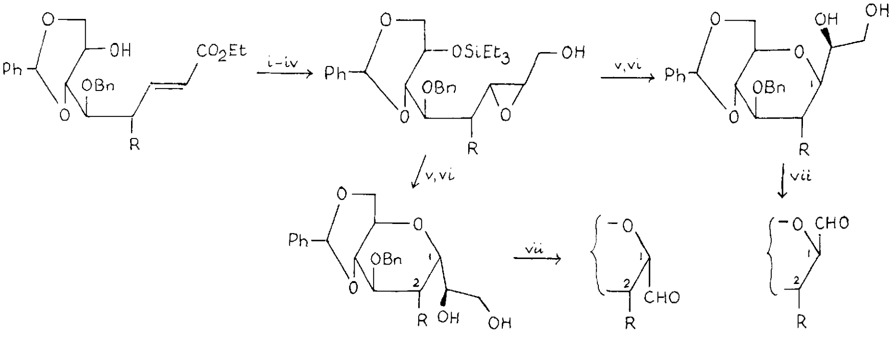


(91) R = Bn
(92) R = Ac



(93)

base, and with acid gives a furan derivative. By contrast the analogous acetylated derivative (92) exists largely as the ring-closed product (93), the ring closure probably being dependent on the presence of the allylic acetoxy group. In agreement with this, 3,4,6-tri-O-acetyl-2-O-benzyl-D-glucose gave a product which did not cyclize.[181] Ingenious work by Sharpless and coworkers on related compounds has led to important new routes to the aldehydes (94) and (95) (Scheme 15). The epoxide leading to the β-glycoside (94) was produced using (+)-diethyl tartrate whereas the isomeric epoxide from which compound (95) was derived was the product of use of the (–)-enantiomer.[182]



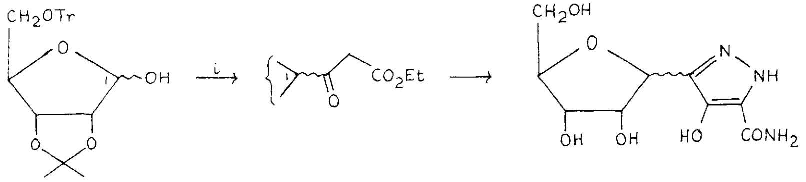
(95) (94)

R = OBn or H

Reagents: i, Et_3SiOTf; ii, Bu^t_2AlH; iii, $Bu^tO_2H-Ti(OPr^i)_4$; iv, Diethyl Tartrate; v, F^-; vi, NaH; vii, IO_4^-

Scheme 15

A related Wittig reaction was the key step in the synthesis of the C-nucleoside analogue pyrazofurin A and its α-anomer pyrazofurin B (Scheme 16),[183] and tetrahydropyrimidine C-glycosides have been reported as products of reaction of various aldose derivatives with free reducing groups, urea and alkyl acetoacetates.[184] The

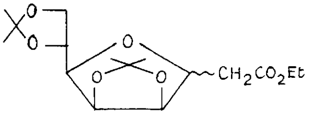


Reagents: i, $Ph_3P=CHCOCH_2CO_2Et$; ii, TsN_3-Et_3N; iii, NaH; iv, NH_3-MeOH; v, H^+

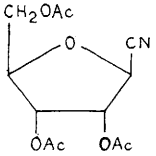
Scheme 16

furanosyl C-glycosides (96) were formed as well as the acyclic unsaturated ester on treatment of 2,3:5,6-di-O-isopropylidene-D-mannose with a Wittig reagent derived from ethyl bromoacetate[185] and, in related fashion, free sugars were converted into C-glycosylnitromethanes by elimination and intramolecular addition reactions applied to the initially formed 1-nitroalditols.[186] Dehydrations of phenylosazones and pentitol-1-yl heterocycles to give furanosyl C-glycosides are reported in Chapter 9.

Treatment of glycosyl acetates with trimethylsilyl cyanide in the presence of a Lewis acid affords a simple synthetic route to C-glycosyl cyanides. 1,2-trans-Related products are obtained when



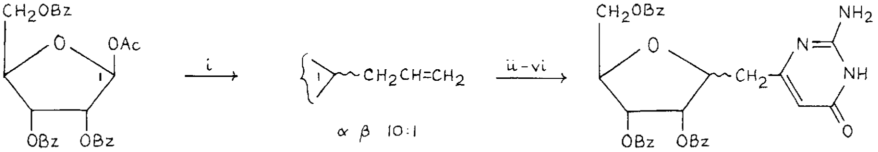
(96)



(97)

a participating group is present at C-2, otherwise mixed anomers are formed.[187] An independent report describes this procedure applied to the synthesis of the D-ribofuranose compound (97) and its tribenzoyl analogue. In the latter case the reaction could be diverted to give a 1,2-cyanobenzylidene product, but this also can be efficiently converted into the β-C-glycoside.[188]

Two groups have reported the interesting direct synthesis of allyl C-glycosides from glycosyl acetates by use of allyltrimethylsilane in the presence of an acid catalyst. Furanosyl and pyranosyl examples were reported,[189] and the initial substituent was elaborated into several new groups, *e.g.*, $-CH_2CO_2H$, $-CH_2CHO$, $-CH_2COCH_2CN$, and the heterocyclic group of compound (98) (Scheme 17).[190]

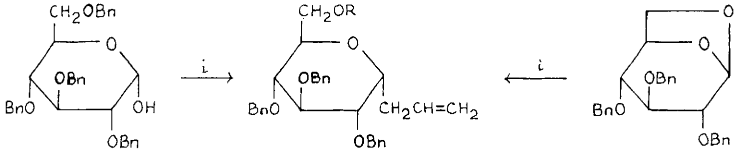


(98)

Reagents: i, $CH_2=CHCH_2SiMe_3$ – TMSOTf; ii, O_3; iii, H_2O_2; iv, $SOCl_2$; v, $EtO_2CCH_2CO_2Li$; vi, Guanidine

Scheme 17

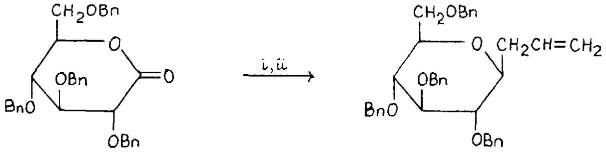
Allyltrimethylsilane with boron trifluoride can be used to give C-glycosides directly from sugars unprotected at C-1 and also from anhydrosugar derivatives (Scheme 18). In the illustrated example



Reagents: i, $CH_2=CHCH_2SiMe_3$ – BF_3 R = H or Bn

Scheme 18

the yield of C-glycosides from tetra-O-benzyl-D-glucose was 55% (α,β, 10:1), but this was increased to 80% if the sugar was firstly converted into its p-nitrobenzoate. A high yield of the β-product (99) was obtained by the reactions illustrated in Scheme 19.[191]

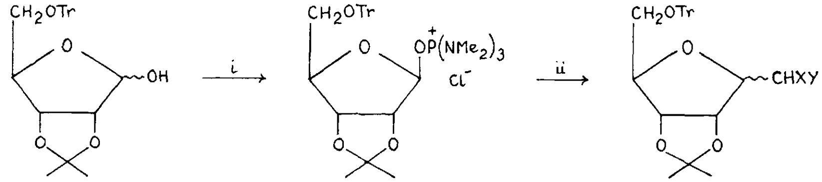


(99)

Reagents: i, $CH_2{=}CHCH_2{-}MgBr$; ii, $Et_3SiH{-}BF_3$

Scheme 19

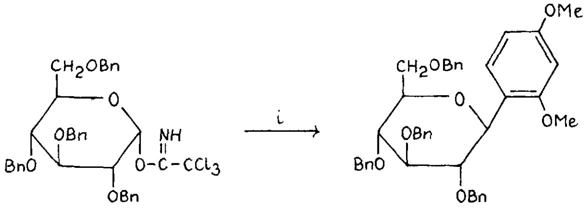
A new and potentially valuable method of making C-glycosides involves the use of phosphonium intermediates (Scheme 20) and carbanions. In the illustrated examples α:β ratios were about 10:1.[192]



Reagents: i, $P(NMe_2)_3 - CCl_4$; ii, NaCHXY   X,Y = CN, CO_2Et

Scheme 20

Trichloroacetamidates can be used to prepare C-glycosides from activated benzenes (Scheme 21),[193] and glycosyl halides have been

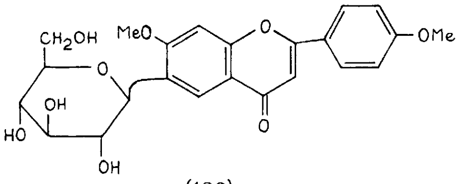


Reagents: i, $m\text{-}C_6H_4(OMe)_2 - BF_3$

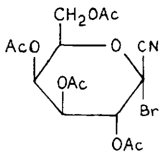
Scheme 21

employed to obtain C-glycosylacetic acids and hence the corresponding substituted ethylamines and ethyltriazines,[194] and the C-glucosylflavonoid (100).[195] Several new closely related C-glycosides have been isolated from plant sources.[196-200] Other work on the synthesis of C-bonded nucleosides is referred to in Chapter 19.

Free radical bromination of glycosyl cyanides has been shown to give 1-bromo products, e.g., compound (101),[201] and a potentially

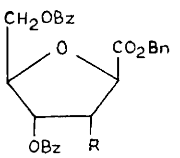


(100)

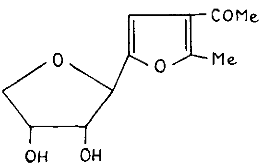


(101)

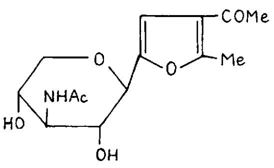
useful route to 2-deoxy-*C*-nucleosides involves conversion of D-*ribo*-compounds (*e.g.*, 102) into their 2-deoxy analogues (*e.g.*, 103) by an elimination, hydrogenation procedure. The method affords mixed α,β-products.[202] 3-Amino-3-deoxysugar *C*-glycosides have been made by standard methods involving periodate oxidation and nitromethane cyclization; thus, the D-erythrofuranosyl compound (104) afforded access to the D-*xylo*-analogue (105).[203]



(102) R = OBz
(103) R = H



(104)



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4

Ethers and Anhydro-sugars

1 Ethers

Dealkylation and de(trialkylsilyl)ation have been covered in a review on selective removal of protecting groups.[1]

Methyl Ethers.- Acetylated mono-, di- and tri-*O*-methyl ethers of methyl α-D-glucopyranoside were obtained following partial methylation and isolated chromatographically;[2,3] partial methylation of methyl glycosides and alditols is mentioned in Chapter 22. Conventional protecting group methods were used to prepare methyl 2,6-di- and 2,3,6-tri-*O*-methyl-D-galactopyranoside,[4] and all the possible mono-, di-, and tri-*O*-methyl ethers of methyl (methyl α-D-galactopyranosid)uronate.[5,6] 3-*O*-Methyl-lactose has been obtained *via* 1,2,6,2',3',4',6'-hepta-*O*-benzoyl-lactose, which was prepared by partial benzoylation of lactose and then methylated with methyl triflate.[7] Selective 3-*O*-methylation and -benzylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside was achieved using conventional reagents.[8] The etherification procedure developed by Avela and co-workers, in which a carbohydrate diol is first converted to a dianion (NaH), then to a copper(II) chelate ($CuCl_2$), and finally allowed to react with excess alkyl iodide, has been shown to be useful for achieving mono-alkylation (>85%) with some regioselectivity. The methylation, benzylation and allylation of eight diols was examined; *e.g.*, methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside gave only the 4-*O*-methyl or -benzyl ether using THF as solvent.[9]

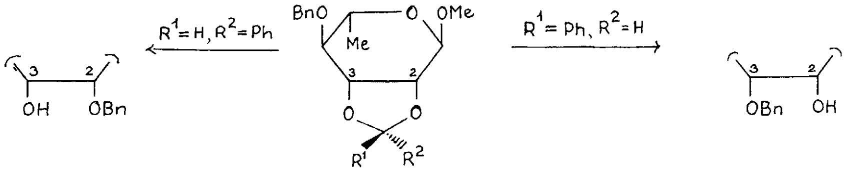
The silver oxide catalysed methylation of 2,4-*O*-benzylidene-D-threose and -D-erythrose is covered in Chapter 5, while a synthesis of 2'-*O*-methyl-uridine is outlined in Chapter 19.

Other Alkyl and Aryl Ethers.- Two references to benzylation and allylation are mentioned in the section on methyl ethers. Partial stannylation of methyl α-D-glucopyranoside with tributyltin oxide, followed by reaction with alkyl halide, gave the 2,6-di-O-allyl, -benzyl, and -trityl ethers as major products, but the regioselectivity was not particularly high; e.g., using 1.5 molar equivalents of tributyltin oxide with benzyl bromide gave a mixture of the 6-mono-, and the 2,6-, 4,6-, and 3,6-di-O-benzyl ethers in 48.6, 30.5, 6.0, and 4.5% yield respectively.[10] Analogous treatment of methyl β-D-galactopyranoside gave the 3,6-di-O-allyl and -benzyl ethers, but the 2,6-di-O-trityl ether; methyl 2,4- and 3,4-di-O-benzyl-β-D-galactopyranoside were then synthesized from the diallylated and ditritylated products respectively.[11] The tin(II) chloride catalyzed benzylation (excess BnBr-Et_3N) of methyl α-L-rhamnopyranoside and its 4-O-benzyl ether, led mainly to 3-O-monobenzylation, with competing 2-O-monobenylation being greater in ethyl acetate than acetonitrile as solvent.[12]

Selective phase-transfer benzylation of methyl 4,6-O-benzylidene-α-D-manno-[13] and -galactopyranosides[14] gave mainly monobenzylated products; while the galactoside gave the 3-O-benzyl ether with one system (BnCl-NaOH-CH_2Cl_2-Et_4NBr), it gave the fully substituted 2,3-di-O-benzyl ether with another (BnCl-KOH-dioxane-Et_4NBr).

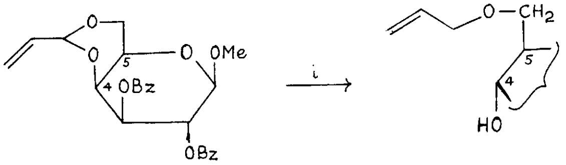
Partial benzylation (BnBr-NaH-DMF) of methyl α-L-fucopyranoside gave complex mixtures; the 2- and 3-O-benzyl ethers (∿2:1, 50%) were obtained from monomolar benzylation, while the 2,4- and 2,3-diethers (∿3:1, 50%) were obtained from dimolar benzylation.[15] Similar monomolar treatment of methyl α- and β-D-galactopyranosides and some of their isopropylidene acetal derivatives was used to obtain monobenzylated products. From either glycoside anomer, the monobenzyl ether fraction was obtained in 50% yield, over half of which was the 6-O-benzyl ether; their 3,4-O-isopropylidene derivatives gave predominantly 2-O-benzyl ethers (∿40%), while the 4,6-O-isopropylidene-β-galactoside gave the 3-O-benzyl ether (∿40%).[16] Partial benzylation of methyl α-D-xylopyranoside gave the 2,4-diether in 70% yield; other isomers were synthesized by direct acetalation of the glycoside (to form mixed 2,3- and 3,4-O-isopropylidene or -cyclohexylidene acetals) then benzylation and separation of the mixed products.[17] Improved syntheses of benzyl 2-acetamido-3,4-di-O-benzyl- and -(4-phenylbenzyl)-2-deoxy-α-D-glucopyranosides were reported, utilizing conditions (e.g., BnBr-NaH-THF) which avoid extensive N-benzylation.[18]

Reductive cleavage of benzylidene acetals has been further examined. Using sodium cyanoborohydride-hydrogen chloride, 4,6-O-benzylidene derivatives of hexopyranosides are opened selectively to give the 6-*O*-benzyl ethers with a free 4-hydroxy group; products derived from 2,3-*O*-benzylidenated hexopyranoside are determined by the configuration at the asymmetric acetal carbon (Scheme 1).[19]



Scheme 1

Analogous reductive cleavage of 4,6-*O*-prop-2-enylidene acetals, *e.g.*, the D-galactoside (1) in Scheme 2, gave the corresponding



(1) (2)

Reagents: i, NaBH$_3$CN-HCl-THF

Scheme 2

6-*O*-allyl ethers, *e.g.* (2), in good yield.[20] By contrast, similar hydrogenolytic ring-cleavage of *O*-substituted benzyl 4,6-*O*-benzylidene-β-D-glucopyranosides with a variety of reagents (*i.e.*, LiAlH$_4$-AlBr$_3$, LiAlH$_4$-AlCl$_3$, Bu$^i_2$AlH, or borane) gave mainly the 4-*O*-benzyl ethers, accompanied by the 6-*O*-benzyl ethers in amounts increasing with the decreasing bulk of the *C*-3 substituent (in the order -OPr, -OBn, -OEt, -OMe, and H). Of the reagents, the first, equivalent to bromoalane (AlH$_2$Br) gave the best selectivity for the 4-*O*-benzyl ethers.[21]

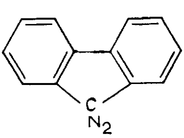
The 4-methoxybenzyl ether protecting group can be removed readily and efficiently with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) in dichloromethane-water, conditions which leave most other protecting groups unaffected.[22] It has been used during the synthesis of oligonucleotides.[23] The synthesis and deprotection of related 4-methoxybenzylated nucleoside derivatives are referred to in Chapter 19.

Regioselective 3-*O*-diarylmethylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside has been accomplished using diaryldiazoalkanes, *e.g.*, (3) and (4), with tin(II) chloride as catalyst; by contrast, these diazoalkanes reacted unselectively with the 4,6-*O*-isopropylidene-mannoside analogue at *O*-2, *O*-3, or both.[24] The diphenylmethylation of carbohydrate hydroxy groups could also be effected by heating with diazo(diphenyl)methane in a solvent (*e.g.*, benzene) in the absence of a catalyst, ester and acetal groups being unaffected by these conditions. The diphenylmethyl group could be readily removed by hydrogenation, yet was sufficiently acid-stable to permit selective hydrolysis of acetal groups in compounds such as (5).[25]

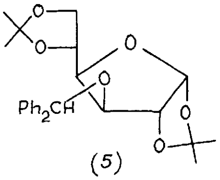
The 3-*O*-benzyl ether of 2-acetamido-1,6-anhydro-2-deoxy-β-D-glucopyranose has been synthesized by way of selective 4-*O*-tritylation; the minor product of this tritylation, the 3-*O*-trityl ether, was converted to the 4-*O*-benzyl isomer.[26]

Ph_2CN_2

(3)



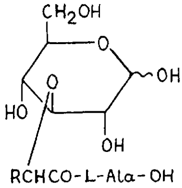
(4)



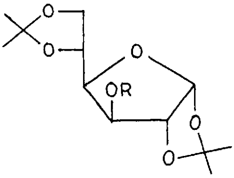
(5)

2-*O*-(Diethylaminoethyl)-D-glucose was the predominant substituted monosaccharide obtained on acid hydrolysis of DEAE-starch, prepared by reaction of starch to D.P. 0.025 with (2-chloroethyl)diethylamine; related DEAE-oligosaccharides were obtained by partial hydrolysis.[27]

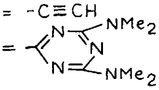
The muramyl-peptide analogues, *N*-[2-(D-glucos-3-*O*-yl)propanoyl and -acetyl]-L-alanine, (6) and (7) respectively, have been synthesized by standard procedure from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (8).[28] The reaction of (8) with acetylene in aqueous potassium hydroxide gave the 3-*O*-ethynyl ether (9); the D-*galacto* isomer gave analogous results.[29] Similarly, reaction of the sodium derivative of (8) with 2-chloro-4,6-bis(dimethylamino)-



(6) R = Me
(7) R = H



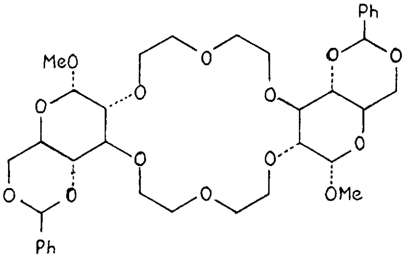
(8) R = H
(9) R = -C≡CH
(10) R =



1,3,5-triazine gave the 1,3,5-triazin-2-ylated glucose (10).[30] Both compounds (9) and (10) could be deacetalated to give the free sugar derivative.

Partial tetrahydropyranylation of meso-erythritol and sorbitol made the products suitable for alkylation using phase transfer catalysis; the advantages of a dimethylsulphoxide-hydrogen chloride system for selective tetrahydropyranylation were outlined.[31]

The [18]-crown-6 compound (11) and its isomer with the syn-alignment of the two pyranoside moieties have been synthesized in 14 and 8% yield respectively from methyl 4,6-O-benzylidene-α-D-glucopyranoside by alkylation with diethyleneglycol ditosylate; a variety of derivatives with different solubility and complex forming characteristics were prepared from compound (11).[32] The bis-dianhydro-D-mannitolo-30-crown-10 derivative (12) was similarly prepared in 14% yield from 1,4:3,6-dianhydro-D-mannitol; both compound (12) and its 1:1:1 complexes with primary ammonium cations and either water or primary amine were characterized by ^{13}C-n.m.r. and X-ray crystal structure studies.[33,34]



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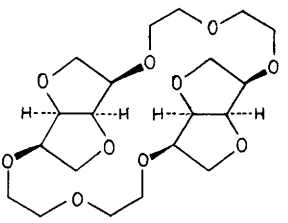
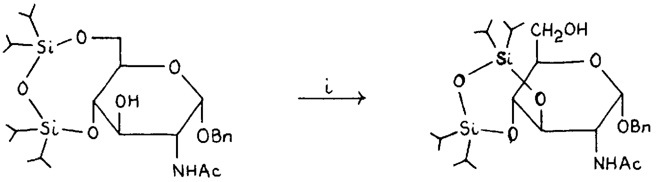


(12)

A 3,3-dimethyl-2-oxobutyl ether of L-ascorbic acid is covered in Chapter 15, while the allylation and benzylation of acetamido-sugars is referred to in Chapter 8.

Silyl Ethers.- The selective tert-butyldiphenylsilylation of sucrose has been examined. Monomolar silylation (Bu^tPh_2SiCl-py-DMAP) gave the 6'-O-monoether (49% yield, without chromatography), while trimolar silylation gave the 6,6'-di- and 6,1',6'-tri-ethers in 78 and 19% yield respectively, and reaction with 4.6 molar equivalents gave the 6,1',6'-triether as the major product. Desilylation (Bu_4NF) of the 6,6'-diether hexabenzoate gave the 4,6'-dihydroxy-compound as a result of 4 → 6 benzoate ester migration.[35]

Acid-catalysed rearrangement of the 4,6-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-derivative (13) gave the 3,4-protected compound (14) (Scheme 3).[36]

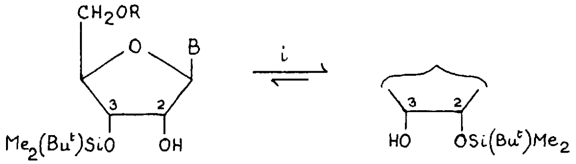


(13) (14)

Reagents: i, H^+-DMF

Scheme 3

2'- and 3'-Mono-, as well as 2',3'-bis-O-(tert-butyldimethylsilyl)-ribonucleosides have been synthesized from corresponding 5'-O-(4-methoxytrityl)-derivatives by partial or complete silylation and the 3'→2' isomerization illustrated in Scheme 4.[37] Other



(15)

R = 4-methoxy-trityl

Reagents: i, Py-H_2O-MeOH

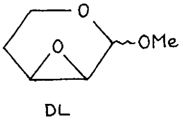
Scheme 4

silylated nucleosides are covered in Chapter 19.

2 Intramolecular Ethers (Anhydro-sugars)

The synthesis and polymerization of 1,2-, 1,3-, 1,4-, 1,5- and 1,6-anhydrosugars has been reviewed.[38]

Oxiranes.- The synthesis of the racemic 2,3-anhydro-4-deoxy-DL-erythro-pentopyranosides (16), 3,4-anhydro-DL-arabinopyranoside (17) and 2,3-anhydro-DL-erythrofuranosides (18) by epoxidation (peroxy-



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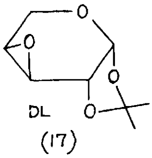

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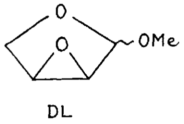
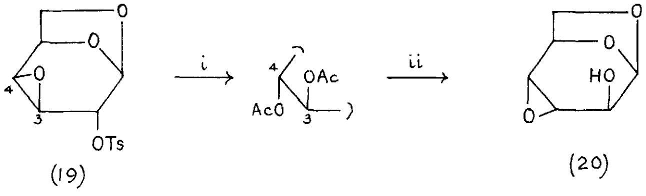


(18)

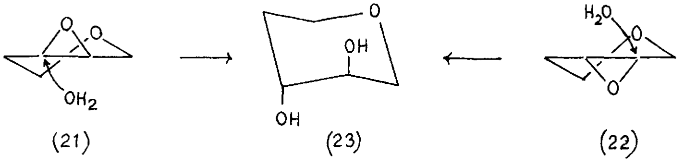
benzimidic acid - K_2CO_3) of the corresponding unsaturated derivatives has been reported.[39] 1,6:3,4-Dianhydro-β-D-altropyranose (20) was synthesized from the galacto-dianhydride (19) as outlined in Scheme 5.[40]



Reagents: i, Ac_2O-AcOH-$BF_3.Et_2O$; ii, NaOMe-MeOH

Scheme 5

The polymerization behaviour of 5,6-anhydro-1,2-O-isopropylidene-α-D-allo- and gluco-furanoses, with and without 3-O-benzyl ether groups, has been examined.[41] Both enantiomers of 3,4-epoxytetrahydropyran [i.e., (21) and (22)] are hydrolysed by rabbit liver microsomal epoxide hydrolase to (-)-(R,R)-trans-3,4-dihydroxy-tetrahydropyran (23); this implies that each reacts from a different chair conformation as shown in Scheme 6.[42]

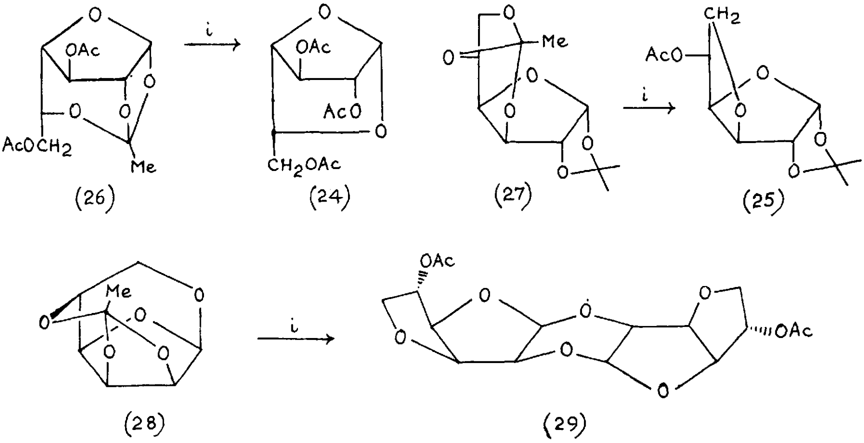


Scheme 6

The conformational analysis of certain 1,2-anhydrohexopyranose derivatives, and the synthesis of branched-chain sugars from epoxide precursors are covered in Chapters 20 and 13 respectively.

Other Anhydrides.- Acetylated anhydrosugars were formed from acid-catalysed rearrangements of internal ("tricyclic") orthoacetates in polar aprotic solvents (see Scheme 7). Thus the 1,5-anhydride (24) and 3,6-anhydride (25) were obtained from the D-galacto- and gluco-furanose derivatives (26) and (27) respectively; 2,3,5-O-ortho-acetyl-1,6-anhydro-α-L-gulofuranose (28), however, gave the 1,2':2,1'-dianhydride (29) of 3,6-anhydro-L-gulofuranose.[43]

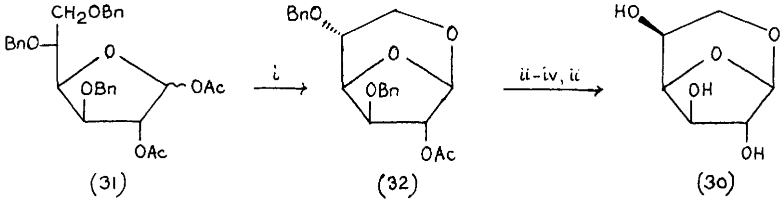
1,6-Anhydro-α-L-idofuranose (30) has been synthesized from the D-glucofuranose derivative (31), which was converted to the 1,6-anhydride (32) following a previously patented procedure; the



Reagents: i, H_2SO_4–$MeNO_2$

Scheme 7

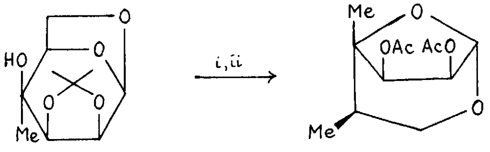
required inversion at C-5 was effected by an oxidation-reduction sequence after selective hydrogenolysis of the axial 5-O-benzyl ether, as set out in Scheme 8. Only 0.08% of anhydride (30) was detected in the equilibrium mixture of L-idose in acidic medium, but it was shown that the amount of 1,6-anhydrofuranose present in such equilibria rises significantly when the 4-hydroxyl is made tertiary, as with 4-C-methyl-D-talose which on liberation from the known anhydride (33) and acetylation, yielded the 1,6-anhydrofuranose derivative (34) in 28% yield (Scheme 9).^{44}



Reagents: i, $TiCl_4$; ii, H_2-Pd/C ; iii, RuO_2-$NaIO_4$-Na_2CO_3 ; iv, $LiAlH_4$

Scheme 8

Improve yields of 1,6-anhydro-β-cellobiose and -maltose, isolated as their hexaacetates in 61 and 78% respectively, have been obtained by alkaline treatment of pentachlorophenyl hepta-O-acetyl-β-cellobioside and -maltoside respectively, these being synthesized in good yield from the glycosyl bromides and sodium pentachloro-

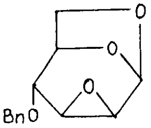


(33) (34)

Reagents: i, H_3O^+; ii, Ac_2O-Py

Scheme 9

phenoxide.[45] Prolonged hydrogenolysis of 1,6:2,3-dianhydro-4-O-benzyl-β-D-mannopyranose (35) yielded small amounts of 1,5-anhydro-2-deoxy-D-arabino-hexitol (36) in addition to the previously observed intermediate products of de-O-benzylation and reductive epoxide-cleavage; this is the first report of 1,6-anhydride cleavage under such conditions.[46]



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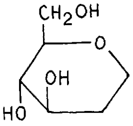
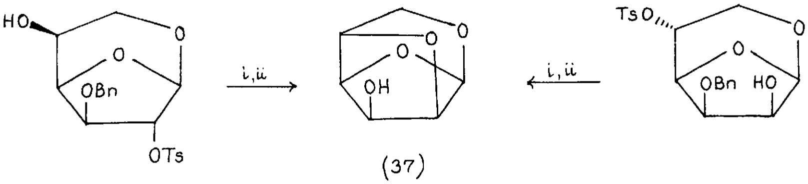


(36)

1,6:2,5-Dianhydro-α-L-gulofuranose (37) has been synthesized by the intramolecular sulphonate displacement reactions shown in Scheme 10.[47]



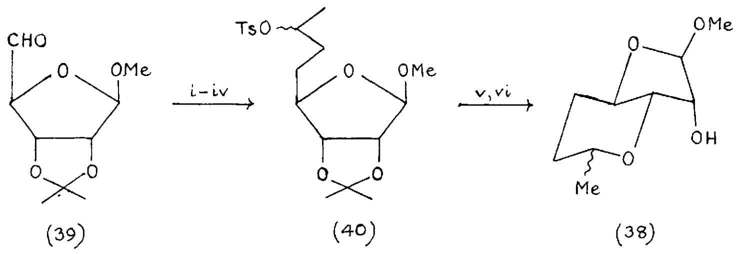
(37)

Reagents: i, KOAc-DMF; ii, H_2-Pd/C

Scheme 10

A separable mixture of methyl 3,7-anhydro-5,6,8-trideoxy-β-D-allo- and α-L-talo-octofuranosides (38), which have the bicyclic ring system found in various Streptomyces metabolites, has been obtained from the readily available dialdose (39) by a Wittig reaction as shown in Scheme 11; the C-7 epimers (40) were cyclized by intramolecular sulphonate displacement following a low yielding (23%) de-isopropylidenation.[48]

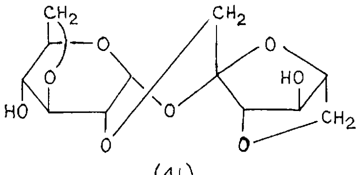
2,1'-Anhydro-sucrose has been synthesized from 6,6'-di-O-trityl-



Reagents: i, $Ph_3P=CHCOMe$; ii, $NaBH_4$; iii, H_2-Pd/C ; iv, TsCl-py ; v, HCO_2H-H_2O; vi, NaH-DMF

Scheme 11

sucrose by selective 1'-*O*-mesylation, base treatment, and detritylation. It was converted to the 2,1':3,6:3',6'-trianhydride (41) by selective 6,6'-di-*O*-mesylation and base treatment; this trianhydride was not identical to a product previously claimed to have this structure (Lemieux and Barrette, 1959). 2,1':3,6-Dianhydrosucrose was synthesized from 3,3',4',6'-tetra-*O*-acetyl-sucrose by selective 6,1'-di-*O*-mesitylenesulphonylation and base treatment, and then converted to trianhydride (41) by C-6' bromination (Ph_3P-CBr_4) and base treatment. 2,1':3,6-Dianhydro-4-chloro-4-deoxy-*galacto*-sucrose (42) was also prepared, 3,3',4',6'-tetra-*O*-benzoyl-sucrose being treated with sulphuryl chloride and the derived 4,6,1'-trichloro-derivative subjected to alkaline hydrolysis.[49]



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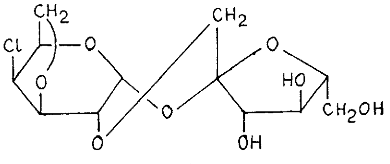
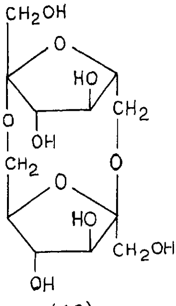


(42)

Di-β-D-fructofuranose 2,6':6,2'-dianhydride (43) was produced by the action of *Arthrobacter ureafaciens* on bacterial levan.[50]

The anomeric configurations in α-D-fructofuranose β-D-fructofuranose 2',1:2,3'-dianhydride, a product formed in high yield by the action of a D-fructotransferase on inulin, have been determined from its ^{13}C-n.m.r. spectrum.[51] A ^{1}H-n.m.r. study on tosylated derivatives of 1,6-anhydro-β-D-glucopyranose is mentioned in Chapter 20.


(43)

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5
Acetals

A review article in Advances in Carbohydrate Chemistry and Biochemistry on the cyclic acetals of aldoses and aldosides is mainly devoted to the reactivity of these derivatives towards oxidation, photolysis, halogenation, hydrogenolysis, action of strong bases, and miscellaneous other reactions.[1] A further review in the same publication concerned with the selective removal of protecting groups in carbohydrate chemistry contains a section on deacetalation.[2]

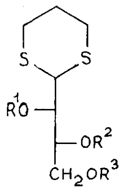
1 Isopropylidene acetals

The full paper on the use of ^{13}C-n.m.r. of isopropylidene acetals to distinguish ring-sizes and ring-fusion has appeared.[3]

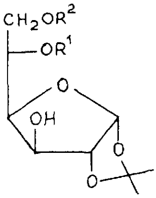
A one-pot preparation of 1,2-O-isopropylidene-(R)-glycerol from L-ascorbic acid via the reduction of its acetonide, periodate cleavage, and further reduction with sodium borohydride has been described.[4]

A detailed analysis of the isopropylidenation of D-glucitol under neutral conditions using 2,2-dimethoxypropane in 1,2-dimethoxyethane has shown that the main product is the 1,2:5,6-diacetal (41%). Other products were the 1,2:3,4:5,6-tri- (9%), 1,3:2,4:5,6-tri- (3.3%), 2,3:5,6-di- (18%), 3,4:5,6-di- (trace), and the 1,2:4,6-di-acetal (6%). The yield of 1,2:5,6-di-O-isopropylidene derivative was increased to 51% by removal of the methanol formed by allowing the reflux condensate to percolate through an activated molecular sieve.[5] Isopropylidenation of the dithioacetal (1) gave the 3,4- (E)-acetal (2) under kinetic control (acetone - copper sulphate) or the 2,3-acetal (3) under thermodynamic control (acetone - copper sulphate - sulphuric acid).[6]

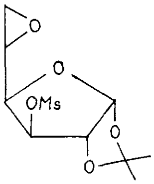
Kinetic isopropylidenation of the β-L-idopyranose derivative (4) (see Chapter 2, Ref. 21), using 2,2-dimethoxypropane-tosic acid, gave the 1,2:5,6-diacetal (5), whereas under equilibrium conditions (prolongued reaction) the 1,2:3,5-diacetal resulted. Reaction of the 5,6-ido-epoxide (6) with acetone - boron trifluoride etherate followed by desulphonation also gave (4), the first application of this reaction to carbohydrates.[7] The major product of the thermodynamically controlled isopropylidenation of *p*-nitrophenyl β-D-galactopyranoside is the 3,4-*O*-acetal.[8]



(1) $R^1 = R^2 = R^3 = H$
(2) $R^1 = H$, $R^2,R^3 = CMe_2$
(3) $R^1,R^2 = CMe_2$, $R^3 = H$



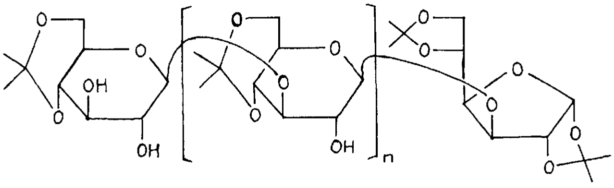
(4) $R^1 = R^2 = H$
(5) $R^1,R^2 = CMe_2$



(6)

The dissolution phase of the reaction between L-sorbose and acetone using an ion-exchange resin catalyst has been described in a mathematical treatment.[9] A similar reaction using macroporous cationic exchange resins gave 2,3:4,6-di-*O*-isopropylidene-L-sorbose. The condensation ratio depended on the characteristics of the resins such as surface area and degree of crosslinkage. Increase in temperature and in particle size increased the rate of reaction while continuous use of the resin reduced its efficacy.[10]

Acetonation of laminaritriose and laminaritetrose gave products (7) and (8) respectively.[11]

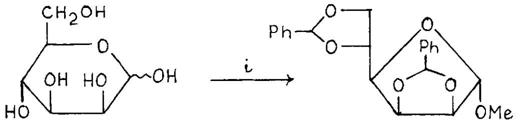


(7) n = 1
(8) n = 2

2 Benzylidene acetals

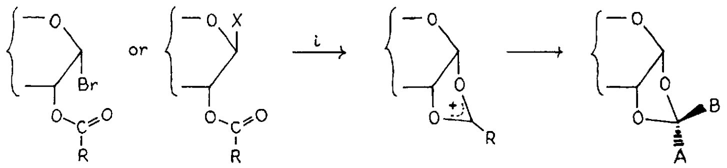
A general method for one - pot benzylidenation and glycosidation of aldoses has been reported. An example is given in Scheme 1.[12] Borohydride reduction of cyclic oxonium salts gives convenient syntheses of 1,2-*O*-benzylidene and -ethylidene derivatives of carbohydrates (Scheme 2). The reactions were applied to glucose, galactose, and mannose derivatives giving good yields (83 - 92%).

The acetal diastereomers were separated as their acetates by column chromatography. It was noted that 90% trifluoroacetic acid completely hydrolyzed the benzylidene derivatives in 2h at room temperature, whereas the ethylidene compounds were unaffected under these conditions; the latter required boiling with aqueous acetic acid for 6h.[13] The two anomers of methyl 4,6-O-benzylidene-



Reagents: i, PhCH(OMe)$_2$-TsOH-MeOH

Scheme 1

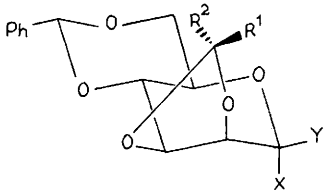


X = Br or I

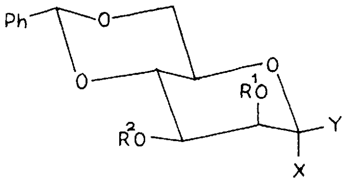
A = H, B = R
or A = R, B = H

Reagents: i, NaBH$_4$ (+ Bu$_4$NI with α-anomer)

Scheme 2



(9) R^1= Ph, R^2= H, X = OBn, Y = H
(10) R^1= Ph, R^2= H, X = H, Y = OMe
(11) R^1= H, R^2= Ph, X = OBn, Y = H
(12) R^1= H, R^2= Ph, X = H, Y = OMe

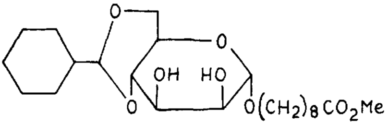


(13) R^1= H, R^2= Bn, X = OBn, Y = H
(14) R^1= H, R^2= Bn, X = H, Y = OMe
(15) R^1= Bn, R^2= H, X = OBn, Y = H
(16) R^1= Bn, R^2= H, X = H, Y = OMe

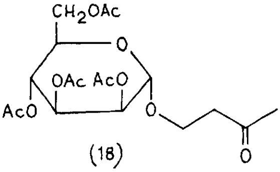
D-galacto- and -gluco-pyranosides have been prepared in 96 - 99% yields by benzylidenation of the corresponding methyl glycosides with α,α-dimethoxytoluene in 1 - 3 min at 100° in methanol containing 10% sulphuric acid. Methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside was also prepared.[14] Benzylidenation of benzyl α-and methyl β-D-mannopyranoside with α,α-dimethoxytoluene has been reported to afford the exo-isomers (9) and (10), and the endo-compounds (11) and (12). Reductive cleavage of (9) and (10) with lithium aluminium hydride - aluminium trichloride in ether gave the 3-O-benzyl-4,6-O-benzylidene compounds (13) and (14), whereas the endo-isomers (11) and (12) gave the 2-O-benzyl-4,6-O-benzylidene compounds (15) and (16).[15]

3 Other acetals

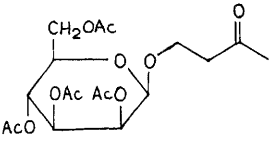
A convenient synthesis for methylene acetals of different carbohydrates using dibromomethane - potassium hydroxide in DMSO at room temperature has been described.[16] Kinetic acetalation of 8-methoxycarbonyloctyl-α-D-mannopyranoside with 1-ethoxycyclohexene gave the 4,6-cyclohexylidene derivative (17).[17] The photocyclization of 3-oxobutyl mannopyranosides (18) and (19) yielded the β-spiroacetals (20) and (21), whose structures were determined by n.m.r. and X-ray crystallography.[18]



(17)



(18)



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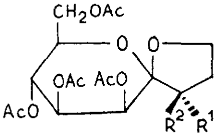

(20) R^1=OH, R^2=Me
(21) R^1=Me, R^2=OH

The ^{13}C-n.m.r. of methyl 3,4-O-(1-carboxyethylidene)-β-D-fuco- and -galacto-pyanosides is referred to in Chapter 20. Reductive cleavages of acetals are described in Chapter 4.

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6

Esters

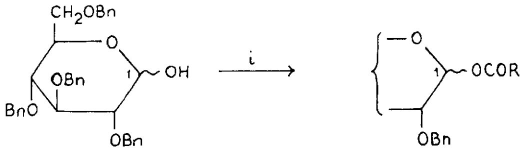
A review on selective removal of protecting groups in carbohydrate chemistry contains many references on de-esterification.[1]

1 Carboxylic Esters

The mass spectrometry of peracetylated monosaccharide formates has been reported.[2]

The use of 3'-O-formyl esters as protecting groups in the synthesis of oligodeoxyribonucleotides is discussed in Chapter 19.

Reaction of perbenzylated glucose with acyl fluorides in the presence of caesium fluoride has been shown to be an excellent method for preparing the glycosyl ester (Scheme 1). Under these essentially neutral conditions yields of between 90 and 100% of α,β-anomers were obtained, the anomeric ratio being controlled by the order of addition. Thus adding the acyl fluoride dropwise to the sugar at room temperature gave ratios of α to β of 9:1, whereas the reverse addition yielded within 10 min. a corresponding ratio of 1:4. In this reaction the caesium fluoride acts as an acid captor and accelerator.[3] β-D-Glucopyranosyl esters have been synthesized directly from the free sugar (1) by reaction with N-acyl-imidazole, N-acyl-1,2,4-triazole, or N-acyl-tetrazole, using pyridine as catalyst and solvent. This method, earlier reported for various polyene-carboxylic esters, was here extended to the synthesis of D-glucosyl benzoate, stearate, diphenylacetate, and pivalate.[4] Glycosyl esters have also been synthesised by reacting



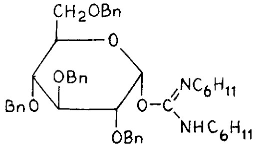
(1)

Reagents: i, RCOF-CsF

R = Ph, $Ph(CH_2)_3$, PhEtCH-, Bu^t, $Me_2C{=}CH$-

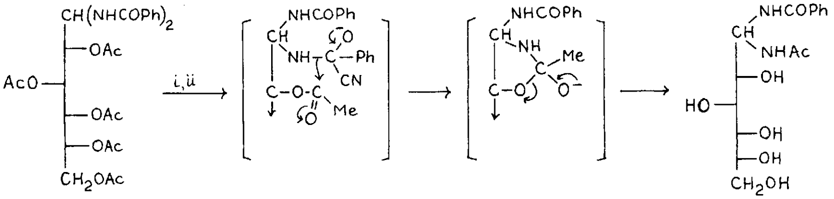
Scheme 1

1,3-dialkyl-O-glycosylpseudoureas with carboxylic acids. Fusion of (1) with DCC in the presence of cuprous chloride gave the pseudourea (2) which underwent exchange with carboxylic acids to yield mainly the β-anomers (β/α ratio between 4 and 7:1). Yields of between 62 and 89% were obtained for various carboxylic acids. Similar reactions were carried out on 2,3:5,6-di-O-isopropylidene-β-D-mannofuranose.[5] 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl esters of 4-amino-3,5,6-trichloro-2-picolinic acid, 2,4-dichlorophenoxyacetic acid, and indole-3-acetic acid, all of which show phytohormonal activity, have been prepared by esterification of the tetraalkyl ammonium salt of the acid with acetobromo- glucose.[6]



(2)

The synthesis of all the methyl mono-O-acetyl-α- and -β-D-xylopyranosides has been achieved by unimolecular acetylation of methyl mono-O-benzyl-D-xylopyranosides, followed by chromatographic fractionation and debenzylation. The three methyl di-O-acetyl-α-D-xylopyranosides were also obtained.[7] Separation by liquid chromatography of the mixtures obtained by acetylation of a tri-O-methyl fraction from partial methylation of methyl α-D-glucopyranoside gave all possible mono-O-acetyl-tri-O-methyl glycosides.[8] Acetylation of D-xylose with acetic anhydride in pyridine at -30° gave 1,2,3-, 1,2,4-, and a trace of 2,3,4-tri-O-acetyl-D-xylopyranose. The various triacetates were also specifically synthesized from 3,4-di-O-acetyl-1,2-O-(1-ethoxyethylidene)-

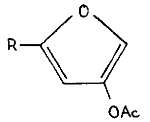


(3)

Reagents: i, $KCN-CH_3CN$; ii, NaOMe-MeOH

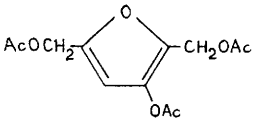
Scheme 2

α-D-xylopyranose.[9] A study of the base-catalysed, intramolecular *O*,*N*-transacylation of per-*O*-acyl-1,1-bis(benzamido)-1-deoxyglucitols in aprotic solvents has led to the proposed mechanism shown in Scheme 2. The effect of added crown ether, other nucleophiles and aprotic solvents and the use of sodium cyanide was to reduce the yields of acetamido-benzamido-glucitol (3).[10] Mention of acetyl migration in the synthesis of amino-deoxy-derivatives of nonulopyranosidonic acid esters is made in Chapter 9. It has been shown that acetylated furanoses of β-D-ribose, β-D-galactose and α-D-fructose predominantly lose two molecules of acetic acid on thermolysis in acetone solution to yield substituted furans; the ribose and galactose derivatives yield the 3,5-substituted furans (4) and (5) respectively, while the fructose yields the 2,3,5-derivative (6) together with the exocyclic (*E*) and (*Z*)-alkenes (7).[11] Chapter 12 contains several references to the products of pyrolysis of sugar esters. The relative reactivities of the hydroxy groups in methyl α- and β-D-xylopyranoside towards selective benzoylation with the usual reagents at -40° are α:2>4>3 and β:2>3>4.[12] (*cf.* tosylation studies mentioned later (ref. 52)). Under conditions which normally remove other benzoyl esters, catalytic sodium methoxide in methanol only removed the *O*-acetyl groups from the rhamnosyl 2-*O*-benzoyl galactoside (8); debenzoylation required equimolar sodium methoxide at reflux for 40h, presumably due to steric hindrance.[13] Use of TPP-DEAD in the presence of *p*-nitrobenzoic acid on the diol (9) gave the 3-*p*-nitrobenzoyl-alloside (10).[14]

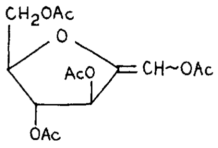


(4) R=CH_2OAc

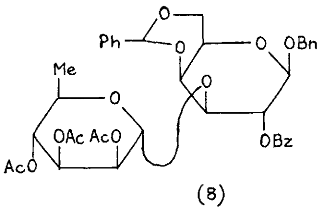
(5) R=$CH(OAc)CH_2OAc$



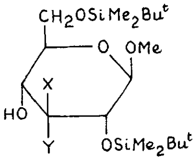
(6)



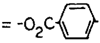
(7)



(8)



(9) X=OH, Y=H

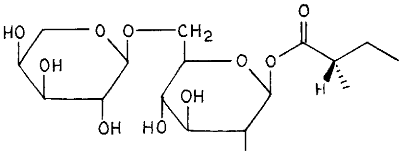
(10) X=H, Y=$-O_2C$NO_2

The selective esterification of laevoglucosan with octanoyl chloride and with hexadecanoyl chloride has been examined, giving anticipated mixtures of mono-, di-, and tri-esters.[15] Regiospecific 3'-*O*-succinoylation of 6-*N*-(3,3-dimethylallyl)-adenosine has been achieved using dibutylstannyl chloride, succinic anhydride, pyridine, tetrabutylammonium bromide, and Dowex-50W resin.[16]

Selective or complete acylation of 2,3,2',3'-tetra-*O*-benzyl-α,α-trehalose with stearoyl chloride and catalytic hydrogenolysis yielded 6-*O*-stearoyl- and 6,6'-di-*O*-stearoyl-α,α- trehalose, and 4,6,4',6'-tetra-*O*-stearoyl-α,α-trehalose respectively. These mono- and di-stearates were shown to be the major components of the mono- and di-ester preparations previously obtained by transesterification between α,α-trehalose and methyl stearate which had shown interesting biological activity.[17] The by-product from acylation of 6,6'-di-*O*-*p*-toluenesulphonyl-α,α-trehalose with potassium corynomycolate was shown to be 3',6'-anhydro-6-*O*-corynomycolyl-α,α-trehalose by comparison with a sample prepared from the hexabenzyl-α,α-trehalose 6,6'-dimesylate *via* the corresponding 6-*O*-corynomycolyl 6'-mesylate and hence debenzylated analogue, which with sodium hydride gave the 3',6',-anhydro product.[18] The antitumour activity of twenty-three fatty acid esters of maltose, sucrose, and α,α-trehalose has been reported.[19] In a continuing study on the effects of substituents on the acid-catalysed thermolysis of sucrose in DMSO (see Vol.15, Ch.2, p.38, ref.158), it has been demonstrated that the rate of degradation is markedly diminished by acetylation, especially at O-1 of the fructosyl residue.[20]

Three new glycosyl esters have been isolated from plants: 1-*O*-caffeyl-β-D-galactopyranose 6-sulphate from the fern, *Adiantum capillus-reneris*, the first such derivative containing a sugar other than glucose;[21] 3,4-di-*O*-palmitoyl-1-*O*-(palmitoyloleanoyl)-α-L-arabinopyranose from flowers of *Ligustrum* species;[22] and the disaccharide, 1-(6-*O*-α-L-arabinopyranosyl-β-D-glucopyranosyl)-(*S*)-2-methylbutyrate (11) from pods of *Acacia sieberana*.[23] Along with the apigenin 7-*O*-β-glucopyranoside (12) and its 6"-mono-acetate, the 2",3"- and 3",4"-diacetates have now been isolated from the flowers of *Matricaria chamomilla*.[24] The oligosaccharide moieties of two triterpenoid saponins from *Gleditsia japonica* have been shown to contain terminal rhamnosyl units diacylated with monoterpene acids, e.g. (13).[25,26]

Several new tannins and galloyl esters have been isolated from plant sources, including the α-glucosyl derivatives (14) from *Nuphar japonicum*,[27] potentillin (15) from *Agrimonia pilosa*,[28] and dimeric ellagitannins, e.g. (16), from *Geum japonicum*.[29,30] Two further gallotannins (17) and (18) were also obtained from *Nuphar japonicum*.[27] Hydrolysable tannins such as (19), containing a valoneoyl group, have been obtained from



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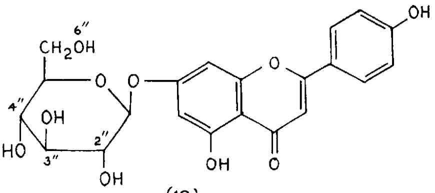

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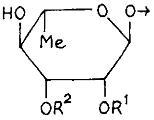
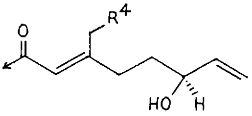
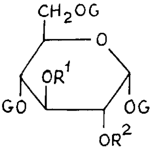


(13)

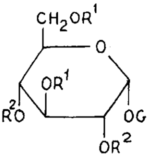
$R^1 = R^3$ (R^4 = H or OH)
$R^2 = R^3$ (R^4 = OH)

R^3 =

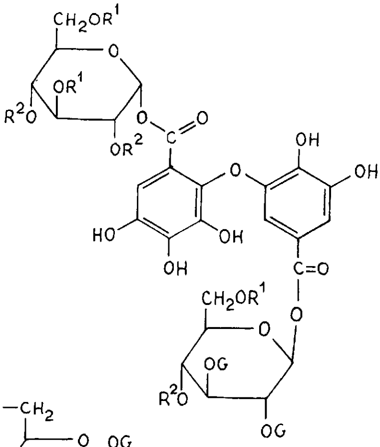




(14) $R^1, R^2 = R^3$
(17) $R^1 = R^2 = H$
(18) $R^1 = R^2 = G$

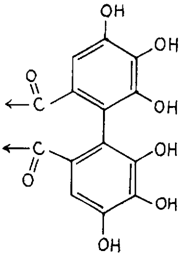


(15) $R^1, R^2 = R^3$

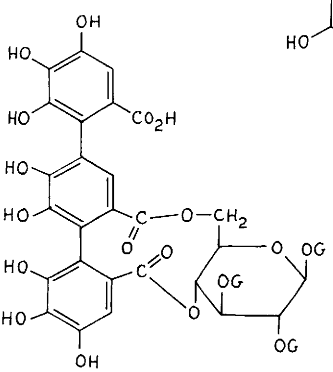


(16)

R^3 =



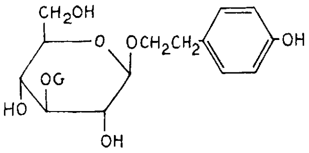
G = Galloyl



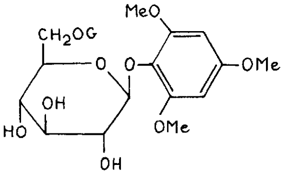
(19)

plant sources, and dimeric and trimeric examples linked *via* this group have also been isolated.[31,32] Seven new galloylated phenolic glucopyranosides, *e.g.* (20), and (21), have been isolated from the bark of the oak, *Quercus stenophylla*.[33] Complex tannins have been obtained from the underground parts of *Sanguisorba officinalis*.[34,35] In a major paper on the metabolism of gallic acid and hexahydroxydiphenic acid in plants, the occurrence of these acids as sugar esters was surveyed and the role of penta-*O*-galloyl-β-D-glucopyranose as the key secondary metabolite was proposed.[36]

The use of 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide and silver salts for the synthesis of β-glucosides has been demonstrated to be very efficient since the formation of orthoesters from attack on the intermediate acyloxonium carbon atom in (22) is sterically hindered.[37]

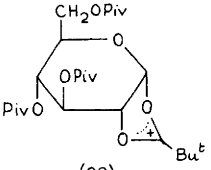


(20)



(21)

G = Galloyl



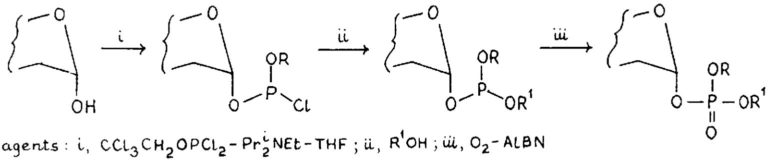
(22)

Piv = Pivaloyl

Cello-oligosaccharide derivatives with ^{3}H- and ^{14}C-labels have been obtained by esterification of ^{3}H-labelled oligosaccharide with [^{14}C]nicotinoyl chloride in DMSO-pyridine.[38]

2 Phosphates and Related Esters

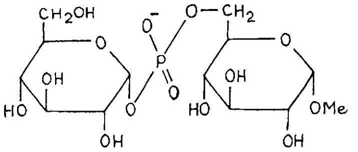
A review of the methods for preparing isotopically enriched glycosyl phosphates and nucleoside diphosphates also covers enzymic preparations and solution conformations.[39] A method for synthesizing aldosyl phosphates involving oxidation of the corresponding phosphite had been outlined (Scheme 3). The method was applied to the synthesis of the diglucosyl phosphate (23) and the corresponding dimannosyl derivative. The same paper describes the preparation of the first free sugar glycosyl phosphite.[40]



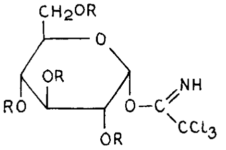
Reagents: i, $CCl_3CH_2OPCl_2$-Pr^i_2NEt-THF; ii, R^1OH; iii, O_2-AIBN

Scheme 3

β-D-Glucopyranosyl phosphates have been prepared in high yield from α-D-glucopyranosyl trichloroacetamidates (24) and phosphoric acid monoesters and diesters. Some β-phosphates were transformed into the corresponding α-derivatives by acid catalysis.[41] The preparation of β-D-glucopyranosyl 1-citronellyl and 1-geranyl phosphates from a glucosyl orthoacetate and the appropriate alkyl monophosphate have been described.[42]

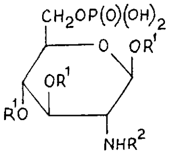


(23)

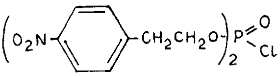


(24) R = Bn, Ac, or Bu^n

The product of phosphorylation of 5,6-protected ascorbic acid has been shown to be the 2-*O*-phosphate by *X*-ray analysis of its dipiperazinium salt dihydrate.[43] Four 2-acylamino-2-deoxy-1,3,4-tri-*O*-dodecanoyl-β-D-glucopyranose 6-phosphate analogues (25) of the repeating unit of the glycophospholipid "Lipid A" have been synthesized.[44] An alternative route has been described for the

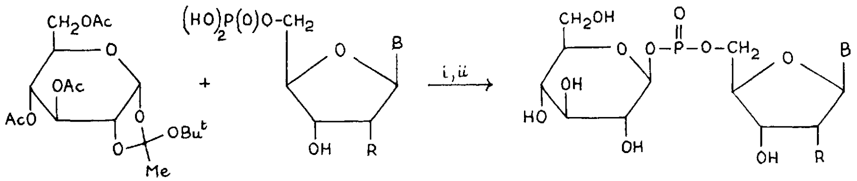


(25) $R^1 = COC_{11}H_{23}$, $R^2 = R^1$, Ac, $COC_{13}H_{27}$, $COCH_2CH(OH)C_{11}H_{23}$



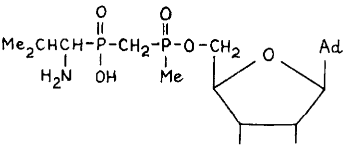
(26)

synthesis of 6,7-dideoxy-α-D-gluco-heptose 7-phosphoric acid. The diphenyl ester intermediate is avoided, using instead the corresponding diethyl ester which is readily dealkylated to the phosphonic acid in the presence of bromotrimethylsilane.[45] A new phosphorylating agent, (26), has been prepared and used for 3'- or 5'-phosphorylation of nucleosides. Excellent yields were obtained.[46] The synthesis of 5'-(β-D-glucopyranosyl monophosphates) of nucleosides and 2'-deoxynucleosides has been accomplished as shown in Scheme 4.[47] In a similar sequence using the adenosine 5'-diphosphate an α-linked D-glucosyl adenosyl diester was obtained, the production of which was thought to be due to anomerization of the initially formed β-product.[48] The diphosphite derivative of adenosine (27) has been prepared.[49] Cyclophosphates and cyclothiophosphates of adenosine are described in Chapter 19.
The methyl 4-O-phosphono (28) and 4-O-(β-D-glucopyranosyl), (29), derivatives of 3-deoxy-β-D-erythro-2-hexulopyranosidonic acid, and the 3-O-phosphono, and 3-O-(β-D-glucopyranosyl) derivatives of 2-deoxy-α-D-arabino-hexopyranose have been synthesized and their behaviour in acidic media examined.[50]



Reagents: i, DMF ; ii, NaOMe-MeOH R = H or OH , B = A,C,G,T,U

Scheme 4



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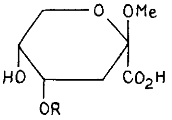


(28) $R = PO_3^{2-}$

(29) R = β-D-Glc-p

Glycoamidophosphites in the pentose series based on methyl 2,3-O-isopropylidene-β-D-ribofuranoside, 1,2-O-isopropylidene-α-D-xylofuranose, xylitan, and 3,5-O-isopropylidene-xylitan were synthesized, and some were used as ligands for palladium complexes. The derived complexes were examined as asymmetric catalysts in hydrogenations.[51]

3 Sulphonate Esters

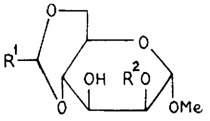
Dimolar tosylation of 1,5-anhydroxylitol gave a mixture of mono-, di-, and tri-sulphonates, in which the 2,4-ditosylate was the major product (69%).[52] Partial tosylation of methyl α- and β-D-xylopyranoside using two moles of tosyl chloride in pyridine gave the 2,4-ditosyslate as the major product in each case (70% and 34% respectively). The major component in the product of reaction of the α-glycoside with one mole of the chloride was the 2-tosylate (79%). The relative reactivity of the hydroxy groups towards tosylation was 2>4>3 in the α-anomer and 4>2>3 in the β-anomer.[53] The methods of preparation and uses of perfluoroalkanesulphonic esters in organic chemistry has been reviewed. Applications of triflates in S_N2 reactions of sugars, particularly for the synthesis of deoxy-sugars, were illustrated.[54]

Reference to the use of sulphonates in ring-contraction reactions leading to branched-chain sugars will be found in Chapter 13.

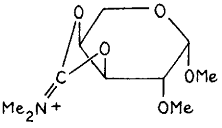
4 Other Esters

The 2',6- and 3',4-disulphates of 2-acetamido-2-deoxy-3-O-(β-D-glucopyranosyl uronic acid)-D-galactose have been isolated from enzymic digestion of chondroitin polysulphate D and K respectively.[55] Diastereoisomeric mixtures of 3-arene sulphinates of 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose were prepared by reaction of the 3-hydroxy-glucose derivative with arene sulphinyl chlorides.[56]

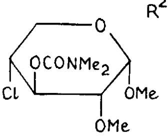
An extensive study of the reactions of N-dichloromethylene-N,N-diethylammonium chloride (Viehe's salt) with sugars has been carried out. Thus reaction of methyl 4,6-O-benzylidene-α-D-mannopyranoside or its 4,6-O-ethylidene counterpart in the presence of triethylamine gave the 2-(N,N-dimethyl)carbamate (30). When pyridine was used as the base the product was the corresponding mannose 2,3-cyclic carbonate. Similar sequences on the D-alloside gave the 3-(N,N-dimethyl)carbamate or the allose 2,3-cyclic carbonate.[57] It was shown that treatment of the cyclic carbonate with amines also gives carbamates.[58] The procedure was used to block selectively the 2-hydroxy group of glucose during an oxidation-reduction sequence leading to the D-allose derivative by inversion at C-3.[58] Methyl 2-*O*-methyl-β-L-arabinopyranoside with Viehe's salt gave the cyclic iminium salt (31). This could be hydrolyzed to yield the cyclic carbonate. In the presence of triethylamine, methyl 4-*O*-(*N*,*N*-dimethylcarbamoyl)-2-*O*-methyl-β-L-arabinopyranoside was obtained. If the intermediate cyclic iminium salt (31) was treated with hydrogen sulphide, cyclic thiocarbonates were produced. This reaction did not occur with the corresponding iminium derivative of methyl 4,6-di-*O*-methyl-α-D-glucopyranoside, although the cyclic carbonate was readily produced.[59] Thermolysis of the cyclic salt (31) gave the β-chloro-deoxy carbamate (32).[60] Similar reaction of Viehe's salt with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose gave, on hydrolysis, the dimeric carbonate and the 3-*O*-(*N*,*N*-dimethyl)-carbamate. Other reactions of the iminium intermediate were studied.[61] The reaction of the glucofuranose diol (33) with the *N*,*N*-diethylammonium analogue of Viehe's salt in the presence of triethylamine gave a mixture of the 5- and 6-(*N*,*N*-diethyl)-carbamates (34) and (35).[62]



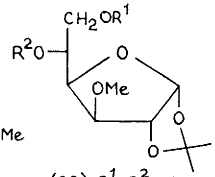
(30) R^1=Me,Ph
R^2=CONMe$_2$



(31)



(32)

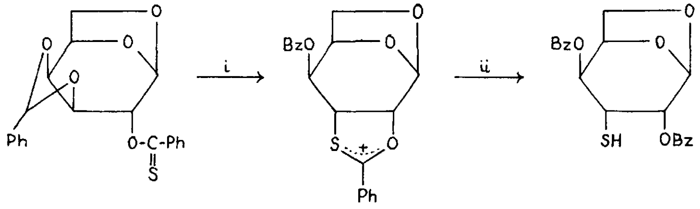


(33) R^1=R^2=H
(34) R^1=CONEt$_2$,R^2=H
(35) R^1=H,R^2=CONEt$_2$

Further studies on carbohydrate dioxalanium ions have been carried out (see Vol.15, p.69, ref.17,18). Neighbouring group participation has been used to introduce nitrogen- and sulphur-bonded groups, as exemplified in Scheme 5. Epimerization at C-3 was also achieved as shown in Scheme 6.[63]

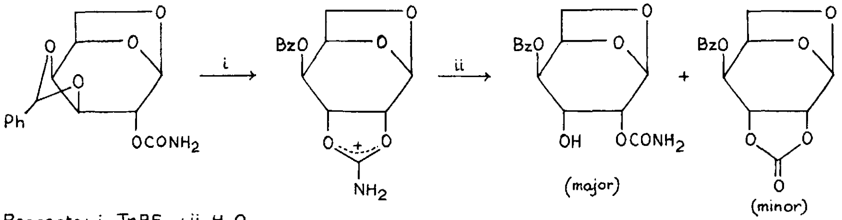
Only low yields were obtained by using the triphenylphosphine-DEAD method to prepare cyclic carbonates from *vic*-diols.[64] A detailed study of the reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-carbonate with methanol in the presence of the acid ion-exchange resin showed that the benzylidene group was rapidly lost and a mixture of methyl α-D-glucopyranoside 2- and 3-*O*-methoxycarbonyl derivatives formed, with the latter predominating.[65] The fluoren-9-ylmethoxycarbonyl (Fmoc) group has been shown to be a useful hydroxyl-protecting function; it is cleaved in triethylamine-pyridine within 2h at room temperature, leaving other base-labile protecting groups intact. The mechanism for its removal is depicted in Scheme 7.[66]

A kinetic and mechanistic investigation of the nitrosation of alcohols and thiols includes some work on D-mannitol, sucrose, and D-glucose.[67]



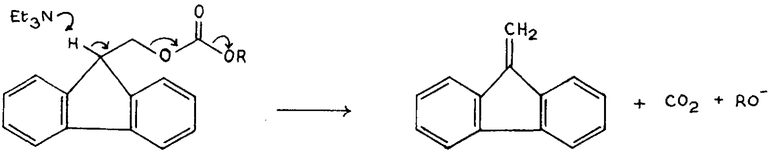
Reagents: i, $TrBF_4$; ii, H_2O

Scheme 5



Reagents: i, $TrBF_4$; ii, H_2O

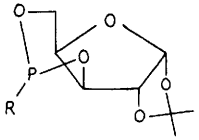
Scheme 6



Scheme 7

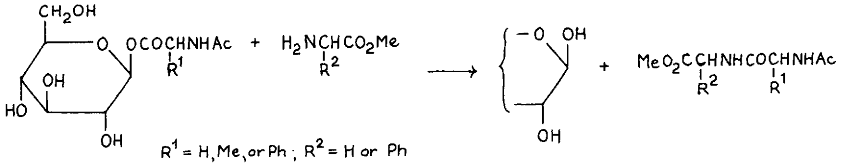
Reduction of the cyclochlorophosphite (36) with tributyl stannane in absolute benzene for 4 days at room temperature gave the parent phosphite (37), which, on heating with sulphur for 2h in benzene at reflux yielded in 72% overall yield the thiophosphite (38).[68]

Peracylglycosyl bromides in dichloromethane treated with alcohols (in particular monohydroxy carbohydrate derivatives) in the presence of silver imidazolate, mercury(II) chloride, and tetrabutylammonium chloride gave the 1,2-orthoesters in high yields.[69] The X-ray crystal structure of 2,3,5-O-orthoacetyl-1,6-anhydro-α-L-gulofuranose has been determined.[70] Reference to the use of thioorthoesters as glycosylating agents will be found in Chapter 3.



(36) R=Cl
(37) R=H
(38) R=SH

Glycosyl esters of N-acylamino acids (glycine, alanine, and phenylalanine) on treatment with the methyl esters of glycine or phenylalanine in DMF undergo rupture of the C-1 ester bond leading to a new peptide bond, the sugar acting as an activating group for the carboxyl end of an amino-acid (Scheme 8).[71]



Scheme 8

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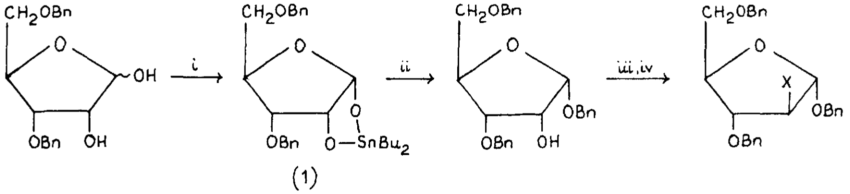
7
Halogeno-sugars

Hydrogen fluoride solvolysis of cellulose and of xylan gives yields of up to 20% α-D-glucopyranosyl fluoride and α-D-xylopyranosyl fluoride respectively.[1]

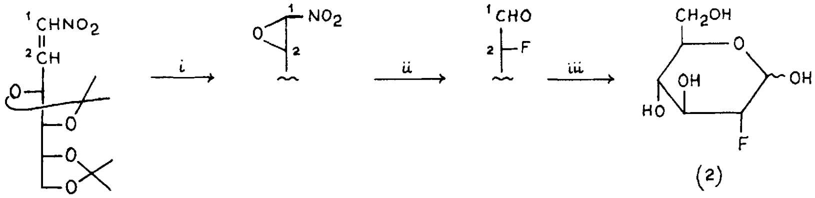
2-Substituted arabinofuranosides have been prepared via the stannane intermediate (1) using the sequence shown in Scheme 1. Substituents introduced included fluoro, chloro, bromo, iodo, and azide.[2]



Reagents: i, Bu_2SnO; ii, BuBr-K_2CO_3; iii, CF_3SO_2Cl; iv, X^-

Scheme 1

Several syntheses of 2-deoxy-2-fluoro-D-glucose (2) have been reported. A simple preparation uses the addition of acetyl hypofluorite (prepared *in situ*) to D-glucal, followed by deacetylation.[3] Another uses triflate displacement in methyl 4,6-*O*-benzylidene-3-*O*-methyl-2 -*O*-triflyl-β-mannopyranoside with caesium fluoride, followed by one step removal of all blocking groups with boron tribromide. Use of $\mathrm{Cs}^{18}\mathrm{F}$ led to the F-18 labelled compound.[4] A third route is depicted in Scheme 2,[5] and another preparation of the F-18 labelled sugar involved addition of fluorine-18[6] to 3,4,6-tri-*O*-acetyl-D-glucal, followed by hydrolysis.

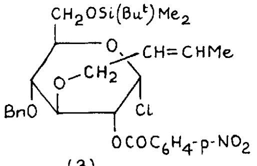


Reagents: i, H_2O_2; ii, KHF_2; iii, $BrCl_3$-CH_2Cl_2

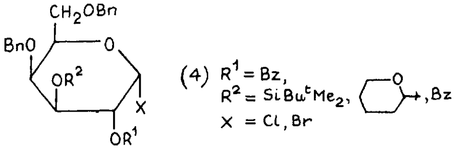
Scheme 2

3,4,6-Trideoxy-3,4,6-trifluoro-α-D-galactopyranosyl fluoride has been prepared from 3-deoxy-3-fluoro-α-D-glucopyranosyl fluoride using the diethylamino-sulphur trifluoride (DAST) procedure, and its stereochemistry determined by detailed multinuclear n.m.r. experiments.[7] The DAST method has also been used to prepare 6,6'-dideoxy-6,6'-difluoro-sucrose from 2,3,4,3',4'-penta-O-benzoylsucrose. The free 1'-hydroxy group was not substituted by fluorine.[8]

The α-D-glucopyranosyl chloride (3) has been synthesized using conventional protecting group methodology; (3) is useful for the synthesis of β-glycosidic linkages in core glycoproteins and is a versatile intermediate for further ramification.[9]

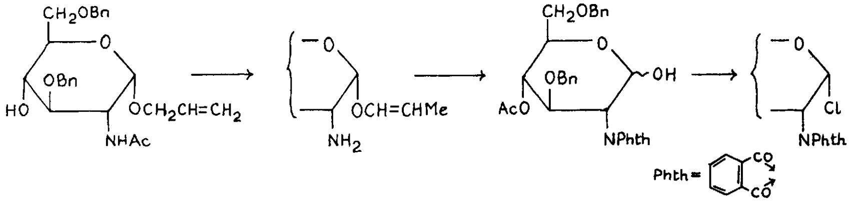


(3)



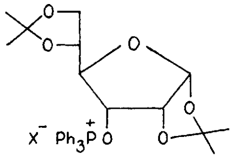
A series of 2-O-benzoyl-4,6-di-O-benzyl-α-D-galactopyranosyl halides (4), suitable as precursors for β-D-galactopyranosyl residues with 2-O- and 3-O-connected units in oligosaccharides, have been prepared by conventional means.[10]

4-O-Acetyl-3,6-di-O-benzyl-2-deoxy-2-phthalimido-α-D-glucopyranosyl chloride has been synthesised as outlined in Scheme 3.[11]



Scheme 3

The isolable, ionic 3-O-phosphonio-D-allo-derivatives (5), readily synthesised from the 3-hydroxy analogue by treatment with DEAD-TPP and various alkylating or acylating agents, on heating undergo smooth displacement at C-3 with inversion by the counter ion to give the gluco-products (6). Analogues of (5) with the gluco-configuration were equally readily synthesized, but, whereas some underwent analogous substitution reactions (e.g., X=I, N_3), others gave rearrangement products. Thus (7) gave a mixture of 3-, 5-, and 6-chloro derivatives (Scheme 4) while (8) yielded products of rearrangement (Scheme 5).[12]



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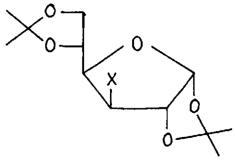

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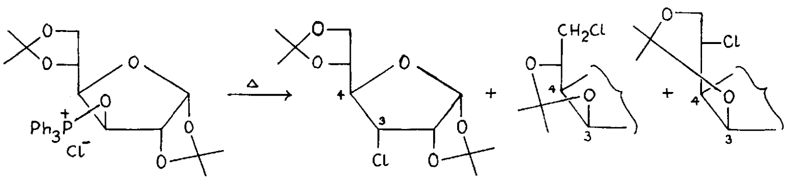
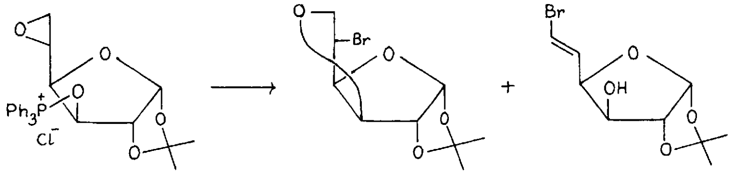


(7)

Scheme 4

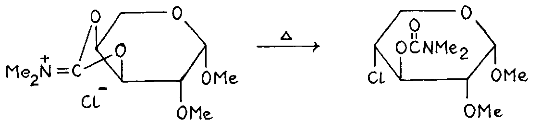


(8)

Scheme 5

The use of 4-chloro-sugars as intermediates in amino-sugar preparations is referred to in Chapter 8.

Viehes' salt and various acyclic, cyclic, and rigid bicyclic α-diols give iminium salts which on thermolysis yield β-chloro-deoxy-α-*N*,*N*-dimethylcarbamates formed in diaxial ring opening reactions (*e.g.*, Scheme 6).[13]

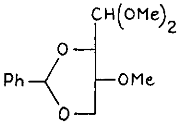


Scheme 6

Treatment of 6'-*O*-*tert*-butyldiphenylsilylsucrose with sulphuryl chloride gives rise to the 4,6,1'-trichlorosucrose derivative which was converted to the parent trichlorosucrose.[14]

The use of 4"-halogeno-derivatives of kanamycin A in syntheses of 4"-deoxykanamycin A derivatives is described in Chapter 18.

The reaction of 2,4-*O*-benzylidene-3-*O*-methyl-D-threose dimethylacetal (9) with N-bromosuccinimide (NBS) led to the expected D-*threo*-bromide (10) and, less expectedly, to the oxidized, inverted D-*erythro*-bromide (11); a 1,2-unsaturated intermediate was postulated.[15] Treatment of the glycosyl cyanides of peracetylated D-galactose and D-xylose with NBS in the presence of benzoyl peroxide caused radical substitution at C-1, yielding the bromodehydro glycosyl cyanides (12) and (13) respectively.[16] 2,5-Dibromo-2,5-dideoxy-D-lyxono-1,4-lactone (14) was produced on treatment of ammonium D-xylonate with hydrogen bromide in acetic acid, and on hydrogenolysis (Pd/C-Et$_3$N) it gave firstly the 5-bromide (15), then the 3-hydroxypentanoic acid (16). Similar treatment of potassium D-arabinonate gave approximately equal amounts of the D-*arabino*-5-bromide (17), the L-*lyxo*-enantiomer of (14) and the D-*ribo*-dibromide (18).[17] Reference to radical-induced dehalogenation of bromo- and iodo-sugars to yield deoxy-sugars will be found in Chapter 11.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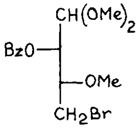
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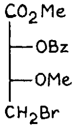
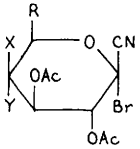
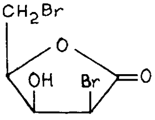

(11)


(12) R = CH_2OAc, X = OAc, Y = H
(13) R = X = H, Y = OAc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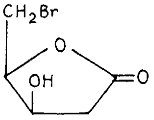
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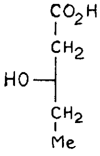
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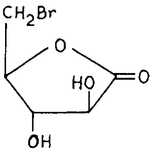
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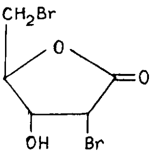
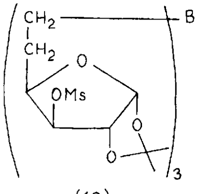

(18)

The carbohydrate boranes (19) and (20) have been prepared from the 5,6-unsaturated sugar by addition with the appropriate borane, and these were converted to the 5,6-dideoxy-6-bromo- and -iodo-compounds (21) by several methods.[18]



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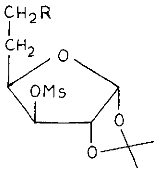
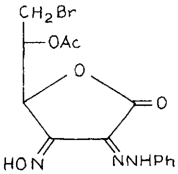


(20) R = BC_6H_{11}

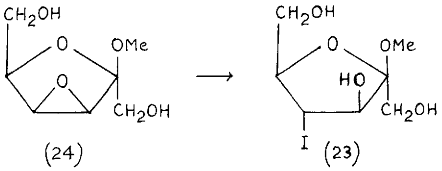
(21) R = Br, I



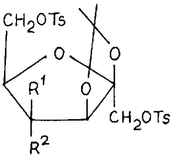
(22)

In the course of work leading to substituted triazoles, dehydro-L-ascorbic acid 3-oxime 2-phenylhydrazone was converted to its 5-O-acetyl-6-bromo-6-deoxy-derivative (22).[19]

The iodo-compound (23) with the D-fructo configuration was obtained on treatment of the β-D-tagato-epoxide (24) with iodide ion. The 4-hydroxy group in compound (25) was found to be difficult to displace with inversion; both sulphuryl chloride and carbon tetrachloride - triphenylphosphine reagents only displace the 6-tosyloxy group by chloride. By contrast, the β-D-tagatofuranose epimer (26) gave the 4-chloro-sugar (27) with sulphuryl cloride, the difference in reactivity being attributed to steric hindrance to an approaching nucleophile at the 4-position in (25).[20] Iodine - imidazole - triphenylphosphine in a 2:1 mixture of toluene and acetonitrile is reported to be an efficient iodinating agent for certain hydroxy groups of carbohydrates. Thus methyl α-D-glucopyranoside gave methyl 4,6-dideoxy-4,6-di-iodo-α-D-galactopyranoside with this reagent. Tri-iodoimidazole in place of iodine - imidazole was also effective.[21] Methyl 3-O-benzyl-2,4,6-trideoxy-6-iodo-α-D-erythro-hexopyranoside has been synthesized from D-glucose. Its potential as a chiral intermediate for the synthesis of inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase was demonstrated.[22]



(24) (23)



(25) R^1=H, R^2=OH

(26) R^1=OH, R^2=H

(27) R^1=H, R^2=Cl

Chapter 11 contains references to syntheses of deoxy-sugars by dehalogenation reactions, Chapter 3 to the use of glycosyl halides in glycosidation reactions, and Chapter 4 to halo-sucroses as intermediates in the synthesis of anhydro-sucrose derivatives.

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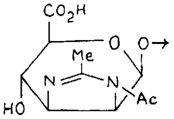
8

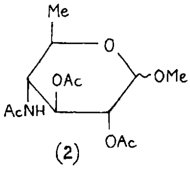
Amino-sugars

1 Natural Products

The chemistry, metabolism, and biological function of sialic acids have been reviewed.[1] 2-Amino-2-deoxy-glucose (*i.e.*, *N*-unsubstituted) has been identified as a component sugar of the cell wall peptidoglucan of *Streptococcus pneumoniae*,[2] while the initial metabolites of the D-[1-^{14}C]-analogue of this sugar in normal and carcinoma human mammary cells have been compared.[3] 2,3-Diacetamido-2,3-dideoxy-D-mannuronic acid and its 2-imidazoline derivative (1) have been identified for the first time in nature as moieties in the O-specific lipopolysaccharide of *Pseudomonas aeruginosa*.[4] Degradation of the antibiotic sporaviridin released the acetylated methyl glycosides of the amino-sugars D-viosamine, D-acosamine, and L-vancosamine [(2)-(4) respectively] and of the neutral sugars D-quinovose and D-glucose; D-acosamine is the second example in nature of a 3-amino-2,3,6-trideoxyhexose having the D- configuration.[5]



(1)



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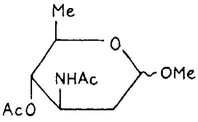

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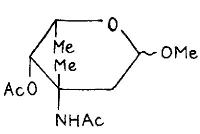
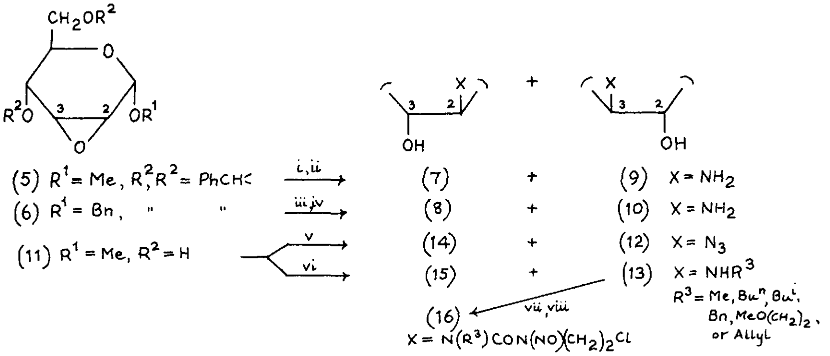


(4)

2 Synthesis

Improvements to the conventional syntheses of 2-amino-2-deoxy-D-[1-^{13}C]glucose hydrochloride and 2-[^{15}N]amino-2-deoxy-D-glucose hydrochloride by the aminonitrile method have been reported.[6] *N*-Acetyllactosamine was synthesized enzymically on an 80 mmol. scale from D-glucose 6-phosphate, *N*-acetyl-D-glucosamine, and phosphoenolpyruvate.[7]

The 4,6-O-benzylidenated D-allo-epoxides (5) and (6) gave predominantly the expected 2-amino-2-deoxy-D-altrosides (7) and (8) by way of diaxial ring-opening with phthalimide[8] and azide ions[9] respectively under newly modified conditions whereby generated oxyanions were rapidly quenched; the 3-amino-3-deoxy-D-glucosides (9) and (10) were obtained as minor products (Scheme 1). The use of ^{15}N-labelled phthalimide led to ^{15}N-labelled amino-sugars. The D-manno-epoxide epimeric to (6) gave the 3-amino-3-deoxy-D-altroside by exclusive diaxial ring opening.[9] By contrast, the conformationally more flexible epoxide (11) underwent predominantly diequatorial ring-opening by azide ion or primary amine to give the 3-substituted D-glucosides (12) or (13), accompanied by lesser amounts of the D-altrosides (14) or (15); nitrosourea derivatives (16) (c.f. refs. 45, 46) with remarkable antitumour activity were synthesized from the D-glucosides (13) (Scheme 1).[10]

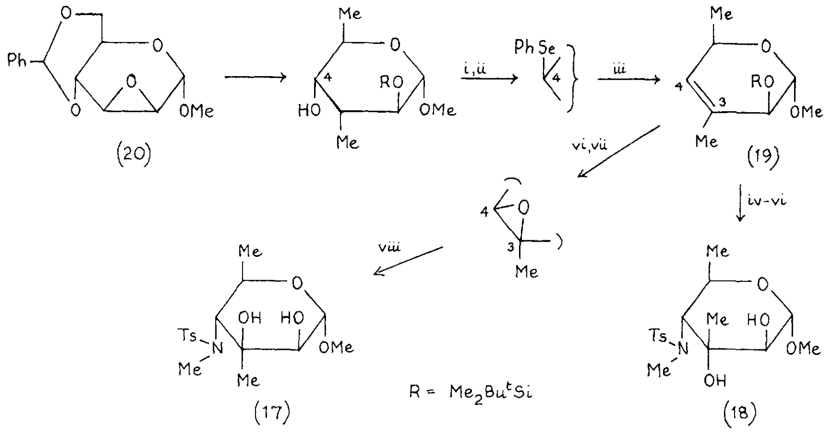


Reagents: i, phthalimide anion—HMPT; ii, NH_2NH_2; iii, NaN_3-CO_2-HMPT; iv, $LiAlH_4$; v, v, NaN_3-$(NH_4)_2SO_4$; vi R^3NH_2; vii, $Cl(CH_2)_2NCO$; viii, N_2O_4-MeOH

Scheme 1

The relative stereochemistry of sibirosamine, the branched-chain amino-sugar present in the benzodiazepinone antitumour antibiotic sibiromycin, was shown to be that in the methyl N-tosyl-α-D-glycoside (17) rather than in its C-3 epimer (18) as had been assigned previously (Vol. 7, p.148; Vol. 9, p.134). The synthesis of these epimers proceeded via 3-ene (19), a close analogue of a key intermediate in Dyong's synthesis of epimer (18) (Vol. 14, p.76; Vol. 15, p. 94), which in this case was obtained from the manno-epoxide (20) as outlined in Scheme 2.[11]

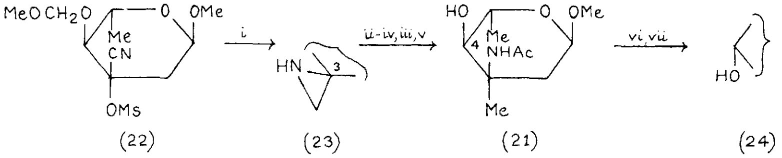
Methyl 3-amino-2,3,6-trideoxy-3-C-methyl-α-L-xylo-hexopyranoside (21), the sugar moiety of which occurs in an antibiotic from



Reagents: i, MsCl-Py; ii, PhSeH; iii, NaIO$_4$; iv, OsO$_4$-chloramine T; v, MeI-KOBu^t; vi, Bu$^n_4$NF; vii, MCPBA; viii, NaN(Ts)Me

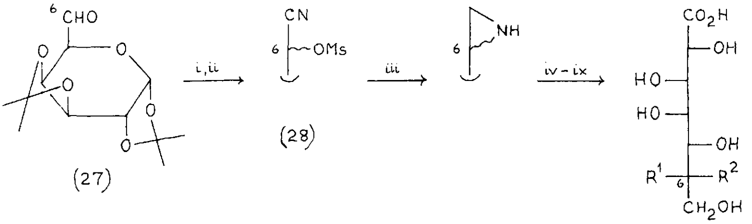
Scheme 2

Streptomyces candidus, was synthesized from the mesylated cyanohydrin (22) via the spiro-aziridine (23), although in only moderate yield (Scheme 3). An oxidation-reduction sequence provided the C-4-epimer (24) stereoselectively.[12] In a closely analogous approach (Scheme 4), 6-amino-6-deoxy-L-glycero-D-galacto-heptonic



Reagents: i, LiAlH$_4$; ii, H$_2$-Ni; iii, Ac$_2$O-Py; iv, MeOH-HCl; v, NaOMe-MeOH; vi, PCC; vii L-selectride

Scheme 3



Reagents: i, HCN-Py; ii, MsCl-Py; iii, LiAlH$_4$; iv, BnOCOCl; v, AcOH; vi, NaOMe-MeOH; vii, H$_3$O$^+$; viii, Br$_2$-BaCO$_3$-H$_2$O; ix, H$_2$-Pd

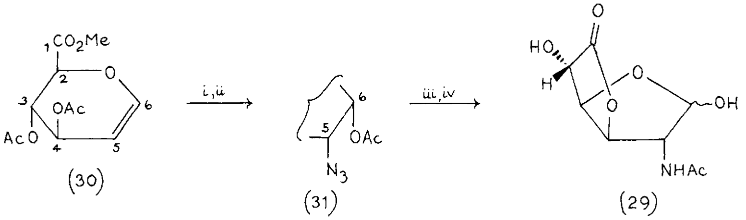
(25) $R^1 = NH_2, R^2 = H$

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

Scheme 4

acid (*i.e.*, destomic acid) (25) and its 6-epimeric D-*glycero*-D-*galacto*-isomer (26) were obtained from dialdose (27), the *C*-6-epimeric heptosiduranonitriles (28) being separated chromatographically; the L-*glycero*-D-*gluco*- (i.e. *epi*-destomic acid) and D-*glycero*-D-*gluco*-isomers were synthesized analogously from the D-*gluco*-dialdose. Destomic acid and *epi*-destomic acid occur naturally as moieties in the destomycin antibiotics.[13] A synthesis of *N*-trifluoroacetyl-L-daunosamine from D-glucose involved stereoselective introduction of the 3-amino group and inversion at C-5 by stereospecific hydrogenation of a 5-methylene pyranose derivative tive.[13a] 6- And 6'-mono-, and 6,6'-di-aminodeoxy-derivatives of sucrose were synthesized in low overall yields, starting with selective mesylation of sucrose, and proceeding *via* iodo- then azido-intermediates.[14] Introduction of amino-functions into cyclitol derivatives by allylic sulphonate displacement is covered in Chapter 17.

2-Acetamido-2-deoxy-D-glucuronic acid, isolated as its 3,6-lactone (29) was synthesized, as shown in Scheme 5, *via* azidonitration of the D-*lyxo*-glycal (30), the crude glycosyl nitrate product being converted predominantly to the α-acetate (31); 2-acetamido-2-deoxy-D-mannuronic acid was obtained as a minor product

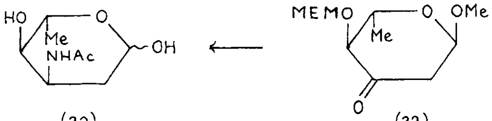


Reagents: i, $Ce(NH_4)_2(NO_3)_6$-NaN_3-MeCN; ii, NaOAc-HOAc; iii, HCl-MeOH; iv, H_2-Pd

Scheme 5

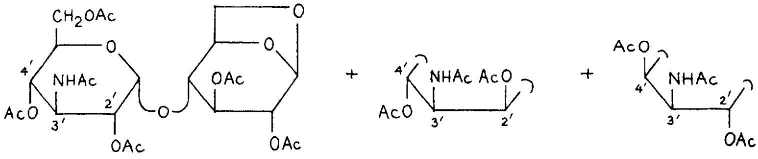
from this sequence, while 2-acetamido-2-deoxy-D-galacturonic acid was obtained by an analogous procedure starting with the D-*arabino*-glycal.[15] The synthesis of 2-amino-2-deoxy-glycosides by photochemical addition of nitrenes to glycals in the presence of alcohols is covered in Chapter 12, while mannopyranosidopyrazoles with 2- or 3-amino-functionality on the sugar moiety are described in Chapter 9.

N-Acetyl-L-ristosamine (32) has been synthesized from the 3-ulose (33), (the synthesis of which is detailed in Chapter 11) by reduction of its oxime derivative.[16,17] Conversions of other keto-derivatives to amino-sugars are covered in Chapters 3 (<u>via</u> oxime) and 13 (<u>via</u> hydantoin synthesis).



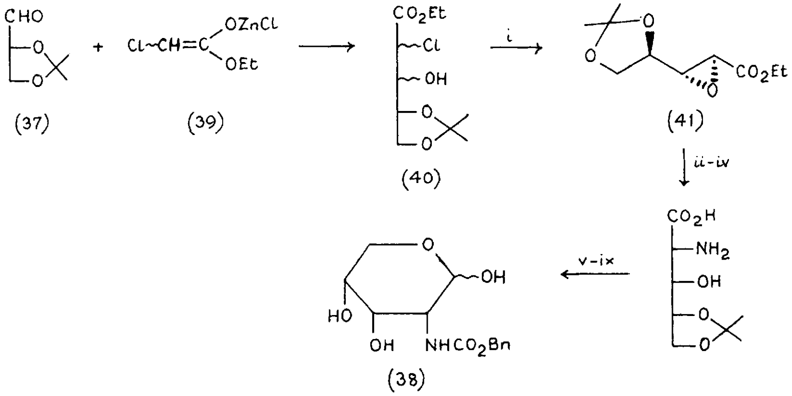
(32) (33)

Regioselective periodate cleavage of 1,6-anhydro-maltose and recyclization with nitromethane gave a 45:9:13 mixture of 1,6-anhydro-3'-deoxy-3'-nitro-disaccharides which were converted into the amino-derivatives (34), (35), and (36) respectively for characterization.[18]



(34) (35) (36)

Three amino-sugar syntheses have employed 2,3-<u>O</u>-isopropylidene-D-glyceraldehyde (37) as a starting material. The 2-amino-2-deoxy-D-ribose derivative (38) was obtained <u>via</u> a stereoselective aldol condensation using an ethoxyacetylene-derived enolate (39); alkaline treatment of the derived α-chloro-β-hydroxy-esters (40) gave a 4:1 mixture of <u>trans</u>-substituted epoxides from which the predominant isomer (41) was isolated chromatographically, aminated, and reduced

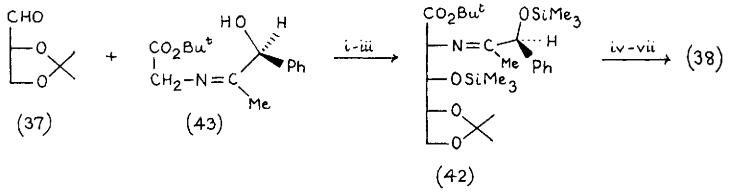


Reagents: i, LiOEt-EtOH; ii, LiOEt-EtOH-H_2O; iii, H_3O^+; iv, NH_3-H_2O; v, BnOCOCl-$NaHCO_3$; vi, CF_3CO_2H-H_2O; vii, Me_2Pr^iSiCl-NEt_3-DMAP; viii Bu^i_2AlH; ix, AcOH

Scheme 6

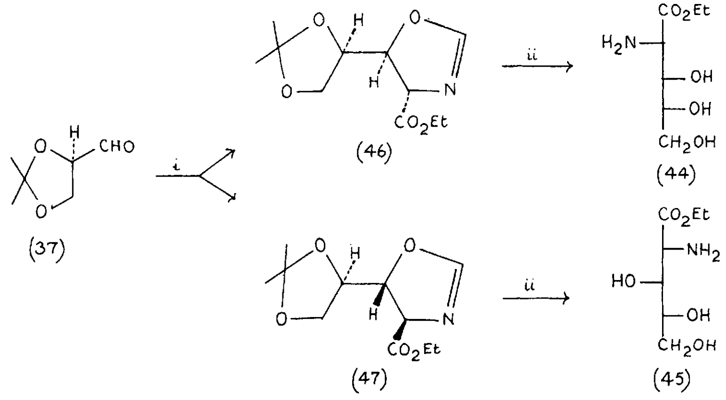
via a 1,4-lactone intermediate (Scheme 6).[19]

In a related condensation synthesis (Scheme 7), the stereochemistry at *C*-2 in 2-amino-2-deoxypentonic acid derivatives (*e.g.*, 42) was induced by the chirality of an imine moiety, while that at *C*-3 was controlled by the chirality in the aldehyde (37); thus, (*S*)-imine (43) gave a 62:20 mixture of D-*ribo*- (41) and D-*arabino*-products, while the (*R*)-imine gave these products in a ratio of 12:73. These pentonic acid derivatives were converted to 2-amino-2-deoxy-D-ribose and -D-arabinose derivatives.[20] Ethyl 2-amino-2-deoxy-D-arabinonate (44) and its *xylo*-isomer (45) were obtained from the separable mixture of oxazolines (46) and (47), synthesized by condensation of aldehyde (37) with ethyl isocyanoacetate (Scheme 8).[21]



Reagents: i, Bu^nMgCl; ii, $KNPr^i_2$; iii, Me_3SiCl; iv, Silica gel; v, $BnOCOCl-Py$; vi, $Na_2CO_3-H_2O$; vii, Steps vi-ix in Scheme 6

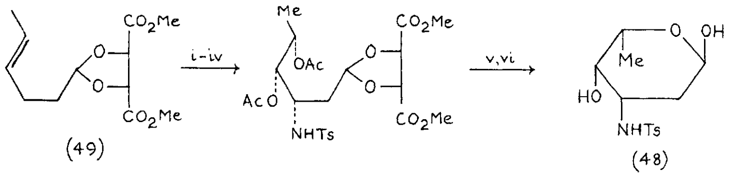
Scheme 7



Reagents: i, $NCCH_2CO_2Et-Bu^nLi$; ii, HCl-MeOH

Scheme 8

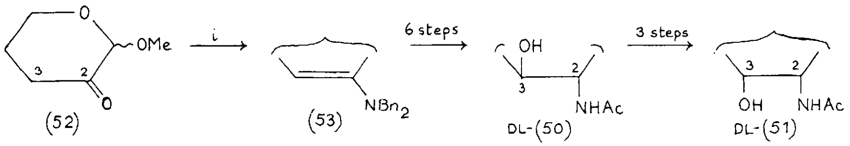
Optically pure *N*-tosyldaunosamine (48) was synthesized on a large scale from the resolved tartrate acetal (49) (Scheme 9); other isomers were also formed.[22] Syntheses of 1-*C*-methyl- and 5-*C*-methyl-L-acosamine from a chiral non-carbohydrate starting material are referred to in Chapter 13.



Reagents : i, TsN=S=NTs ; ii, NaOMe ; iii, AcNHBr ; iv, AgOAc ; v, H$^+$-MeOH ; vi, H$_3$O$^+$

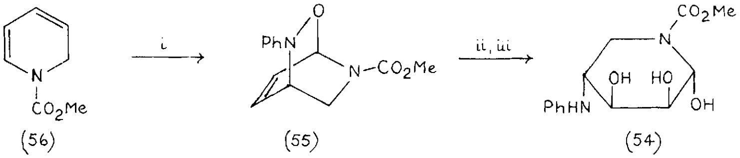
Scheme 9

The racemic methyl 2-amino-2,4-dideoxy-DL-pentopyranosides (50) and (51) were synthesized from tetrahydro-2-methoxypyran-3-one (52) by hydroboration of the enamine (53) to give the DL-*threo*-isomers (50) which were converted to the DL-*erythro*-isomers (51) by sulphonate displacement at *C*-3 (Scheme 10).[23] Racemic 4,5-dideoxy-5-methoxycarbonylamino-4-phenylamino-DL-lyxopyranose (54) was obtained from the Diels-Alder cycloadduct (55) of nitrosobenzene and 1-methoxycarbonyl-1,2-dihydropyridine (56) (Scheme 11).[24]



Reagents : i, Bn$_2$NH

Scheme 10

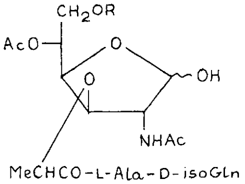


Reagents : i, PhNO ; ii, KMnO$_4$, iii, H$_2$-Pd

Scheme 11

3 Reactions

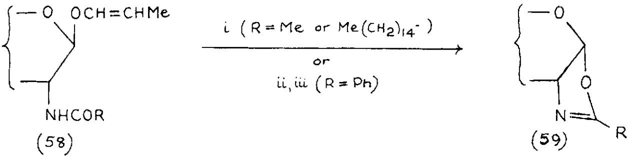
N-Acetylmuramoyl dipeptide (MDP) analogues continue to be an important synthetic target. Two 1-deoxy-MDP analogues, namely 2-acetamido-1,5-anhydro-2-deoxy-3-*O*-[(*R*)-2-propanoyl-L-alanyl-D-isoglutamine]-D-glucitol and its 6-(2-docosanoyloxy-2-methylpropanoate)[25] and three 5,6-acylated furanosyl-MDP analogues (57)[26] were elaborated from available amino-sugar derivatives by standard methods. Disaccharide and di- and tri-amino-sugar MDP analogues are described in Chapter 3 and later in this chapter respectively.



(57) R = Ac, Stearoyl, or $Me(CH_2)_{20}CO_2C(Me)_2CO\rightarrow$

Nitrous acid deamination of sialic acid moieties in glycopeptides resulted primarily in the formation of 3-deoxy-D-glycero-D-galacto-nonulopyranosonic acid derivatives, by replacement of the 5-amino-function with a 5-hydroxy group with retention of configuration;[27] these results are in direct conflict with those of Strecker et al., (Anal. Biochem., 1981, 111, 17) who considered the main product to have arisen from a pyranose to furanose ring contraction. A ^1H-n.m.r. study of sialic acid derivatives is referred to in Chapter 20.

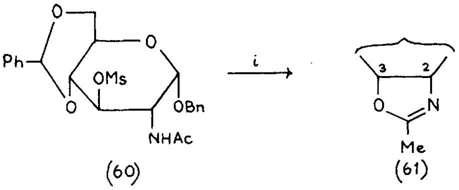
Four new syntheses of oxazolines have been reported. Peracetylated 2-amino-2-deoxy-α-D-glucopyranose, available in 90% yield from the free amino-sugar, was converted into its 2-methyloxazoline derivative in 82% yield on treatment with stannic chloride in dichloromethane.[28] A general, two-step synthesis of related 2-methyloxazoline derivatives from peracetylated 2-amino-2-deoxy-sugars involved selective 1-O-deacetylation (N_2H_4.AcOH-DMF) followed by sulphonylation ($MeSO_2Cl$-sym-collidine).[29] Prop-1-enyl 2-acylamino-2-deoxy-β-glycosides (58) were transformed into oxazoline derivatives (59) by a novel iodination procedure[30] (markedly superior to methods employing mercury(II) salts) or by a more conventional hydrolysis-sulphonylation procedure (Scheme 12).[31] Syntheses of β-glycosides from such oxazoline derivatives, including an unusual furanosyl oxazoline to pyranoside conversion, are covered in Chapter 3, while a glycosyl pyridinium salt byproduct is mentioned in Chapter 9.



Reagents; i, I_2-THF-DBU; ii, Hg^{2+}-H_2O; iii, MsCl-2,6-Dimethylpyridine-Et_4NBr

Scheme 12

Attempted azide displacement of the 3-O-mesyl group in compound (60) led to the 2,3-fused 2-methyloxazoline (61) by neighbouring group participation (Scheme 13).[32] A similar fused oxazoline derivative is described in Chapter 12.



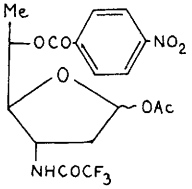
Reagents: i, NaN_3

Scheme 13

Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside was converted to its *galacto*-isomer by direct oxidation (Br_2-H_2O) to the 4-keto-derivative, isolated by way of the oxime, and reduction (H_2-Pd/C); reduction of the oxime led to the 2,4-diamino-2,4-dideoxy-D-galactoside.[33]

Furanosyl derivatives of daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) (62), and epidaunosamine (the D-*ribo*-isomer), suitable as glycosylating reagents for the synthesis of furanosyl analogues of natural antibiotics, have been synthesized *via* *N*-trifluoroacetylated diethyl dithioacetal derivatives by mercury(II) ion mediated ring closure; methanolysis gave anomeric methyl furanosides.[34] Structural and conformational studies on 3-benzamido-2,3,6-trideoxy-L-hexoses have been conducted by ^{1}H- and ^{13}C-n.m.r. methods.[35]

Borohydride reduction of 2-amino-2-deoxy-D-manno- and -D-gluco-furanurono-3,6-lactones gave the 1-deoxynojirimycin analogues (63) and (64) respectively in good yield.[36] The dissociation of the nojirimycin-bisulphite adduct has been examined and the cyclic structure (65) suggested.[37] The anomeric effect in nojirimycin is referred to in Chapter 20.



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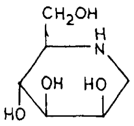

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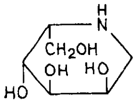

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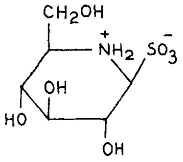
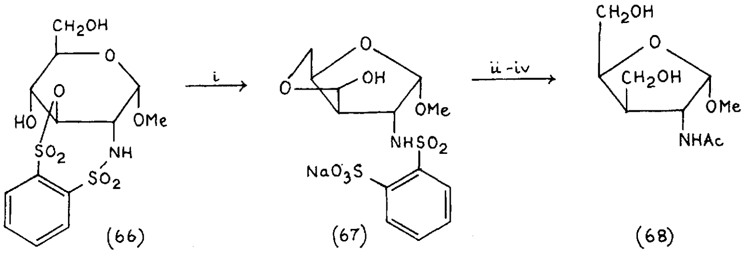


(65)

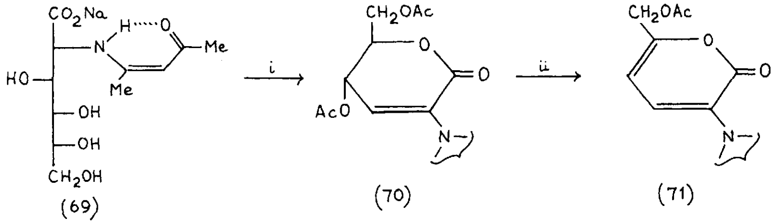
The cyclic N,O-disulphonate (66) underwent ring-contraction to give hemiacetal (67), which was further transformed into branched-chain amino-sugar derivatives such as (68) (Scheme 14).^{38}



Reagents: i, NaOMe-MeOH; ii, Li-NH$_3$; iii, Ac$_2$O-MeOH; iv, NaBH$_4$

Scheme 14

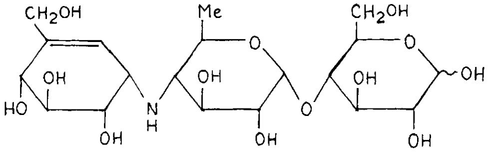
2-Amino-2-deoxy-D-gluconic acid and its 4,6-O-benzylidenated ethyl ester gave enamines, e.g., (69), on reaction with β-dicarbonyl compounds; these could be lactonized and dehydrated to α,β-unsaturated lactones, e.g., (70), and thence converted into pyranones e.g., (71), (Scheme 15).^{39,40}



Reagents: i, Ac$_2$O; ii, EtOH-Δ

Scheme 15

Four 2-acylamino-2-deoxy-1,3,4-tri-O-dodecanoyl-β-D-glucopyranose 6-phosphates, analogues of the repeating unit in the glycophospholipid, "Lipid A", have been synthesized by a standard route.^{41} The pseudotrisaccharide (72), a constituent of several α-glucosidase inhibitors of microbial origin, was synthesized by coupling a chiral cyclohexyl bromide with a 4'-amino-disaccharide derivative.^{42} Benzyl 2-amino-2-deoxy-α-D-glucopyranoside has been converted to N-substituted derivatives (i.e., with 2-NHCONH$_2$ and 2-Me$_3$N$^+$Cl$^-$ substituents), and to the disaccharide (73) by Amadori reaction with D-glucose.^{43} The N-substituted derivative (74) was one of a variety of products in which cytotoxic 1,3,5-triazines were linked to sugars.^{44} A number of nitrosourea derivatives, some with strong antitumour activity, were elaborated from methyl 2-amino-2-deoxy-α-D-glucopyranoside (c.f. ref. 10); standard coupling procedures gave compounds in the series (75),[45] or compounds in the series (76) by way of seldom reported *N*-alkylamino-sugars that were synthesized by borohydride reduction of Schiff base adducts.[46] Several protected *N*-nitroso-*N*-(glycos-2-yl)amino acid methyl esters in the *gluco*- and *galacto*-series, such as compound (77), were synthesized by an alkylation-nitrosation sequence applied to *O*-acetylated amino-sugars.[47]



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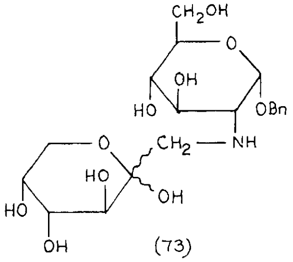

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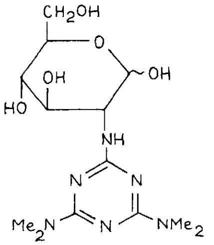

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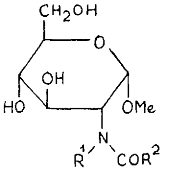
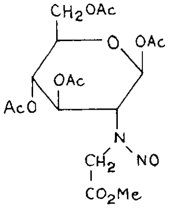


(75) $R^1 = H, R^2 = CH(X)NHCON(NO)(CH_2)_2Cl$ where X = H, Me, etc.

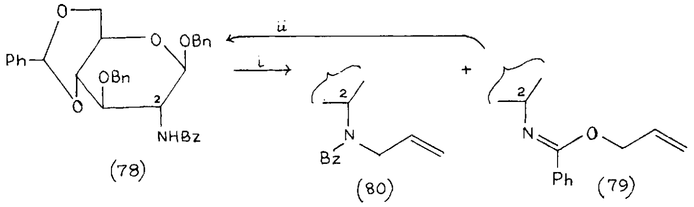
(76) R^1 = Me, Et, etc. $R^2 = N(NO)(CH_2)_2Cl$



(77)

While allylation and benzylation of acetamido-sugars yielded *N*-alkylated derivatives with only traces of the corresponding imidates, similar treatment of benzamido-sugars such as (78) yielded ~25% of the readily recycled imidate (*e.g.* 79) in addition to the *N*-alkylated product (*e.g.* 80) (Scheme 16).[48] Direct reduction ($LiAlH_4$) of benzamido-groups proceeds to give *N*-benzylamino-groups only in modest yield, but this transformation can be effectively performed if the group is *N*-allylated[48] or *N*-silylated[49] prior to reduction and de-*N*-protection.

3-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucose has been used to resolve an "ansa" pyridoxal analogue *via* the corresponding Schiff base.[50] The chelation of metals by amino-sugar derived Schiff bases is covered in Chapter 16. Other chapters include references to the alkylation of 2-acetamido-1,6-anhydro-2-deoxy-β-D-glucopyranose (Chapter 4), the reaction of bisulphite with 2-



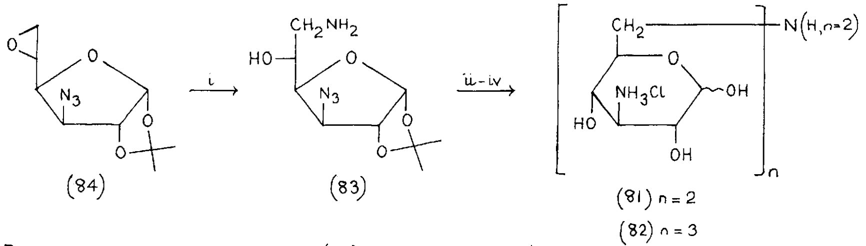
Reagents: i, Allyl bromide–NaH ; ii, PyH$^+$TsO$^-$

Scheme 16

amino-2-deoxy-D-glucose (Chapter 9) and Chapter 18 includes references to amino-sugar reactions.

4 Di- and Tri-amino-sugars

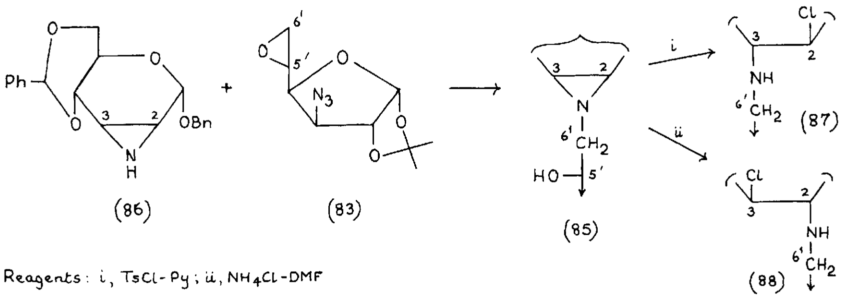
Thirteen pseudo-di-, tri-, tetra- and penta-saccharides with secondary and tertiary amine inter-residue linkages as exemplified in compounds (81) and (82), have been synthesized by variations on the strategy outlined in Scheme 17 in which an amino-sugar such as (83) is condensed with a 5,6-epoxide such as (84).[51] The use of 2-deoxystreptamine as the amino-sugar provided a number of analogues incorporating cyclitol moieties.[52] The N-substituted 2,3-epimine (85) has been synthesized by two routes, the more efficient route (Scheme 18) involving condensation of epoxide (83) with N-unsubstituted 2,3-epimine (86). This pseudo-disaccharide (85) underwent either diaxial or diequatorial ring opening depending upon reaction conditions, to give compound (87) or (88) respectively.[53]



Reagents: i, NH_3–MeOH ; ii, Compound (84) ; iii, H_2–Pd ; iv, H_3O^+

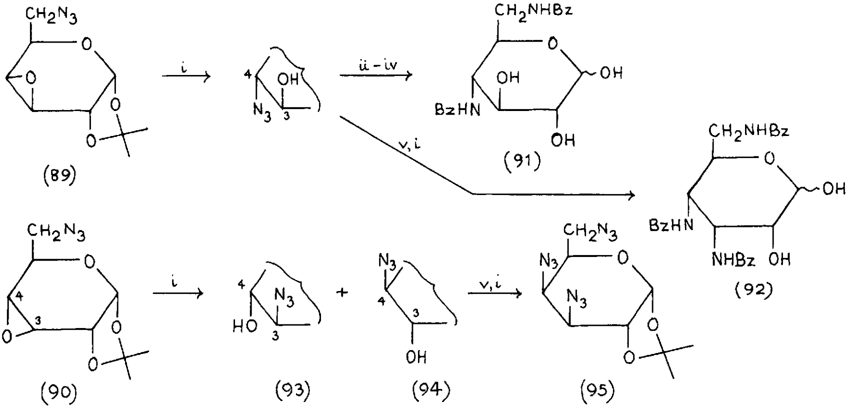
Scheme 17

Di- and tri-amino-sugars have been synthesized from the 6-azido-3,4-epoxides (89) and (90) (Scheme 19), which were themselves prepared from 1,2-O-isopropylidene-α-D-glucofuranose. Epoxide (89) underwent stereoselective ring opening with azide, leading to the



Reagents: i, TsCl-Py; ii, NH$_4$Cl-DMF

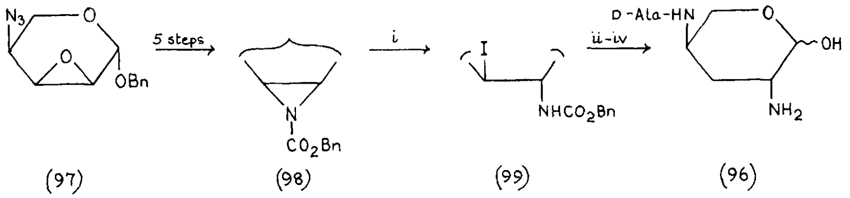
Scheme 18



Reagents: i, NaN$_3$; ii, H$_2$-Pd; iii, Bz$_2$O; iv, H$_3$O$^+$; v, (CF$_3$SO$_2$)$_2$O-Py

Scheme 19

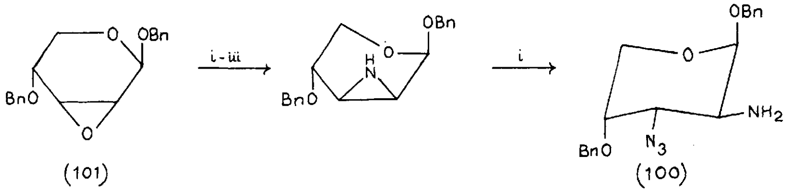
4,6-diamino-D-glucose derivative (91) and the 3,4,6-triamino-D-allose derivative (92), but isomeric epoxide (91) gave a 3:2 mixture of diazides (93) and (94), both of which, however, gave the same 3,4,6-triazido-D-galactose derivatives (95) via sulphonate displacement reactions.^{54} Other diamino-sugar syntheses have involved the initial transformation of an epoxide into an epimine derivative of inverted configuration. Thus 3-deoxyprumycin (96), a more potent antifungal agent than prumycin itself and several related analogues (syntheses of which were also reported), was synthesized (Scheme 20) by ammonolytic ring opening of the known epoxide (97) followed by intramolecular sulphonate displacement to give the epimine intermediate (98) in 62% yield after five steps; subsequent opening of the epimine ring gave mainly the 3-iodide (99)



Reagents: i, NaI; ii, H_2-Ni; iii, D-Ala-N-CO_2Bn-DCC; iv, H_2-Pd-H^+

Scheme 20

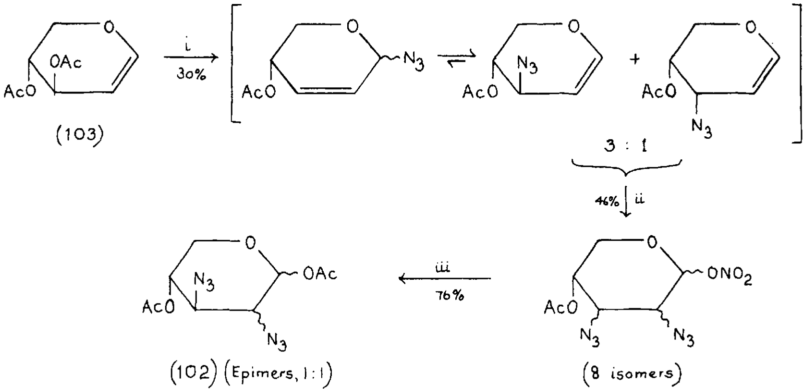
which was readily de-iodinated.[55] Similarly, syntheses of the 2,3-diamino-2,3-dideoxy-D-arabinopyranoside (100) (Scheme 21) and



Reagents: i, NaN_3-NH_4Cl; ii, MsCl-Py; iii, $LiAlH_4$

Scheme 21

its *xylo*-analogue, from epoxide (101) and its 2,3-epimer respectively, proceeded *via* the epimines with inverted configuration. Ring opening of these epimines, in both cases, gave products contrary to the Fürst-Plattner rule of diaxial ring opening, minor conformational isomers apparently being the reactive species.[56] A rapid synthesis of a separable mixture (102) of 2,3-diazido-D-*xylo*- and D-*lyxo*-isomers was achieved by an entirely different approach from

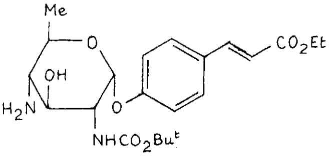


Reagents: i, NaN_3-BF_3·Et_2O; ii, NaN_3-$Ce(NH_4)_2(NO_3)_6$-MeCN; iii, Ac_2O-NaOAc

Scheme 22

D-xylal diacetate (103) (Scheme 22), without separation of the isomeric products until the last step.[56]

Ethyl 4,6-diamino-2,3,4,6-tetradeoxy-α-D-erythro- and threo-hexopyranosides were obtained from a 2,3-dideoxy-2,3-unsaturated sugar by azide displacement of sulphonate esters at positions 4 and 6 followed by hydrogenation.[57,58] Two key intermediates (104) and (105) for the total synthesis of glycocinnamoylspermidines have been synthesized. Two similar routes to the 2,4-diaminoglucosyloxycinnamate (104) from D-galactose were reported, both involving the following key steps: a) a new α-glycosidation procedure using a 2-azidoglycosyl chloride and a silylated phenolic receptor; b) introduction of the 4-amino-function by sulphonate displacement with azide; and c) selective reductive detosyloxygenation at C-6 under conditions ($NaBH_3CN$-NaI) which left the cinnamoyl double bond intact.[59,60] The two moieties of the disaccharide (105) were elaborated from D-xylal via azidonitration and glycoside coupling; the triaminodisaccharide (106) was then obtained via a 2',3'-epimine intermediate.[60] Conventional azide displacement of sulphonate transformed the 2-azido-precursor of compound (7) into a 2,3-diamino-2,3-dideoxy-D-mannopyranoside derivative,[9] but similar reaction of 3-O-mesylate (107) with azide led to isomers (108) and (109) via epimines formed by neighbouring 2,4-dinitrophenylamino-group participation (Scheme 23).[32]



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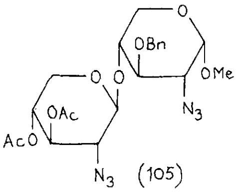

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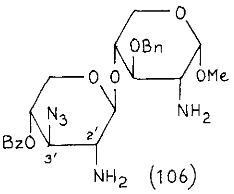

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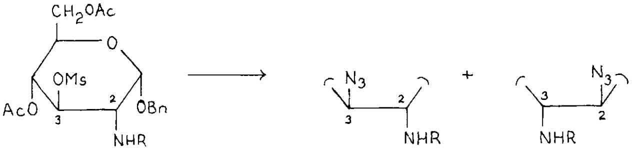


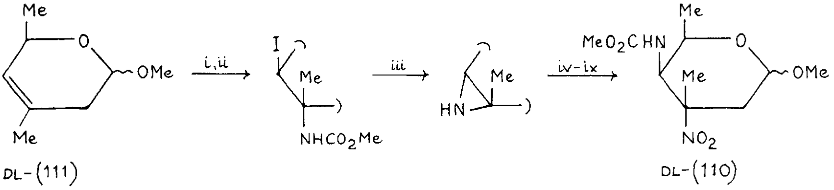
(107) (108) (109)

(R= 2,4-DNP)

Scheme 23

A variety of di- and tri-amino-sugar N-acetylmuramoyl dipeptide (MDP) analogues have been synthesized by a Japanese group. Thus 2,6-diacylamino-MDP analogues bearing lipophilic N-octanoyl, N-hexadecanoyl or N-eicosanoyl groups were synthesized from a 2-amino-2-deoxy-D-glucofuranoside derivative via tosylate displacement by azide at C-6.[61] Similar sulphonate displacement reactions led to 4,6-modified D-galacto-MDP analogues including 4,6-diamino-derivatives,[62] while 2,4-di- and 2,4,6-tri-acetamido-D-gluco-MDP analogues were obtained via hydroxy→chloro→azide conversion with overall retention of configuration.[63]

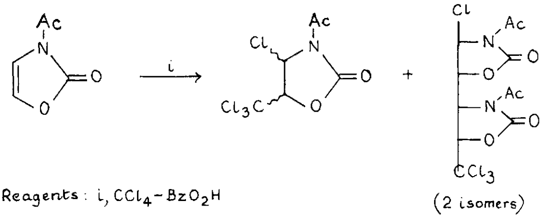
Methyl α- and β-DL-tetronitrosides (110) have been synthesized from the racemic 3,6-dihydro-2H-pyran (111), via an epimine intermediate as outlined in Scheme 24.[64]



Reagents: i, INCO; ii, NaOMe-MeOH; iii, KOH-MeOH; iv, NaN_3-NH_4Cl; v, BnOCOCl-Py; vi, $NaBH_4$-$NiCl_2$; vii, MeOCOCl-Py; viii, Et_3SiH-Pd; ix, MCPBA

Scheme 24

Radical induced telomerization of N-acyl-2-oxazolones gave mixtures of adducts, such as those shown in Scheme 25, of potential value in the synthesis of amino-sugar derivatives.[65]

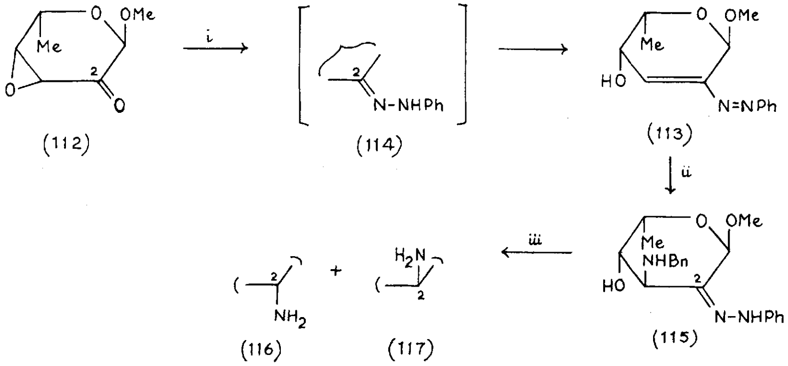


Reagents: i, CCl_4-BzO_2H

Scheme 25

A variety of substituted amino-sugars, in particular several diamino-derivatives, have been synthesized using the reaction of sugar epoxyketones with arylhydrazines. Thus epoxyketone (112) gave the unsaturated derivative (113) by rearrangement of the intermediate phenylhydrazone (114); the use of p-nitrophenylhydrazine likewise led to a rearranged product, but the reaction stopped at the hydrazone derivatives with o-nitrophenylhydrazine. Various nucleophiles (e.g., MeO^-,H^-,N_3^-, amine) added in a 1,4-fashion to compound (113); thus, addition of benzylamine led to hydrazone (115) which was further converted into a 3:2 mixture of diamino-derivatives (116) and (117) (Scheme 26).[66] The synthesis of a

2,4-diaminohexose is detailed in section 3 (Ref. 33).



Reagents: i, $PhNHNH_2$; ii, $BnNH_2$; iii, H_2-Ni

Scheme 26

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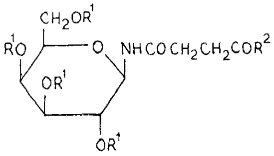
9
Miscellaneous Nitrogen Derivatives

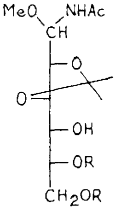
1 Glycosylamines

Rates of formation and degradation of N-(p-methoxyphenyl)glycosylamines from a variety of aldoes have been compared in connection with an h.p.l.c. analysis of sugars.[1] A 2-benzamido-2-deoxy-β-D-glucopyranosyl pyridinium salt was obtained during an attempted glycosidation using a phenyloxazoline derivative in the presence of pyridine.[2] N-Glycosylamidophosphites were prepared by phosphorylation of 2,3:5,6-di-O-isopropylidene-N-methyl-D-mannofuranosylamine anomers.[3]

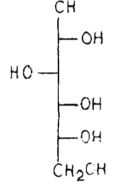
Compounds such as (1) and (2), N-acylated with functionalized succinic acid moieties which can be converted into azides and nitrenes, or carbenes respectively upon u.v.-irradiation, were prepared for photoaffinity-labelling of sugar binding sites of lectins and D-galactose transport systems.[4] The coupling of N-(6-aminohexanoyl)-β-D-glycosylamines to agarose to provide β-glucosidase affinity chromatography materials has been described.[5] N-(L-Glutam-5-oyl)-α-D-glucopyranosylamine and a trisaccharide analogue, required as model compounds for natural D-glucose-containing glycopeptides, have been synthesized by acylation of O-acetylated α-glycosylamines with a suitably protected glutamic acid derivative using the diethyl phosphorocyanidate method.[6] Isopropylidenation [$Me_2C(OMe)_2$-TsOH] of N-acetyl-α-D-glucofuranosylamine led to the acyclic acetals (3) (66%) and (4) (4%) together with small amounts



(1) $R^1 = H, R^2 = NHNH_2$
(2) $R^1 = Ac, R^2 = CHN_2$



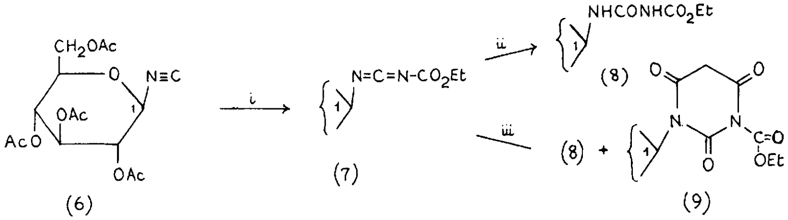
(3) R = H
(4) R,R = $Me_2C<$



(5)

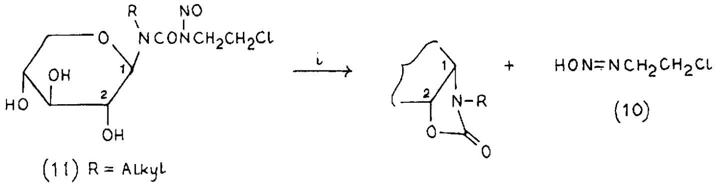
of the expected furanosyl 5,6-acetal (3%).[7] The base-catalysed intramolecular *O*,*N*-transacylation of per-*O*-acetylated 1,1-bis(benzamido)-1-deoxy-D-glucitol has been studied, in which the *N*-acetyl-*N*-benzoyl derivative (5) is formed using potassium cyanide with subsequent de-*O*-acetylation, and a mechanism has been proposed.[8]

Photochemical addition of a nitrene to the isonitrile (6) led to the carbodiimide (7), which added water to give urea (8) and malonic acid to give the potential glycosyl barbiturate synthon (9) (Scheme 1).[9] A review on the derivatives of carbohydrates with urea fragments has appeared.[10] Fifteen glycosyl ureas were obtained in 50-70% yield by transglycosylation of *N*-(*m*-nitrophenyl)-glycosylamines with urea.[11] The previously reported synthesis of 3-alkylated 1-(2-chloroethyl)-3-(glycopyranosyl)-1-nitrosoureas (Vol.15, p.108) has been extended by the same Japanese group to include α-D-arabino-, α-L-arabino-, β-D-xylo-, and β-D-ribopyranosyl derivatives. The potent antitumour activity displayed by many of these nitrosoureas appears to be due to the non-enzymic release of chloroethyl diazohydroxide (10) by intramolecular carbamate formation as shown for the L-arabinose derivative (11) in Scheme 2.[12] An important step in the synthesis of these nitrosourea derivatives involves the facile isomerization of isomeric aldosyl ureas in formic acid. As a representative example, 3-(L-



Reagents : i, $h\nu$ - N_3CO_2Et ; ii, H_2O ; iii, $CH_2(CO_2H)_2$ - THF

Scheme 1

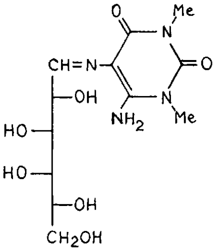


Reagents : i, pH 7·4, aqueous buffer

Scheme 2

arabinosyl)-1-(2-chloroethyl)-3-(3-methoxy-n-propyl)urea, produced by sequential treatment of L-arabinose with 3-methoxy-n-propylamine then 2-chloroethyl isocyanate, was shown to be a 3:2:1 mixture of α-pyranose, β-furanose, and β-pyranose isomers; isomerization gave the β-pyranose isomer as the sole product, the α-pyranose isomer rearranging via the β-furanose form.[13]

Six mono- and di-saccharide isothiocyanates were prepared in good yields by heating peracetylated glycosyl bromides with lead or silver thiocyanate.[14] N-Glycosyl-thioureas were obtained by condensing such glycosyl isothiocyanates with amine[15] and hydrazine[16] derivatives, while N-glycosylaminated heterocyclic derivatives were prepared from both glycosyl isothiocyanate and thiourea derivatives by condensation or cyclization reactions.[17,18] Condensation of D-galactose with 1,3-dimethyl-4,5-diaminouracil gave the acyclic galactosylidenimine derivative (12), not the β-D-galactosylamine derivative as previously reported, although cyclization could be achieved.[19] Similar condensations with D-glucose appear to give mixtures of D-glucosylidenimine and D-glucosylamine derivatives, or, in the presence of acetic acid, pteridines (e.g., 13).[20]



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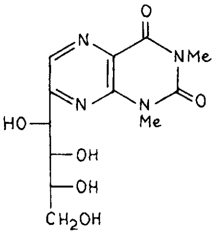


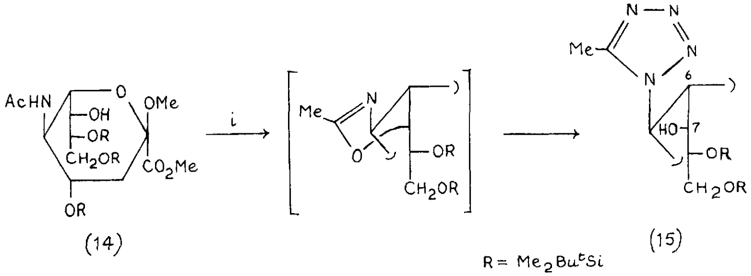
(13)

Various N-glycosylated heterocycles are covered in Sections 5 and 6, and in Chapter 19.

2 Azido-sugars

This year, azido-sugars have largely been utilized as intermediates in the synthesis of amino-sugars, and most references are therefore to be found in Chapter 8. 2-Azido-2,4-dideoxy- and 3-azido-3,4-dideoxy-D-erythro-pentopyranoside derivatives have been obtained via triflate displacement reactions.[21] The displacement of a hydroxy group by azide using the DEAD-TPP reagent system afforded a 3-azido-3-deoxy-D-allopyranoside derivative selectively from a 3,4-

unprotected D-glucoside.^{22} Neighbouring N- and O-acetyl group participation has been encountered in the use of this reagent system; thus attempted displacement of the 7-hydroxy group in compound (14) with azide, led instead to the 7-epimer (15) (Scheme 3).^{23}

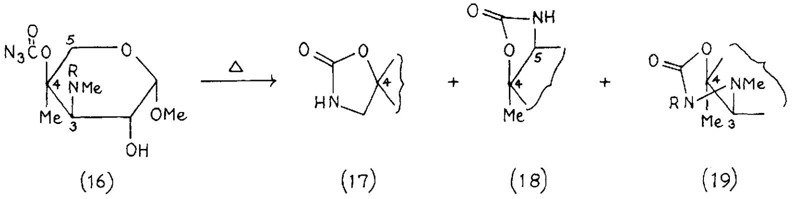


R = Me_2Bu^tSi

Reagents: i, HN_3-DEAD-TPP

Scheme 3

The acyl nitrene generated from compound (16) led to products (17) and (18) by insertion, and product (19) by a novel intramolecular transacylation (Scheme 4); various similar model systems were studied, culminating in a synthesis of 6"-aminated gentamicin C_2 (Chapter 18).^{24} A branched chain azido-sugar is referred to in Chapter 13.

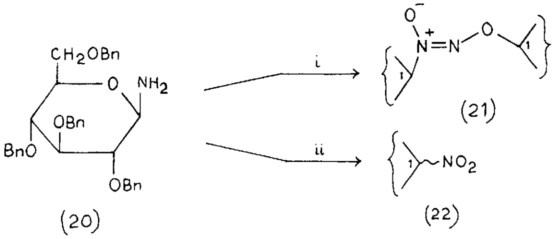


R = CO_2Bn

Scheme 4

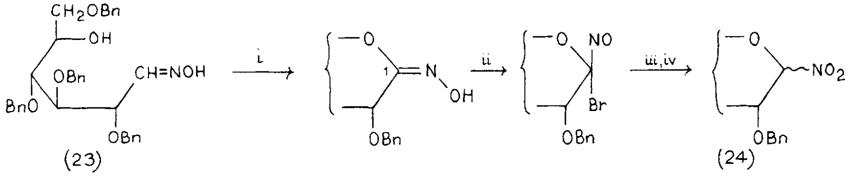
3 Nitro- and Cyano-sugars

Methods for synthesizing 1-deoxy-1-nitroaldoses have been developed. Oxidation of the O-protected D-glucopyranosylamine (20) gave the dimer (21) under mild conditions, but gave the nitroaldoses (22) under more vigorous conditions (Scheme 5).^{25} Direct oxidations of aldose oximes were not generally satisfactory, although oxidation (Bu^tO_2H-vanadylacetylacetonate) of 2,3:5,6-di-O-isopropylidene-D-mannose oxime gave the corresponding 1-deoxy-1-nitroaldofuranose in 54% yield.^{26} However, initial oxidative conversion of the oxime to a hydroximinolactone[25] followed by sequential bromine oxidation, ozonization, and borohydride reduction constituted a more general method, as illustrated for conversion of oxime (23) to nitroadose (24) (Scheme 6).[26]



Reagents: i, MCPBA-CH_2Cl_2, reflux ; ii, MCPBA-$(CH_2Cl)_2$, reflux

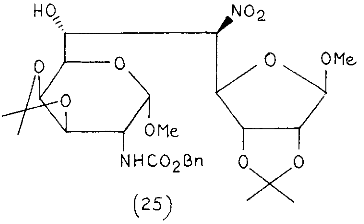
Scheme 5



Reagents: i, $NaIO_4$-NaOAc-EtOH-H_2O ; ii, Br_2-NaOH-H_2O-CH_2Cl_2 ; iii, O_3 ; iv, $NaBH_4$

Scheme 6

As part of a study of higher-carbon sugars related to the undecose of the nucleoside antibiotic tunicamycins, a Japanese group has synthesized a single undecose (25) and two stereoisomeric mixtures of dodecoses by condensation of 5- or 7-nitroaldose derivatives with aldehydo-sugar derivatives.[27-29] The synthesis of C-glycosyl-nitromethanes is referred to in Chapter 3.



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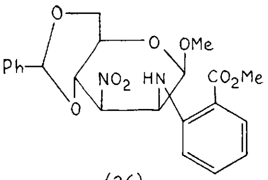

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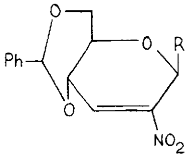


(27) R=H

(28) R=OMe

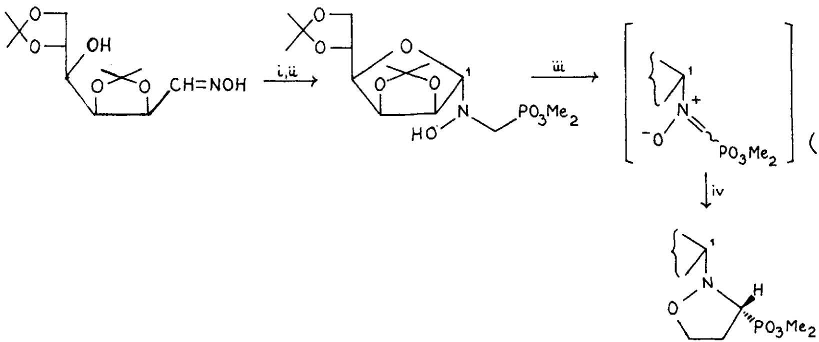
The results of an X-ray structure determination suggested that the unusual yellow colour of crystalline 3-nitro-sugar (26) was due to intramolecular C-H...O bonding between the ortho-aromatic hydrogen and an oxygen atom of the nitro-group, the orientation of the anthranilate moiety being fixed by the hydrogen bonding pattern of the N-H group.[30]

The synthesis of the 1,5-anhydro-2-nitro-hex-2-enitol derivative (27), and its epoxidation, Michael-type addition, and borohydride reduction reactions have been examined,[31,32] as have addition reactions to its methyl glycoside analogue (28) and to a 1,5-anhydro-2-nitro-D-ribo-hex-1-enitol analogue.[33] Synthesis of the tetronitrosides, (branched-chain amino-nitro-sugar derivatives) is covered in Chapter 8, while derivatives prepared by reduction of the branched-chain nitro-sugar in the antibiotic everninomycin are covered in Chapter 18.

5-Chlorobenzothiazole derivatives have been obtained from peracetylated aldononitriles or from peracetylated β-D-glycosyl cyanides on reaction with 2-amino-4-chlorobenzenethiol.[34]

4 Oximes and Hydroxylamines

A mechanism for the mutarotation of Z-D-arabinose oxime has been proposed, and involves cyclic N-arabinosyl hydroxylamine intermediates.[35] Separable mixtures of N-glycosylated L-α-aminophosphonic acid derivatives [e.g., (29)] and their D-aminophosphonic acid diastereoisomers in a ratio ~3:1 have been synthesized by the route outlined in Scheme 7, involving 1,3-dipolar cycloaddition of ethylene to in situ generated N-glycosyl-C-dialkyloxyphosphonoylnitrones [e.g., (30)]; the free L-α-aminophosphonic acids could be liberated from the major products.[36] References to other sugar



(30)

Reagents: i, HCHO; ii, HPO_3Me_2; iii, O_2-p-benzoquinone; iv, C_2H_4

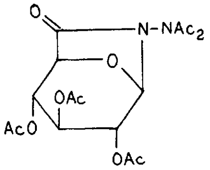
(29)

Scheme 7

oxime and hydroxylamine chemistry can be found in Section 3 and Chapter 18 respectively.

5 Hydrazones, Osazones, and Derived Heterocycles

Acetylation of the isonicotinoylhydrazone of sodium D-glucuronate (which exists in the β-pyranose form) gave the 6,1-lactam derivative (31), the conformation of which was examined in detail.[37] A variety of N-β-D-glucopyranosylated heterocycles have been synthesized by condensation of 2,3,4,6-tetra-O-benzyl-D-glucose hydrazone (which exists as a mixture of ring and chain isomers) with acetylacetone [leading to the synthesis of the 3,5-dimethylpyrazole derivative (32)], (ethoxymethylene)malondinitrile, (ethoxymethylene) cyanoacetate, N-(ethoxymethylene)oxalate, or various activated formic acid derivatives.[38]



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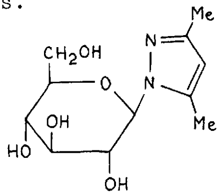

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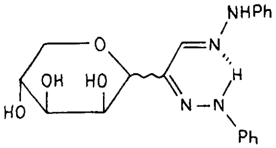
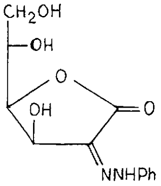


(33)

A reinvestigation of the dehydration of D-*galacto*-heptulose phenylosazone showed the product to be a mixture of the 3,7-anhydrides (33) with a pyranosyl ring, and not the furanosyl 3,6-anhydro-counterparts as previously claimed (Vol.14, p.88); further data on such dehydration reactions is detailed in Section 6.[39] Further details on the dehydrative cyclization of the phenylosazones of L-*lyxo*- and L-*xylo*-hexulose and 7-deoxy-L-*manno*-heptulose have been reported (Vol.14, p.88; Vol.15, p.112).[40,41]

L-*xylo*-Hexulosono-1,4-lactone 2-phenylhydrazone (34) was obtained by borohydride reduction of dehydro-L-ascorbic acid 2-phenylhydrazone, and underwent 3,6-anhydride formation upon acetylation.[42] Dehydrative cyclization (Br_2-H_2O) of dehydro-L-ascorbic acid 3-oxime 2-phenylhydrazone yielded the 1,2,3-triazole derivative (35) from which a variety of derivatives were synthesized.[43]

The action of hydrogen bromide in acetic acid on dehydro-L-ascorbic acid 2-phenylhydrazone[42] and its 3-oxime[43] gave 5,6-dibromo and 6-bromo derivatives respectively, from which a variety of derivatives were prepared.



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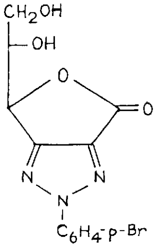

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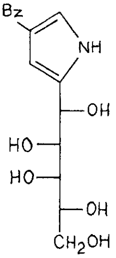

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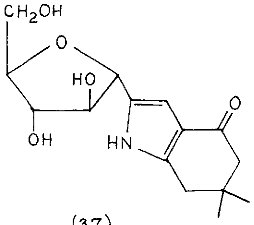


(37)

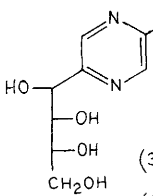
6 Other Heterocyclic Derivatives

Pyrrole derivatives (*e.g.*, 36) were prepared by cyclization of keto-enamines prepared from 2-amino-2-deoxyheptoses.[44] Dehydrative cyclizations of D-*gluco*- or D-*manno*-pentitol-1-yl-heterocycles initially gave the same α-D-arabinofuranosyl derivatives (*e.g.*, 37) which then rearranged to their more stable α-pyranosyl analogues; in contrast, D-*galacto*-pentitol-1-yl heterocycles formed anomeric D-lyxopyranosyl derivatives directly due to the strained nature of the transition state required for the formation of furanosyl products.[39]

The D-*arabino*-tetritol-1-yl pyrazine derivative (38) has been synthesized by treatment of a 2-amino-2-deoxy-D-glucose oxime - glyoxal mixture with sodium bisulphite,[45] while the disubstituted pyrazine (39) was obtained by similar treatment of 2-amino-2-deoxy-D-glucose itself.[46] The (*S*,*S*)-palythazine (40) has been stereospecifically synthesized from D-glucose, *via* 2,3,4,6-tetra-*O*-benzyl-D-glucal which was converted to the key intermediate (41) in six steps; self-condensation (Gutknech conditions) and oxidation provided the isomer (40) which has the (*S*,*S*)-configuration now assigned to the natural product.[47]

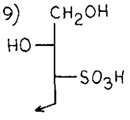
1,4-Bis(4*H*-benzoxazin-4-one-2-yl)-*galacto*-tetritol tetraacetate (42) was obtained by condensation of anthranilic acid with the bis-acid chloride of tetra-*O*-acetylgalactaric acid, and dehydration with acetic anhydride.[48]

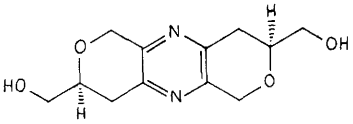
Dipolar cycloaddition of diphenylnitrile imine $(Ph\bar{N}-N=\overset{+}{C}Ph)$ with a 2,3-unsaturated sugar derivative gave a 4:1 mixture of the mannopyranosido[3,2-*C*]pyrazole (43) and its [2,3-*C*]regioisomer,[49]



(38) $R = SO_3H$

(39)





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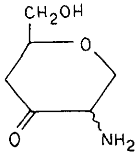
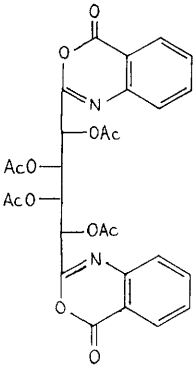


(41)

while analogous reaction of benzonitrile oxide gave the mannopyranoside[2,3-d]isoxazole (44).[50] Oxazoline derivatives were mentioned in Chapter 8, and other heterocyclic derivatives can be found in Chapter 19.



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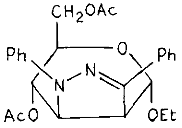

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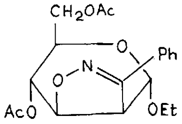

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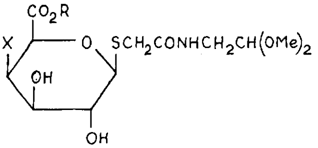
10
Thio- and Seleno-sugars

The synthesis of carbohydrates containing selenium including selenoglycosides and derivatives with selenium in the sugar ring has been reviewed.[1]

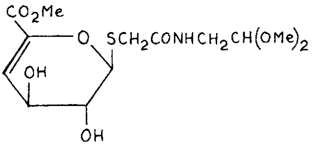
Ab initio molecular orbital calculations on methanedithiol and thiolmethanol have been used as models for the anomeric effect in S-C-S and O-C-S carbohydrate systems. The lower anomeric effect in sulphur systems was attributed to lower dipolar contributions to the total energy compared to the oxygen systems.[2]



(1) R = H, X = OH

(2) R = Me, X = OH

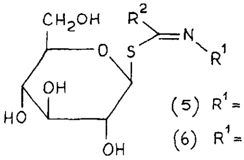
(4) R = X = H



(3)

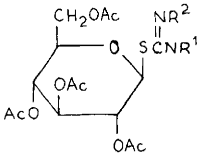
The (2,2-dimethoxyethyl)aminocarbonylmethyl 1-thioglycosides of D-galacturonic acid (1) and its methyl ester (2) have been synthesized. In the course of deacetylation with triethylamine - methanol, the 4,5-unsaturated derivative (3) was produced as a by-product. Hydrogenation of this using hydrogen - palladium on charcoal gave the 4-deoxy compound (4).[3] Synthesis of fully-protected 1-*S*-(acylaminoaryl)- D-glucopyranoses from 1-thio-β-D-glucopyranose tetra-acetate and *N*-acylamino acids using DCC and imidazole as condensing agents has been reported.[4] Chemical ionization m.s. has been used to identify mustard oil glycosides (5) and their desulphoglucosinolates, (6). Although no molecular ions were observed, the intense fragment ions allowed identification of the side-chain and hence the whole structure.[5] Substitution at the imino-nitrogen atom of the 1-thio-guanidine derivatives (7) has been achieved using phenyl isocyanate and phenyl isothiocyanate. Thus products of the type shown in (8) were obtained.[6]

6-Mercapto-purine reacts with the peracetylated glycosyl bromide of methyl glucuronate to give the *S*-glycoside, isolated as its ammonium salt (9) or its amide (10). The hydrolysis by bovine liver β-glucuronidase was examined.[7] Alkoxyphosphinegold chlorides, prepared by a novel alkoxy-interchange reaction, have been used to prepare S-diethylalkoxyphosphinegold 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranosides (11).[8] Details of the preparation and



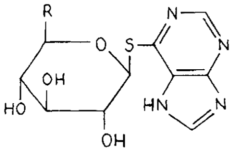
(5) $R^1 = OSO_3$, R^2 = Alkyl or Aralkyl

(6) $R^1 = OH$, R^2 = Alkyl or Aralkyl



(7) R^1 = Aryl, R^2 = H

(8) R^1 = Aryl, R^2 = C(=X)NHPh , X = O or S

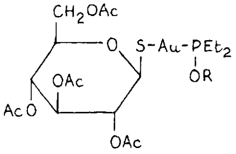


(9) $R = CO_2NH_4$

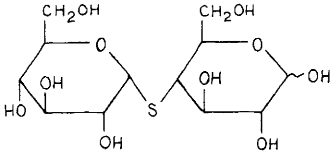
(10) $R = CONH_2$

interconversions of the glycosyl thio- and thiono-phosphates of 2,3,4,6-tetra-O-acetyl-D-glucose previously reported have appeared.[9] The synthesis of thiomaltose (12) has been achieved[10] (see Chapter 3).

Methyl 2-acetamido-4,6-di-O-acetyl-3-S-acetyl-2-deoxy-3-thio-α-D-mannopyranoside (13) has been synthesized by the route shown in Scheme 1.[11]



(11)



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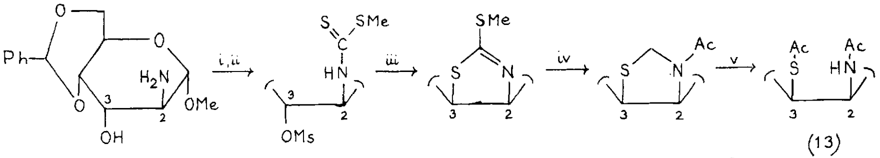
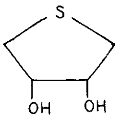


Reagents: i, CS_2-NEt_3-MeI ; ii MsCl-Py ; iii , Py ; iv, Al-Hg-Ac_2O ; v, $HgCl_2$-HgO-Ac_2O-Py

Scheme 1

Glycoside and nucleoside derivatives of 3-amino-3-deoxy-4-thio-DL-threofuranose have been synthesized starting from the thiane diol (14). Thus the 4-thioglycoside (15) was prepared from the heterocycle (16), itself obtained from (14) in seven steps, <u>via</u> a Pummerer rearrangement of the intermediate sulphoxide as shown in Scheme 9.[12] Intramolecular cyclization of D-threose dithianes leads to γ-halopropyl 1,4-dithio-β-D-threofuranosides.[13] The mechanism is depicted in Scheme 3.



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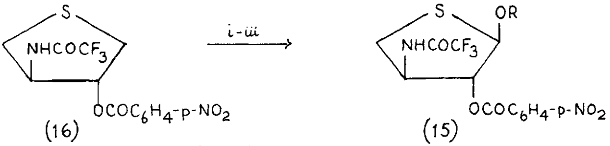
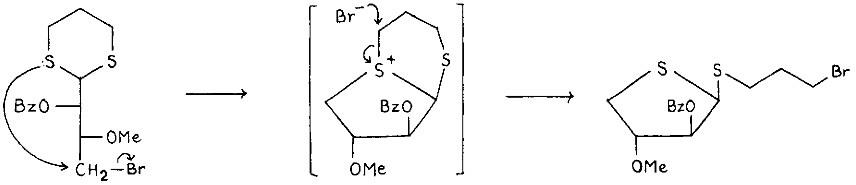


Reagents; i, H_2O_2; ii, $(CF_3CO)_2O$; iii, ROH-TsOH

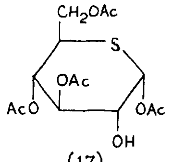
Scheme 2



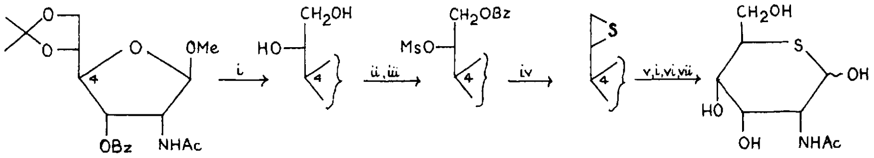
Scheme 3

2,3,4,6-Tetra-<u>O</u>-acetyl-5-deoxy-5-thio-β-D-glucopyranosyl bromide has been prepared conventionally from the corresponding 1,2,3,4,6-penta-<u>O</u>-acetyl compound. Significant differences in the U.V. spectra of the α- and β-anomers (α, λ_{max}^{EtOH} 246 nm, ε 1840; β, λ_{max}^{EtOH} 208 nm, ε 680) provide a useful test of anomeric configuration. The β-bromide did not mutarotate, attributed to the weaker anomeric effect of sulphur. The anomers also showed a different reactivity towards silver acetate in benzene: the α-bromide gave the expected mixture of the anomeric acetates, whereas the β-bromide gave the 2-hydroxy-glycosyl acetate (17) in addition to the normal anomeric acetates.[14] 2-Acetamido-5-deoxy-5-thio-D-allose (18) has been synthesized as shown in Scheme 4.[15]

The reaction of the adenosylsulphonium ion (19), an enzyme model compound, was shown to follow route (a) exclusively in aqueous oxyanion buffer to give ring-closure, but to follow both routes (a) and (b) competitively in amine buffers (Scheme 5).[16]



(17)

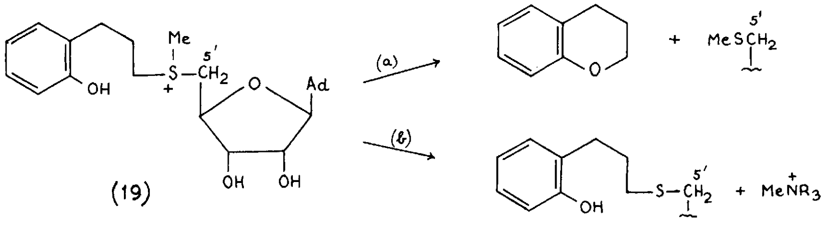


(18)

Reagents: i, H^+; ii, BzCl-Py; iii, MsCl-Py; iv, $CS(NH_2)_2$; v, NaOAc; vi, Ac_2O-Py; vii, NaOMe-MeOH

Scheme 4

The diastereoisomeric 1-phenylethyl dithioacetals of arabinose, lyxose, fucose, rhamnose, galactose, glucose and mannose have been prepared and separated conventionally.[17]



(19)

Scheme 5

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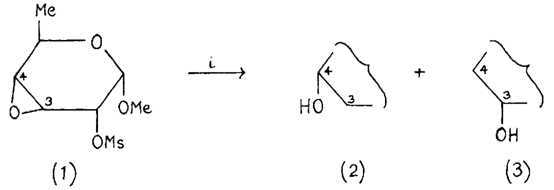
11

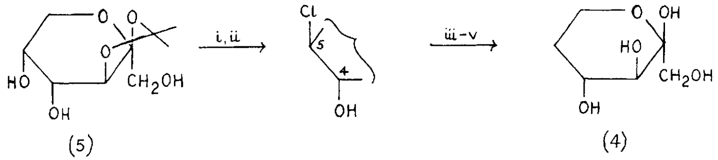
Deoxy-sugars

Lithium triethylborohydride reductions of tosylate derivatives of methyl 4,6-O-benzylidene-α-D-glucopyranoside were highly regioselective and gave good yields of deoxy-sugars via epoxide intermediates; thus, the 3-mono- and 2,3-di-O-tosylates gave the same 2-deoxy-D-ribo-hexopyranoside, while the 2-O-tosylate provided its 3-deoxy-D-arabino-analogue. In contrast, tosylates of the β-anomer gave mixtures of products. Reductions with lithium triethylborohydride were compared with those using lithium aluminium hydride.[1] Reduction of the conformationally flexible 3,4-anhydro-D-alloside (1), which led to a mixture of the paratoside (2) and its D-ribo-isomer (3) (Scheme 1), has been investigated at different temperatures.[2] 5-Deoxy-D-threo-hexulose (4), which is much sweeter than L-sorbose and almost as sweet as D-fructose, has been synthesized from the isopropylidenated L-sorbose derivative (5) by selective chlorination, 4,5-epoxide formation, and reduction (Scheme 2).[3]



Reagent: i, $LiAlH_4$

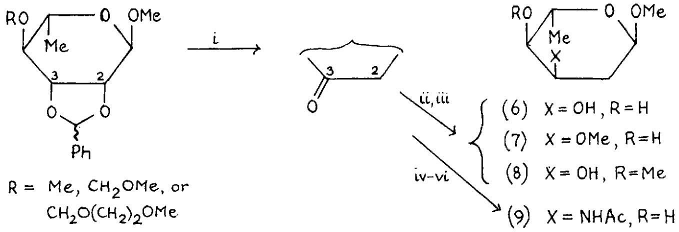
Scheme 1



Reagents: i, SO_2Cl_2; ii, MeONa-MeOH; iii, OH^-; iv $LiAlH_4$; v, H_3O^+

Scheme 2

The cleavage of a benzylidene acetal group with n-butyllithium (Vol.10, .33) was used in the synthesis of methyl glycosides (6-9) of L-digitoxose, L-cymarose, a kijanimycin sugar component, and N-acetyl-L-ristosamine respectively (Scheme 3).[4-6]



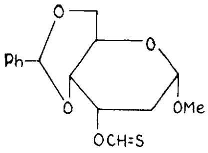
Reagents: i, Bu^{n}Li ; ii, NaBH$_4$; iii, H$_3$O$^+$; iv, NH$_2$OH ; v, H$_2$-PtO$_2$; vi, Ac$_2$O

Scheme 3

The reaction of 2-hydroxypropyl-(2)-radicals (i.e., •CMe$_2$OH), generated by δ-radiolysis of 2-propanol-acetone, with 3-bromo-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose and its 3-iodo-D-gluco- and 3-iodo-D-allo-analogues, has been examined in detail as a contribution towards understanding the radical-induced dehalogenation of bromo- and iodo-sugars. The reactions studied were chain reactions which proceeded to completion, and were less susceptible to steric influences under alkaline conditions where radical anions were present. The most favourable conditions for photolytic dehalogenation were predicted from this study.[7]

Carbon radicals are markedly stabilized by oxygen atoms bonded to the β-carbon, so that radical reactions, such as tributyltin hydride reduction of O-thiocarbonyl and isonitrile derivatives, proceed in many carbohydrate derivatives to give deoxy-sugars, while not proceeding in model compounds devoid of β-oxygen functionality. That the β-oxygen could be part of another ring was evident from the 3-deoxygenation (29% yield) of the thioformate (10).[8]

Tertiary hydroxy groups adjacent to formyl groups in branched-chain sugars can be replaced by hydrogen through free-radical deoxygenation of the benzoate, or even better the 4-cyanobenzoate,



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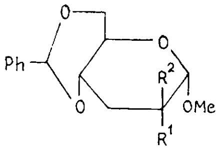
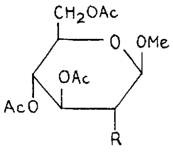


(11) R^1 = NC-C$_6$H$_4$-CO$_2$, R^2 = CH(OMe)$_2$
(12) R^1 = CH(OMe)$_2$, R^2 = H

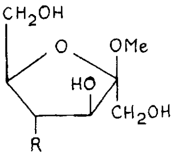


(13) R = H
(14) R = Br

esters with tributyltin hydride; thus compound (11) was reduced to compound (12).[9] A tributyltin hydride induced deoxygenation of an *O*-(imidazol-1-yl)thiocarbonyl ester is covered in Chapter 19.

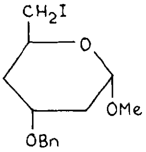
2-Bromo-2-deoxy-sugars, derived from glycals, can be photochemically converted into 2-deoxy-sugars on irradiation in 2-propanol; thus compound (13) was obtained from bromide (14).[10] Photolytic de-iodination was utilized in a synthesis of L-streptose (Chapter 13).

Various deoxy-sugars have been obtained from halogeno-derivatives by reductive displacement reactions. Methyl 4-deoxy-β-D-*threo*-hexulofuranoside (15) has been obtained by Raney nickel-hydrazine de-iodination of 3-iodide (16) (see Chapter 7); its resistance to hydrolysis by invertase (β-D-fructofuranosidase) demonstrated that not only a 1- and 6-, but also a 4-hydroxy group is necessary for enzyme bonding.[11] 5-Deoxy-D-ribofuranose derivatives, and various 5-deuteriated and 5,5-dideuteriated analogues were synthesized from D-ribose, D-xylose and D-glucose by conventional routes involving 5-halogenated pentofuranose derivatives,[12] and were then used for the synthesis of nucleoside analogues (Chapter 19). Other examples of reductive dehalogenation appear in Chapters 3, 7, 8 and 18.



(15) R = H

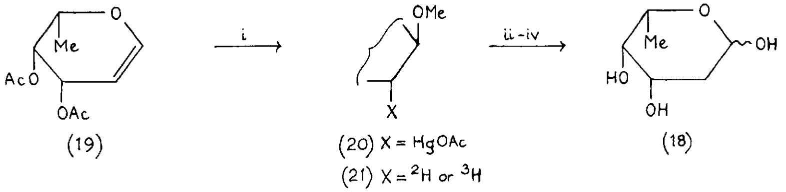
(16) R = I



(17)

Reductive detosyloxygenation ($NaBH_4$-DMSO) was a key step in the conversion of a methyl 2-deoxy-4-*O*-tosyl-α-D-*ribo*-hexopyranoside derivative into the 2,4,6-trideoxy-6-iodo-derivative (17), required as a chiral intermediate for the synthesis of certain natural enzyme inhibitors related to mevinolin (see also Chapter 23).[13] Various reductive and other conventional deoxygenation reactions have been employed in pheromone syntheses (see Chapter 23).

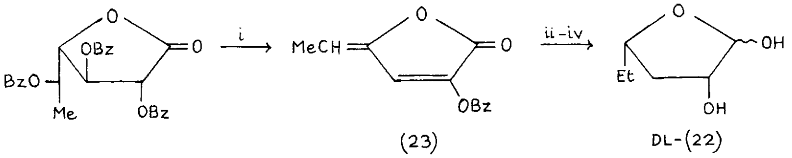
Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*- and *lyxo*-hexopyranoside anomers were obtained on acidic ion-exchange resin-catalysed addition of methanol to the corresponding glycals.[14] 2-Deoxy-L-fucose (2,6-dideoxy-L-*lyxo*-hexose) (18) has been obtained from glycal (19) by way of an acetic acid addition (AcOH-TsOH) or by a methoxymercuration-demercuration sequence (Scheme 4). Reduction of the mercurated intermediate (20) with sodium boro-deuteride or -tritide occurred with retention of configuration to give the labelled derivatives (21), which were tested biochemically.[15]



Reagents: i, $Hg(OAc)_2$-MeOH; ii, $NaBH_4$; iii, $Ba(OH)_2$-MeOH; iv, H_3O^+

Scheme 4

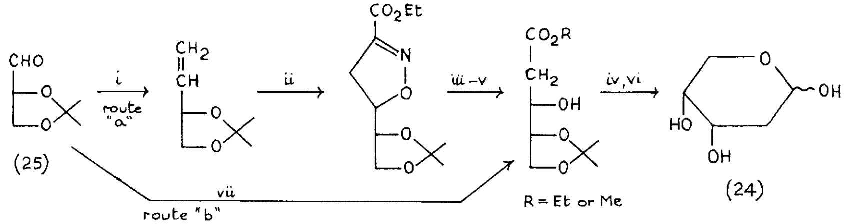
3,5,6-Trideoxy-DL-*threo*-hexose (22) has been obtained from L-rhamnono-1,4-lactone by a sequence (Scheme 5) involving benzoylation, elimination, hydrogenation, and lactone reduction; the first step in the hydrogenation of furanone (23) involved saturation of the exocyclic double bond.[16] Analogous treatment of L-rhamnono-1,5-lactone gave products in the pyranose series, including 3-benzoyloxy-6-methylpyran-2-one.[17] 2,3-Unsaturated glycosyl cyanides which could be hydrogenated to provide deoxy-derivatives are referred to in Chapter 3.



Reagents: i, Et_3N-$CHCl_3$; ii, H_2-Pd/$BaSO_4$; iii, Disiamylborane; iv, NaOMe-MeOH

Scheme 5

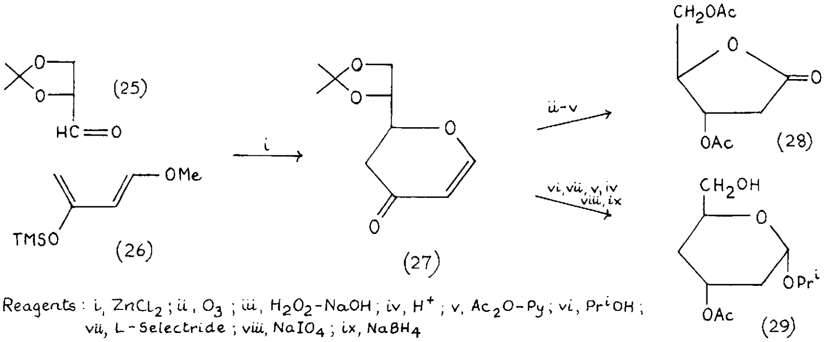
2-Deoxy-D-*erythro*-pentose (24) has been elaborated from 2,3-*O*-isopropylidene-D-glyceraldehyde (25) either by a stereoselective dipolar cycloaddition reaction (Scheme 6, route a)[18] or by a stereoselective aldol condensation involving a boronated ester enolate reagent (route b).[19] The DL-analogue of (24) has been synthesized from 1,3:2,4-di-*O*-benzylidene-erythritol by mono-bromination (Hanessian's procedure with NBS) to give a 1-bromo-3-*O*-benzoate, displacement of bromide by cyanide, and reductive conversion of the cyano-group to an aldehyde.[20] Chain extension procedures that have been used in the syntheses of 2-deoxy-α-hexopyranosides and of 6-deoxyhepturonic acid derivatives are covered in Chapters 3 and 15 respectively.



Reagents: i, Ph_3PCH_2; ii, $EtO_2CC{\equiv}N{\rightarrow}O$; iii, OH^-; iv, H_3O^-; v, CH_2N_2; vi, Disiamylborane;
vii, $\begin{matrix}EtO\\Ph_2BO\end{matrix}\!\!>C{=}CHX$ (X = H or HgOAc)

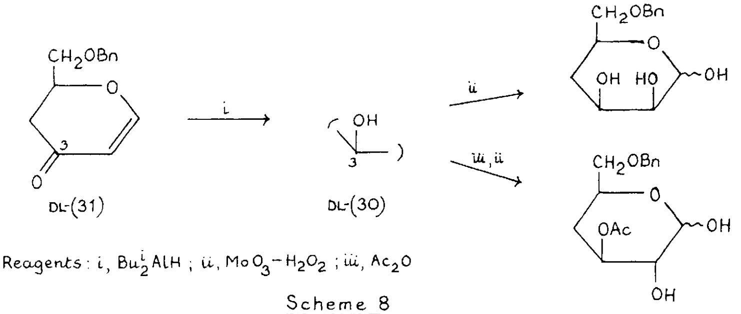
Scheme 6

Danishefsky and co-workers$^{21-23}$ have developed a versatile deoxy-sugar synthesis, the key step of which involves the Lewis acid-catalysed (BF_3 or $ZnCl_2$) hetero-Diels-Alder reaction between an aldehyde and the 1,3-disubstituted-butadiene (26) to obtain a dihydropyrone derivative. The use of D-glyceraldehyde derivative (25) (Scheme 7) provided the chiral enone (27), which was transformed into the 2-deoxypentonolactone (28) via oxidative C2-C3 cleavage, or into the 2,4-dideoxy-α-D-erythro-hexoside (29) via oxidative C6-C7 cleavage. The use of achiral aldehydes provided a wide range of racemic enones, from which various racemic deoxy-sugars (including DL-chalcose) were synthesized. Molybdenum trioxide catalysed cis-dihydroxylation of the glycal (30), obtained on reduction of the DL-enone (31), occurred syn to a 3-hydroxy substituent, but anti to a 3-acetoxy-substituent (Scheme 8).^{22}



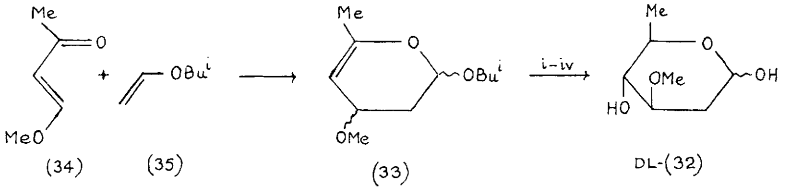
Reagents: i, $ZnCl_2$; ii, O_3; iii, H_2O_2-NaOH; iv, H^+; v, Ac_2O-Py; vi, Pr^iOH;
vii, L-Selectride; viii, $NaIO_4$; ix, $NaBH_4$

Scheme 7



Reagents: i, Bu^i_2AlH; ii, MoO_3–H_2O_2; iii, Ac_2O

Scheme 8

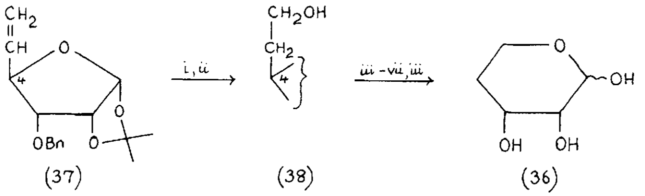


Reagents: i, $BH_3.Me_2S$; ii, OH^-; iii, H_2O_2; iv, H_3O^+

Scheme 9

Racemic oleandrose (2,6-dideoxy-3-O-methyl-arabino-hexose) (32) was synthesized from the Diels-Alder adduct (33) of 4-methoxy-3-buten-2-one (34) and isobutyl vinyl ether (35), by a highly stereo-selective hydroboration-oxidation procedure (Scheme 9).[24]

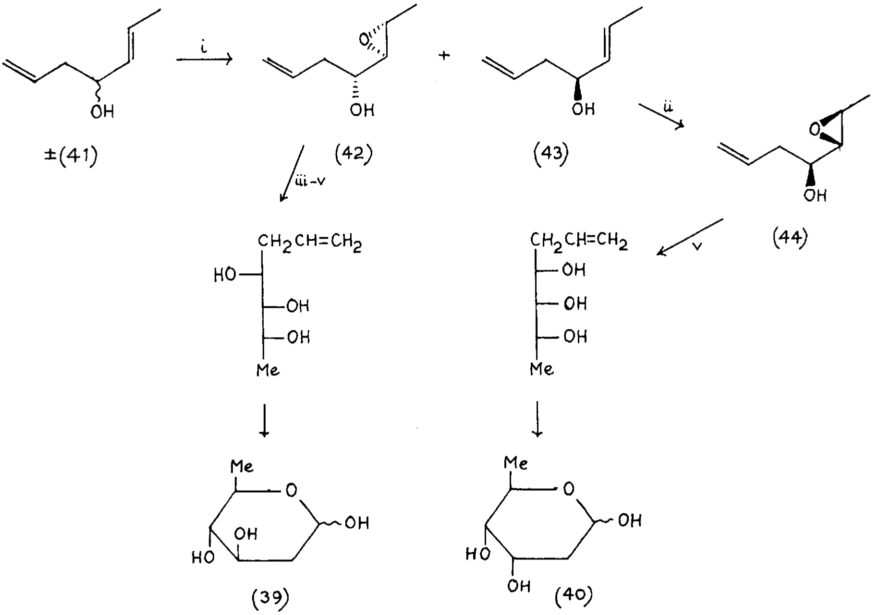
4-Deoxy-D-erythro-pentose (36) was synthesized from the known 5-ene (37) (available from D-glucose) by hydroboration to give the 5-deoxy-derivative (38), and periodate induced C1-C2 cleavage (Scheme 10).[25]



Reagents: i, $(Pr^iMeCH)_2BH$; ii, H_2O_2; iii, H_3O^+; iv, $NaIO_4$; v, OH^-; vi, MeOH-HCl, vii, H_2-Pd

Scheme 10

The Sharpless asymmetric epoxidation-kinetic resolution procedure (see also Chapters 3 and 11), by which chiral α-hydroxy-epoxides can be obtained from racemic allylic alcohols in good optical purities (>95% e.e.), has been applied in the synthesis of D-olivose (2,6-dideoxy-D-arabino-hexose) (39) and of D-digitoxose (the D-ribo-isomer) (40) (Scheme 11). Thus, epoxidation of racemic (41) in the presence of (-)-tartrate ester led to (+)-epoxide (42), while epoxidation of the remaining unreacted (-)-alkene (43) in the presence of (+)-tartrate ester provided the enantiomeric (-)-epoxide (44). Opening of the epoxide ring in (42) with neighbouring group participation led to D-arabino-products, while acid hydrolysis of epoxide (44) led to D-ribo-products.[26]



Reagents: i, $Bu^tO_2H-Ti(OPr^i)_4-$(-)-diisopropyl tartrate; ii, $Bu^tO_2H-Ti(OPr^i)_4-$(+)-diethyl tartrate; iii, PhNCO-Py; iv, $BF_3\cdot Et_2O$; v, H_3O^+; vi, O_3, then Me_2S

Scheme 11

Base-catalysed isomerizations of 4-deoxyaldoses have been examined using a variety of reagents [$Ca(OH)_2$, Et_3N, py, and DCC], the last proving to be the most efficient. 4-Deoxy-D-xylo-hexose was thus converted into a mixture containing 4-deoxy-D-threo- and erythro-hexuloses and 4-deoxy-D-lyxo-hexose in 50, 10 and 2% yields respectively.[27] An enzymic-colourimetric assay for 2-deoxyhexoses is outlined in Chapter 22, while deoxysugar components of an antibiotic compound are detailed in Chapter 18.

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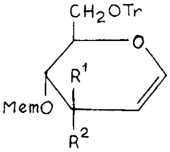
12

Unsaturated Derivatives

A set of provisional recommendations for naming unsaturated sugar derivatives have been proposed by IUPAC-IUB,[1] and a very extensive review of conjugated enones derived from monosaccharides has appeared.[2]

1 Glycals

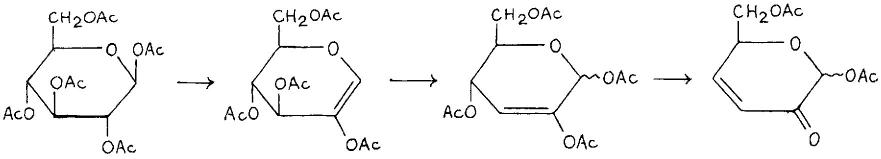
Three O-acetyl-di-O-benzyl-D-galactals have been described,[3] and the epimeric branched-chain compounds (1) and (2) have been made from the corresponding enone which was produced from D-glucal.[4]



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

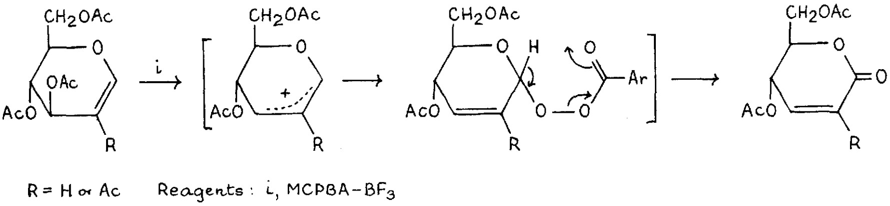
(2) $R^1 = OH$, $R^2 = Me$

2-Hydroxy-D-glucal tetra-acetate is produced by thermolysis of acetylated D-gluco- or D-manno-orthoacetates in solvents such as chlorobenzene,[5] and aldopyranose peracetates with the 1,2-trans-configuration likewise initially give products of 1,2-syn-elimination of acetic acid when pyrolysed at 350°C in acetone. The initial products then isomerize and lose acetic anhydride as shown in Scheme 1.[6]



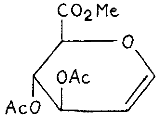
Scheme 1

A simple method for converting glycal and 2-hydroxyglycal esters into unsaturated lactones involves treatment with m-chloroperbenzoic acid in the presence of boron trifluoride (Scheme 2);[7] similar products are obtained by heating in water (to effect solvolysis with allylic rearrangement) followed by oxidation with pyridinium chlorochromate.[8]



Scheme 2

Syntheses involving additions to glycal derivatives have included the following: 2,6-dideoxy-L-lyxo-hexose from di-O-acetyl-L-fucal by addition of acetic acid or by methoxymercuration;[9] 2-deoxy-2-fluoro-D-glucose and -D-galactose by additions of acetyl hypofluorite to tri-O-acetyl-D-glucal and -D-galactal;[10] methyl 3,4,6-tri-O-benzoyl-2-deoxy-D-arabino- and -D-lyxo-hexopyranoside by acid-catalysed addition of methanol to tri-O-benzoyl-D-glucal and -D-galactal;[11] and 2-acetamido-2-deoxy-D-glucuronic acid following initial azidonitration of the uronic acid glycal derivative (3).[12] A nonspecific photochemical additon of a nitrene to a glycal derivative is illustrated in Scheme 3.[13]



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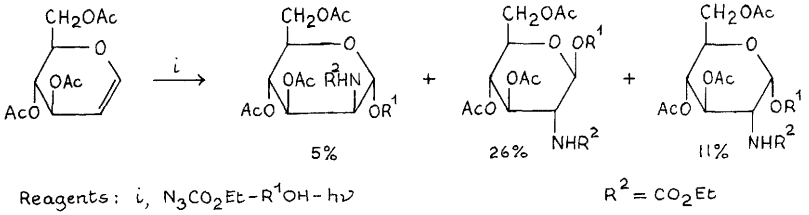


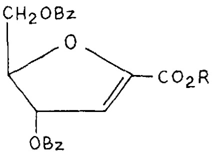
Scheme 3

Allylic rearrangements of glycal esters continue to be used; di-O-acetyl-D-xylal afforded 2,3-unsaturated glycosyl azides together with the isomeric 3-azido-3-deoxyglycal epimers on treatment with sodium azide in the presence of boron trifluoride. The latter, on azidonitration, afforded routes to 2,3-diamino-2,3-

dideoxy-D-xylo- and D-lyxo-pentose.[14]

C-Glycosides are increasing in importance, and the synthesis of several 2,3-unsaturated C-pyranosides produced by allylic rearrangement reactions of glycals are referred to in Chapter 3.

In the area of 1-C-substituted glycals (which are related to C-glycosides), esters (4) were prepared in good yield by treatment of the 2,5-anhydro-D-allonic acid (5) with 2-chloro-N-methylpyridinium iodide in the presence of triethylamine and alcohols (ROH).[15] The related pyranoid derivative (6) was formed by way of (7) by pyrolysis of α-L-sorbopyranose penta-acetate (8) in acetone in a flow system at 250°C as shown in Scheme 4; β-D-fructopyranose penta-acetate behaved similarly. Compounds (7) and (6), on hydrogenation, gave 1,5-anhydro-D-glucitol and the 2,6-anhydro-3-deoxy-L-lyxo-hexose tetra-acetate, respectively.[16]



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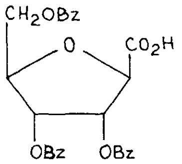

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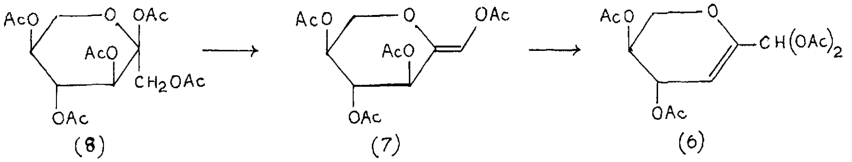
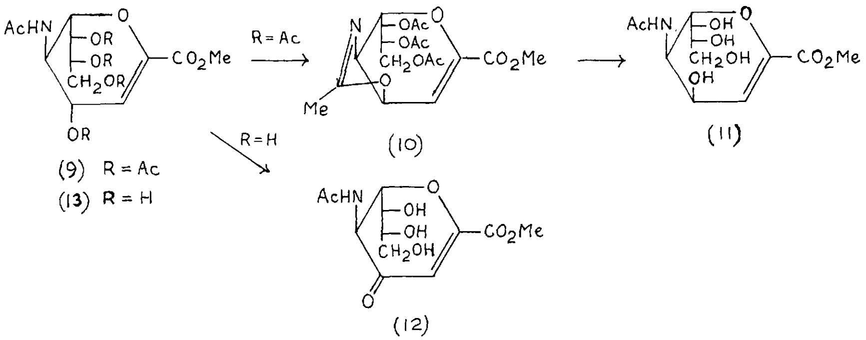


Scheme 4

Treatment of the "dehydroneuraminic" acid derivative (9) or its



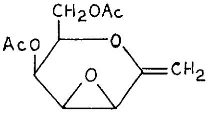
Scheme 5

C-4 epimer under acidic conditions resulted by allylic displacement in the formation of the oxazoline (10) which could be readily hydrolysed to the alcohol (11),[17] and the same group of workers prepared the enone (12) by tritylation of the primary position of compound (13), allylic oxidation, and detritylation (Scheme 5).[18]

2 Other Unsaturated Derivatives

An improved method of converting 1,2-diols into alkenes via the thionocarbonates involves use of 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (prepared from N,N-dimethylethylenediamine and dichlorophenylphosphine). An example in the alditol series and one with a pyranoid compound were given; yields were in the region of 80%.[18a]

The 1,2-unsaturated 2,6-anhydroheptitol derivative (14) which is related to 6-deoxyhex-5-enopyranoses has been prepared from the iodotosylate (15) by standard methods,[19] and the related, furanoid compounds (16) (Z and E isomers) are present amongst the products of thermolysis of α-D-fructofuranose penta-acetate in acetone solution at 265°C. Furanoid peracetates, however, generally lose two molecules of acetic acid under these conditions and give furans as main products.[20]



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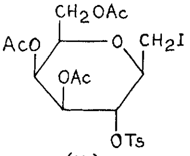

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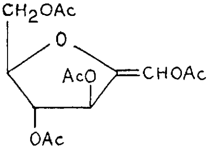
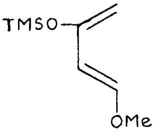


(16)

Hetero Diels-Alder reaction of the oxygenated dienes (17)-(20) with diethyl mesoxalate gave a set of 5,6-dihydro-(2H) pyrans containing the structural unit (21) which are related to 2,3-unsaturated pyranoid compounds.[21] Both furanoid and pyranoid



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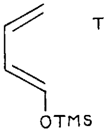

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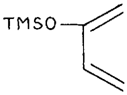

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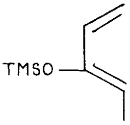

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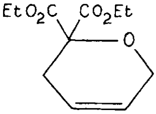
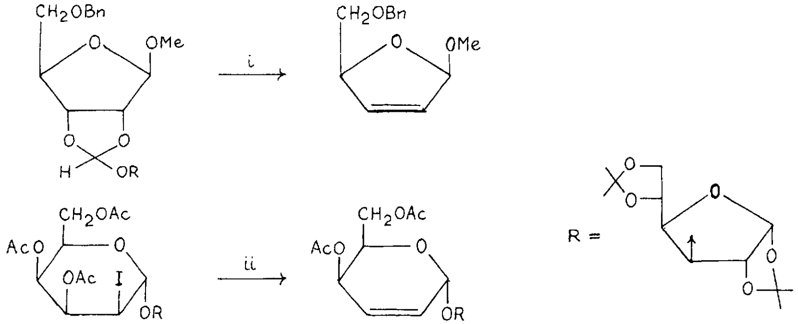


(21)

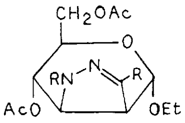
compounds with 2,3-double bonds have been made by (a) the pyrolysis of orthoformates,[22] and (b) by treatment of α-iodoacetates with zinc-acetic acid,[23] illustrated in Scheme 6. The latter procedure was used to prepare a 2,3-unsaturated nucleoside from 3-deoxy-3-halogeno-D-xylo-hexose derivatives.



Reagents: i, Δ ; ii, Zn-HOAc

Scheme 6

Dipolar cycloadditions of diphenylnitrile imine[24] and benzonitrile oxide[25] to ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside gave compounds (22) and (23) as main products, respectively, and a slightly modified epoxidizing reagent (peroxybenzimidic acid, produced from benzonitrile and hydrogen peroxide, and potassium carbonate) reacted efficiently with a selection of 2,3-unsaturated pyranoid and furanoid compounds (and other alkenes).[26]



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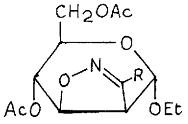

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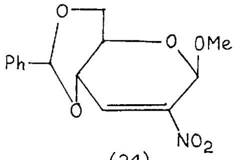
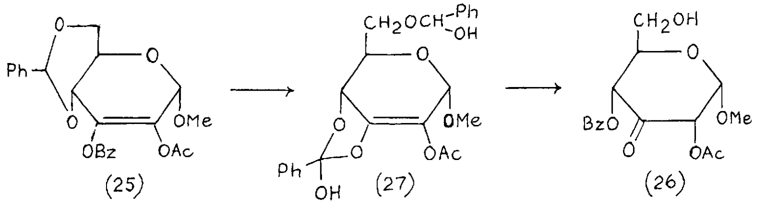


(24)

Michael additions to the nitro-compound (24)[27] have been further examined. Differences were noted with change in the reagent, and the results were discussed in conformational terms and in comparison with those obtained with a related 2-nitroglycal derivative. Photolysis of the enediol ester (25), which was formed on treatment of methyl 3-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside with DMSO-acetic anhydride, gave the unexpected glycosidulose (26), possibly by way of (27) (Scheme 7).[28]

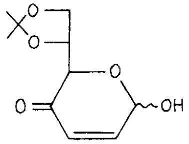
An ingenious route to the enone (28) involves ring expansion of



(25) (27) (26)

Scheme 7

the furan derivative (29) which was produced by condensation of 2,3-O-isopropylidene-D-glyceraldehyde with furan,[29] and the product afforded a route to D-glycero-D-manno-heptose (see Chapter 2).



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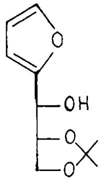
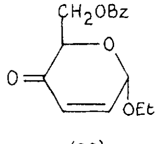


(29)

Various benzannelations of the related enone (30) with oxygenated dienes gave products such as (31),[30] and an interesting use of



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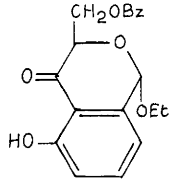
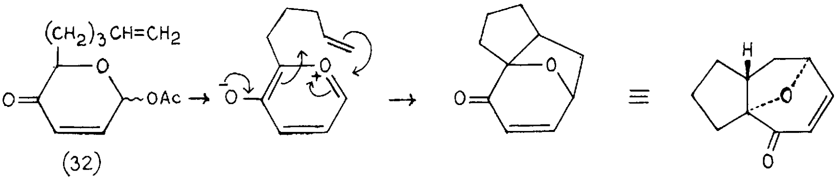


(31)

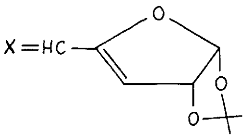
related compounds in the synthesis of the perhydroazulene skeleton has been reported. Elimination of acetic acid from enone (32) afforded a pyrylium zwitterion which underwent intramolecular cycloaddition as shown in Scheme 8.[31] Vineomycin A (Chapter 18) contains a related enone derived from a 6-deoxyhexose as a glycosidically bonded unit.[32]



(32)

Scheme 8

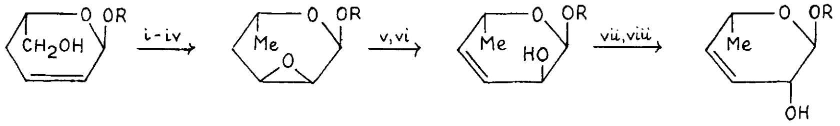
Synthesis of the 3-ene (33) was readily effected from 1,2-O-isopropylidene-3-O-methanesulphonyl-α-D-glucofuranose by periodate oxidation followed by heating in pyridine; it was then used in Wittig reactions to give a series of dienes such as (34).[33] An



(33) X=O

(34) X=$CHCO_2Me$

interesting way of using 4-deoxy-2-enes is illustrated in Scheme 9, and in this manner a series of disaccharides have been prepared

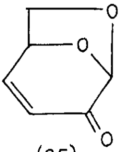


Reagents: i, TsCl-py; ii, NaI; iii, Bu_3SnH; iv, $PhCN-H_2O_2$; v, Me_3SiI-DBU; vi, KF; vii, DCC-DMSO; viii, $LiAlH_4$

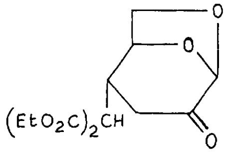
Scheme 9

following hydroxylations of the products,[34] (see Chapter 3). Gentamine C_{1a} has been made from neamine by similar methods involving a 3,4-unsaturated unit.[35]

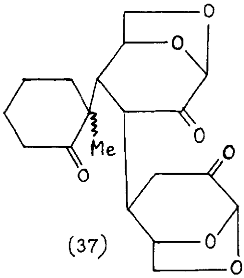
Interesting work continues on the cellulose pyrolysis product levoglucosenone (35), C-4-branched-chain derivatives having been produced by Michael addition reactions. Direct adducts such as (36) were obtained but, in addition, a 2:1 product (37) was



(35)



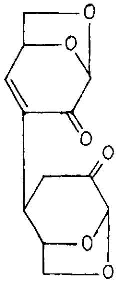
(36)

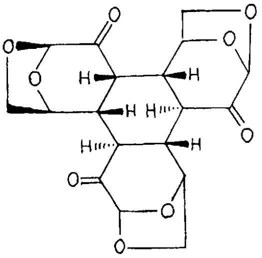


(37)

isolated following reaction with 2-methylcyclohexanone.[36] Self condensation of (35) in aqueous triethylamine gave the dimer (38) and the saturated and unsaturated trimers (39) and (40) in 8, 18 and 56% yield, respectively.[37]

4-Azo-3-enes, e.g., (41), have been obtained from the


(38)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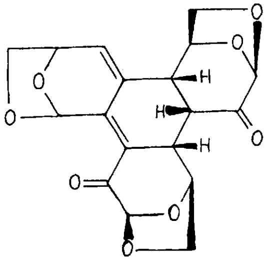
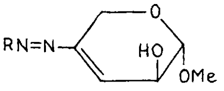
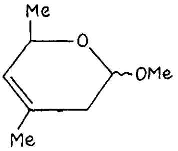
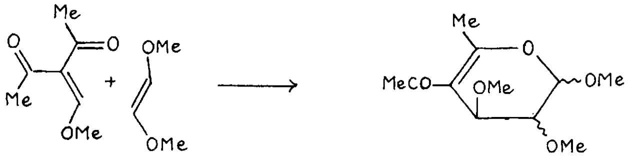

(40)

corresponding 2,3-anhydro-4-uloside.[38] The 3-methyl-glyc-3-enoside (42) has been used in the preparation of a complex branched-chain nitro-sugar (see Chapter 9).[39]


(41) R = Ph or $\underline{p}$-$C_6H_4NO_2$

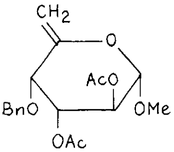

(42) (DL)

The hetero Diels-Alder reaction illustrated in Scheme 10 provides a route to racemic 4,5-unsaturated pyranosides which have potential as precursors of sugar derivatives.[40] Glyc-4-enosides are also referred to in Chapter 18.

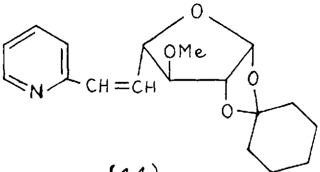

Scheme 10

Reduction of the 5-ene (43) with ${}^1H_2$-${}^3H_2$ (10:1) over palladium-charcoal gives a product which has incorporated 95% of the tritium at the C-6 position. This is because vinyl hydrogen exchange at that centre is faster than the addition process.[41] The 5,6-unsaturated furanoid-heterocyclic compound (44) has been made by a Wittig reaction; related substances were similarly derived from other sugar aldehydes.[42]

In the area of acyclic alkenes, compounds (45) and (46) have both been made in good yield by controlled reduction of 2,3,4,6-tetra-*O*-

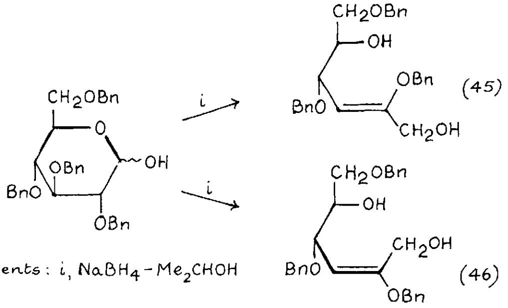


(43)



(44)

benzyl-D-glucose with sodium borohydride in propan-2-ol under different conditions (Scheme 11). Rationalizations for the

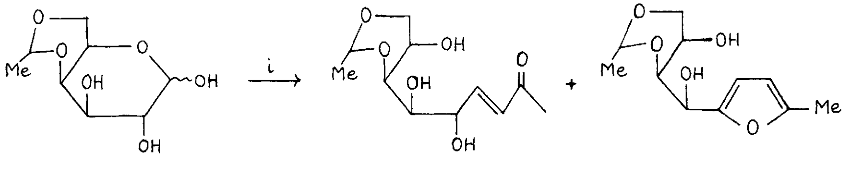


Reagents: i, $NaBH_4-Me_2CHOH$

Scheme 11

results were provided, and the stereochemistries of the products determined by examining spin-lattice relaxation rates as protons in the vicinities of the double bonds were replaced by deuterium. 2,3,5-Tri-O-benzyl-D-arabinose gave the corresponding E-alkene only.[43]

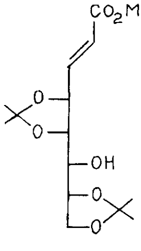
Scheme 12 summarizes the results of a Wittig reaction with 4,6-O-ethylidene-D-galactose; the formation of the unexpected furan was rationalized.[44] In related fashion, 2,3:5,6-di-O-



Reagents: i, $Ph_3P=CHCOMe$

Scheme 12

isopropylidene-D-mannose and 2,3,4,6-tetra-O-benzyl-D-glucose have been converted to the octonic acid derivatives (47)[45] and (48),[46] respectively. Under Wittig conditions the former cyclized partially to give a furanoid C-glycoside (see Chapter 3) and the latter, when made by the Knoevenagel-Doebner conditions, isomerized to give a product with the D-*gluco*-configuration. Compound (48) did not cyclize by Michael-type addition although its 2,3,4,6-tetra-*O*-acetyl analogue existed largely as a mixture of α- and β-*C*-glycosides. Additions to 2,3-*O*-isopropylidene-D-glyceraldehyde have yielded compounds (49) and (50).[47]



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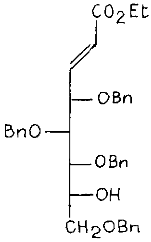

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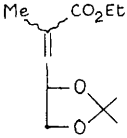

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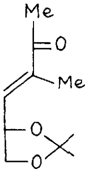

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13

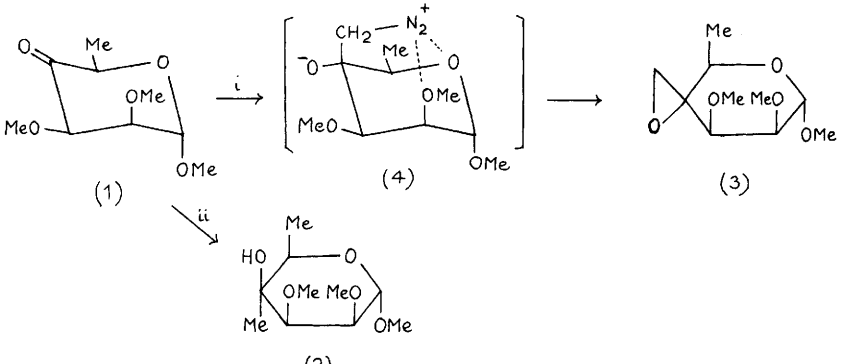
Branched-chain Sugars

Provisional recommendations for naming branched-chain sugars have been published.[1] A review on the chemistry and biochemistry of branched-chain sugars has appeared (in Japanese).[2]

6-Deoxy-3-C-methyl-L-gulose has been identified as the carbohydrate constituent of the antibiotics chrysomycin A and B, linked as a β-pyranose C-glycoside.[3]

1 Compounds with an R^1-C-OR^2 Branch

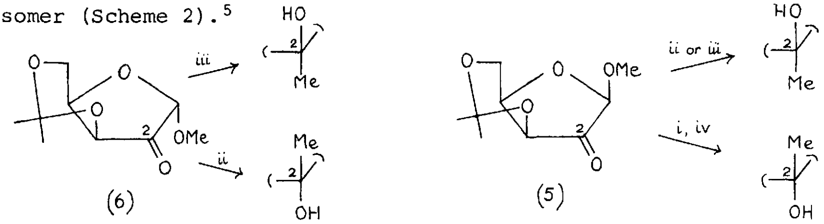
The reactions of methyl 6-deoxy-α-D-hexopyranosid-4-uloses with diazomethane and Grignard reagents have been compared; whereas methyl magnesium iodide favours equatorial attack on the lyxo derivative (1), leading to the talose derivative (2), diazomethane gives predominantly the mannose spiro oxiran (3), axial addition being encouraged by electrostatic attraction between the C-2 axial and ring oxygens and the diazo cation intermediate indicated in (4) (Scheme 1).[4]



Reagents: i, CH_2N_2; ii, MeMgI

Scheme 1

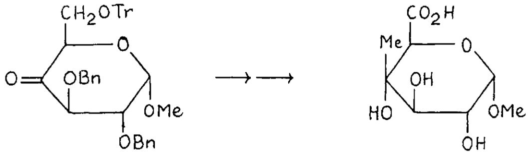
A similar stereochemical dichotomy is seen in the reaction of these reagents with the β-D-threopentofuranosid-2-ulose (5), diazomethane leading to the 2-C-methyl-xylose derivative, whereas methyl magnesium iodide or methyl lithium give the lyxose isomer. By contrast, the α-glycoside (6) leads to the xylose derivative with the Grignard reagent, while methyl lithium still yields the lyxose isomer (Scheme 2).[5]



Reagents: i, CH_2N_2 ; ii, MeMgI ; iii, MeLi ; iv, $LiAlH_4$

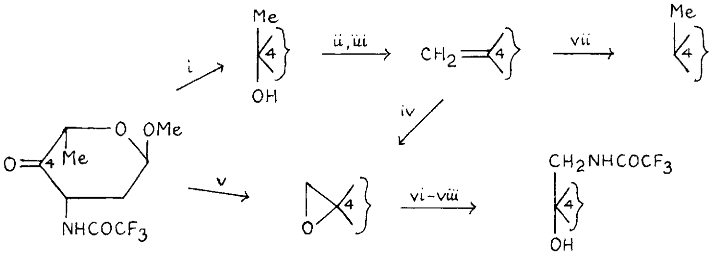
Scheme 2

The 4-ulose (7) derived from glucose reacts stereospecifically with methyl lithium at -78° to give the 4-C-methyl glucose adduct which was used to prepare the moenuronic acid glycoside (8); at the same temperature, methyl magnesium iodide gave the D-galacto-isomer specifically.[6,7]



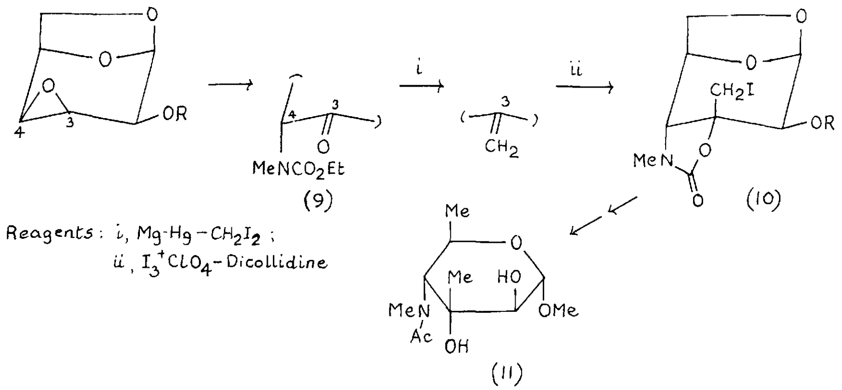
(7) (8)

L-Daunosamine has been used as a source of a 4-ulose derivative which was then used to prepare the C-4 branched-chain analogues indicated in Scheme 3.[8]



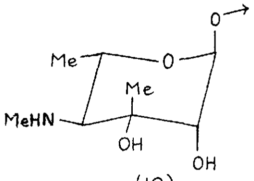
Reagents: i, MeMgI ; ii, $SOCl_2$; $NaHCO_3$; iv, MCPBA ; v, CH_2N_2 ; vi, NaN_3 ; vii, H_2-Pd ; viii, $(CF_3CO)_2O$

Scheme 3



Scheme 4

The 1,6-anhydro-3-keto-amino sugar (9), prepared from 3,4-1,6-dianhydro D-talopyranose, gave the 3-*C*-iodomethyl altrose derivative (10) by the part sequence shown in Scheme 4, which was then converted by standard reactions to the analogue (11).[9] This was thought at the time to be a derivative of the naturally occurring aminosugar sibirosamine, but the latter has now been shown to be the mannose stereoisomer by a synthesis which is mentioned in Chapter 8 (ref. 11) and a further report indicates that the natural form is the L-enantiomer which occurs as the α-glycoside (12) in sibiromycin.[10]

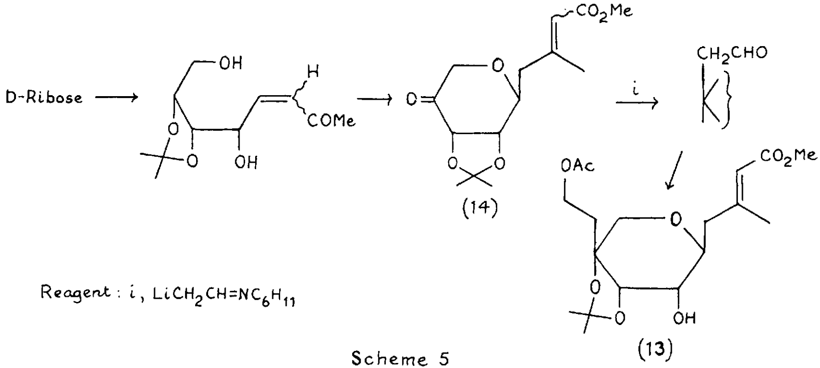


(12)

Scheme 5 outlines an enantioselective synthesis of the key intermediate (13) required for the synthesis of pseudomonic acids; D-ribose was used as source material for the ketose (14) which undergoes aldol condensation with lithiated ethylidene cyclohexylamine.[11]

The 1,5-anhydro-hexen-3-ulose (15) obtained from triacetyl glucal gave an equimolar mixture of *ribo*- and *arabino*-3-*C*-methyl branched-chain derivatives (16) on treatment with methyl lithium.[12]

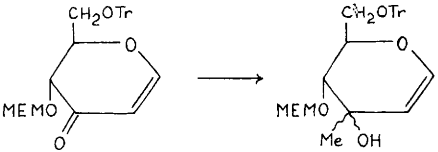
A synthesis of L-streptose from L-arabinose has been described



Reagent : i, $LiCH_2CH{=}NC_6H_{11}$

Scheme 5

which utilizes photochemical reactions to deoxygenate the 5-position (via a 5-iodo intermediate) and to form the required 3-ulose (via a 3-pyruvyl ester intermediate), the branched-chain formyl group being derived from the corresponding 3-C-nitromethyl sugar obtained from the keto-sugar using nitromethane.[13] Further investigation of the products obtained by photochemical addition of furan to 1,2;5,6-di-O-isopiopylidene-D-glucofuranos-3-ulose (see vol. 9, p. 110) has shown that all four of the predicted cis-oxetan adducts are obtained, the major component (55%) being the isomer (17).[14]



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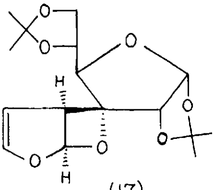

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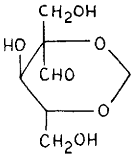
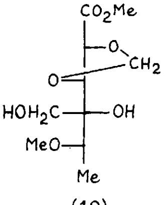


(18)

The formation of a cyanhydrin from a glycosid-3-ulose is mentioned in Chapter 11.

Mannitol has been converted to a mixture of 2-C-hydroxymethyl-DL-ribose and -xylose derivatives by periodate oxidation of its 2,5-O-methylene acetal followed by an intramolecular aldol condensation of the resulting dialdehyde; the ribose enantiomers (18) predominate.[15]

Conventional transformations on 4-C-hydroxymethyl and 4-C-α-hydroxyethyl branched-chain sugar precursors have served to prepare the L-idonate and D-galactonate derivatives (19) and (20) respectively, thereby confirming the structures of 2,3-O-methylene-aldonolactones present in orthosomycin antibiotics.[16] Yoshimura's group have also confirmed the structure of the naturally occurring aldonolactone 2-C-methyl-D-erythrono-1,4-lactone by conventional oxidation of 2-C-methyl-D-erythrose,[17] derived in turn from 3-C-methyl-allose;[18] the latter paper also describes the synthesis of 3-C-methyl-L-threose.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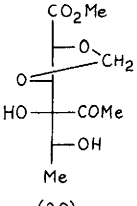
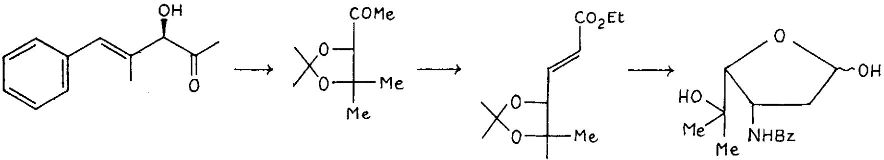
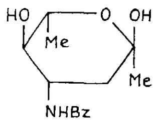

(20)

Asymmetric synthesis using enzymes to produce chiral precursors has been employed to prepare optically pure N-benzoyl-5-C-methyl-L-acosamine (21) by the sequence summarised in Scheme 6. A related strategy was used to prepare the isomeric ketose analogue (22).[19]


(21)

Scheme 6

Branched-chain sugars produced in the formose reaction are referred to in Chapter 2, and their analysis in Chapter 22. The

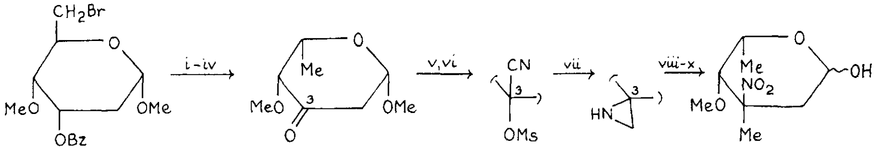


(22)

use of branched-chain sugars as chiral precursors for the synthesis of pheromones is mentioned in Chapter 23.

2 Compounds with an R-C-N Branch

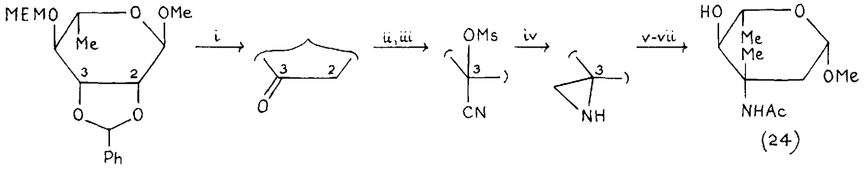
Rubranitrose has been characterized as 2,3,6-trideoxy-3-C-methyl-4-O-methyl-3-nitro-L-xylo-hexose (23) by X-ray crystal analysis of its β-acetate[20] and confirmed as an L-series sugar derivative by a synthesis from 2-deoxy-D-ribo-hexose using the cyanhydrin aziridine chacin-branching procedure outlined in Scheme 7.[21] This procedure has also been further investigated by Brimacombe's group, and applied to a synthesis of the vancosamine 4-epimer (24) from rhamnose (Scheme 8); they also showed that the D-arabino isomer of (24) could be efficiently epimerized at C-4 by an oxidation-reduction sequence.[22] The preparation of methyl DL-tetronitrosides from dihydropyran is covered in Chapter 8.



(23)

Reagents: i, AgF-Py; ii, H$_2$-Pd; iii, MeO$^-$; iv, PCC; v, HCN-Py; vi, MsCl-Py, vii, LAH; viii H$_2$-Ni, ix, MCPBA; x, H$^+$

Scheme 7

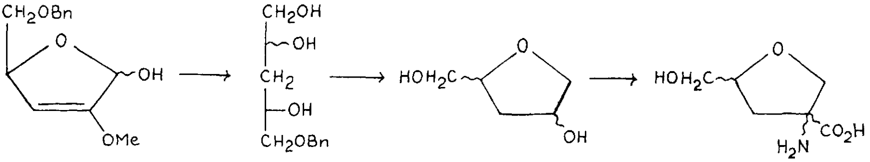


(24)

Reagents: i, BuLi-THF; ii, KCN; iii, MsCl-Py; iv, LAH; v, H$_2$-Ni, vi, Ac$_2$O-Py; vii, H$^+$-MeOH

Scheme 8

All four stereoisomers of 4-amino-(2-hydroxymethyl) tetrahydrofuran 4-carboxylic acid (a 2-*C*-hydroxymethyl pentonic acid derivative) (25) have been synthesized from D-glucose or D-ribose derivatives as outlined in Scheme 9, the *threo*-isomers spontaneously forming δ-lactones; the 2S,4S (D-*erythro*) isomer was then shown to be the one previously detected in an acid hydrolysate of diabetic urine.[23]


(25)

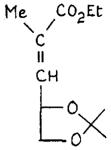
Scheme 9

Branched-chain amino sugars are also covered in Chapter 8.

3 Compounds with an R-C-H Branch

A variety of approaches to deoxy branched-chain sugars have been reported.

Knoevenagel-Doebner condensation of 2,3-O-isopiopylidene-D-glyceraldehyde with monoethyl methylmalonate gave the E/Z isomers of the branched-chain aldonic acid (26); α-methylacetoacetic ester gave either the corresponding unsaturated or saturated branched-chain hexulose derivatives (27) and (28) depending on the conditions.[24] Condensation of pentoses and hexoses with methyl acetoacetate in the presence of Lewis acid gave the acetyl branched-chain products (29) which underwent acid-catalysed cyclization to the corresponding anticipated furan derivatives.[25]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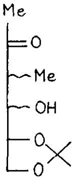
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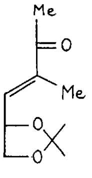
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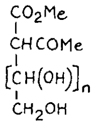
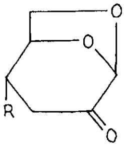
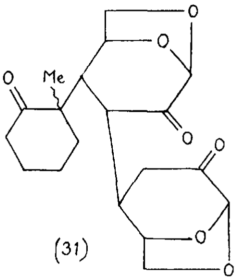

(29)

Michael addition to levoglucosenone with various carbon nucleophiles under base or bis (2,4-pentanedionate)-nickel(II) catalysis gave a series of 4-*C*-alkyl-4-deoxy branched-chain hexosuloses (30); 2-methylcyclohexanone yielded both its 2- and 6- substituted regioisomers, and the dimeric derivative (31) was also isolated.[26] Diacetyl-L-arabinal has been used as a source of the malonic ester derivative (32) in another approach to the synthesis of pseudomonic acids (see ref. 11 above).[27]



R = $CH(CO_2Et)_2$,
$CH(CN)CO_2Et$,
$C(NO_2)Me$

(30)



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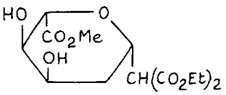

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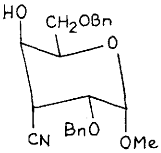

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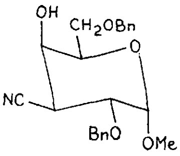

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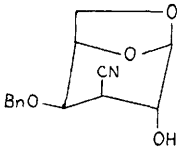
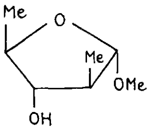


(35)

Cleavage of a 3,4-anhydro-D-galactoside derivative with diethylaluminium cyanide gave the expected 3-*C*-cyano guloside (33) together with the 4-*C*-cyano glucoside regioisomer in a 4:1 ratio; on base-catalysed equilibration, (33) isomerized to the epimeric galactoside (34) with an equatorial cyano group which predictably predominated (6:1). A preferred, more regiospecific route to 3-*C*-cyano galactose derivatives utilized the 1,6-anhydro-3-*C*-cyano-galactose (35) obtained by similar cleavage of 4-*O*-benzyl-1,6;2,3-dianhydro-D-gulopyranose.[28] Treatment of methyl 2,3-anhydro-5-deoxy-D-ribofuranoside with lithium dimethyl cuprate gave the 2-*C*-methyl arabinose and 3-*C*-methyl xylose derivatives (36) and (37) respectively in a 5:1 ratio.[29]



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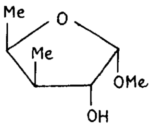

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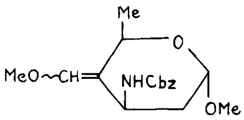

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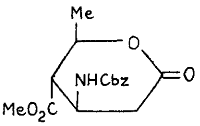
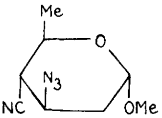


(39)

A Wittig reaction was used to prepare the methoxymethylene branched-chain amino-sugar (38), which was then modified conventionally to the diacid derivative (39) and hence converted to thienamycin (described in Chapter 23).[30] Another synthesis of thienamycin from the same 3-azido-2,3,6-trideoxy-D-arabino-hexoside precursor used for preparing (38) adopted a double inversion technique to make the 4-C-cyano sugar (40), displacing triflate esters first by acetate and then by cyanide (18% overall yield).[31]

Base-catalysed rearrangement of the disulphonyl derivative (41) of glucosamine yielded the 3-C-formyl sugar (42), which adopts a hemi-acetal structure.[32]



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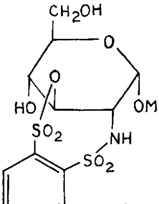

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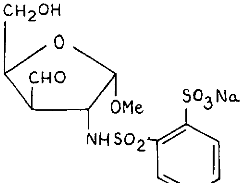
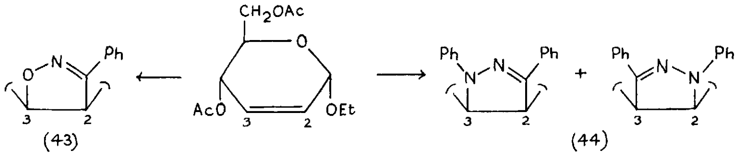


(42)

4 Miscellaneous Branched-Chain Sugars

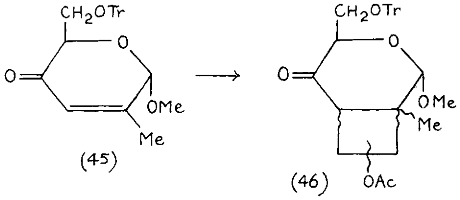
A full paper on the synthesis of gem-di-C-carbon substituted sugars by Michael addition to nitromethylene branched-chain sugar precursors has appeared (see Vol. 12, p. 120).[33]

Fused-ring derivatives have been obtained by dipolar additions to glyc-2-enose derivatives, giving the mannose derivatives (43)[34] and (44)[35] (Scheme 10). Photolysis of the branched-chain glycenosulose (45) with vinyl acetate yielded a mixture of the



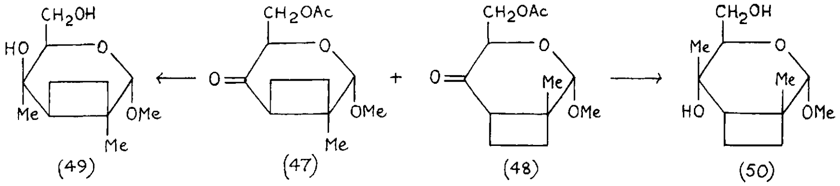
Scheme 10

cyclobutane isomers (46), and the cyclobutane epimers (47) and (48) obtained on irradiation in presence of ethene on further reaction with methyl lithium yielded the poly-branched-chain derivatives (49) and (50).[36] A related glycenosulose underwent

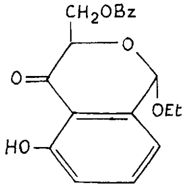


(45) (46)

Diels-Alder addition with the silyl ether of buta-1,3-dien-1-ol in the presence of DDQ to yield the fused-phenol derivative (51), which was further modified by standard reactions.[37] A bicyclo-sugar derivative (52) arises by Dieckmann cyclization of the branched-chain sugar diester (53); in the presence of 18-crown-6, the enolized form of the isomeric β-ketoester (54) is the only product, obtained in low yield (Scheme 11).[38]



(49) (47) (48) (50)



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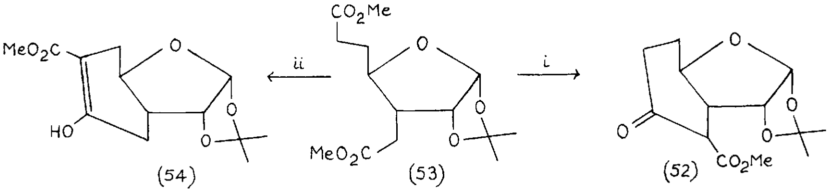
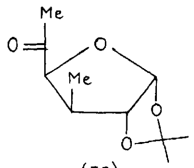


Reagents: i, KOBu^t-C_6H_6; ii, KOBu^t-C_6H_6-18-Crown-6

Scheme 11

A 3-deoxy-3-C-methyl-D-glucose derivative has been used to prepare the 5-ulose (55) by conventional steps, and this was then transformed to 3,5-dideoxy-3,5-di-C-methyl-L-idose derivatives (56) and (57) via Wittig reaction with methylene triphenylphosphorane.[39]



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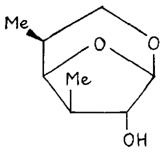

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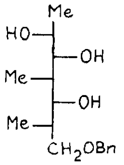

(57)

Tertiary hydroxy groups adjacent to formyl groups in branched-chain sugars can be replaced by hydrogen through free-radical deoxygenation of the benzoate, or preferably the 4-cyanobenzoate, ester with tributyl tin hydride.[40]

The use of 3-deoxy-3-C-methyl altrose in a pheromone synthesis is referred to in Chapter 23.

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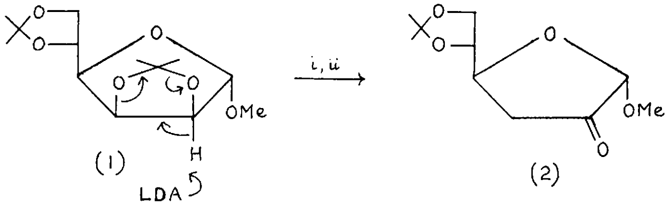
14

Dicarbonyl Compounds and Their Derivatives

The use of pyridinium chlorochromate as a reagent for the oxidation of alcohols to aldehydes and ketones (including carbohydrate ketones) has been reviewed,[1] and a review in Japanese on nucleophilic additions to carbohydrate-derived ketones has been published.[2] A review on enones is referred to in Chapter 12, which also contains several references to unsaturated derivatives of compounds based on dicarbonyl sugars.

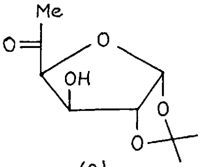
A quantitative synthesis of D-gluco-hexodialdose from D-glucuronic acid involves diethylborane reduction of α-D-glucofuranuronic acid 1,2:3,5 bis-ethylboronate.[3]

On treatment with lithium di-isopropylamide the α-D-mannofuranoside (1) gave the 2-ulose compound (2) (Scheme 1), and the 5-ketone (3) was obtained similarly from 1,2-O-isopropylidene-3,5,6-O-methylidyne-α-D-glucofuranose.[4] Oxidation of methyl 3-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside with DMSO-acetic anhydride gave the 2-ketone (4) which, on continued exposure to the reagents, was converted to the enediol ester (5). This underwent a novel photochemical conversion to the 3-ketone (6) (Scheme 2)[5]



Reagents: i, $LiNPr^i_2$; ii, H_2O

Scheme 1



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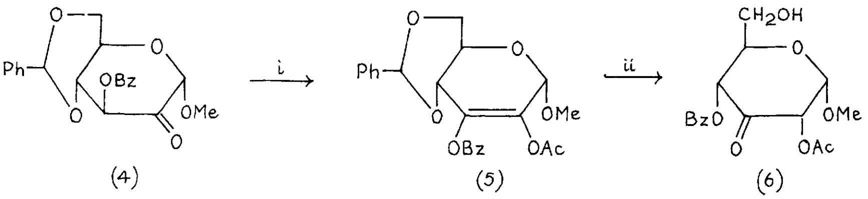
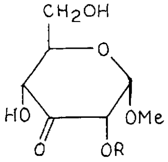


Reagents: i, DMSO-Ac_2O ; ii, hν

Scheme 2

(See Chapter 12 for possible route). ^{13}C Spectra of 2- and 3-keto derivatives of some disaccharides are referred to in Chapter 20.

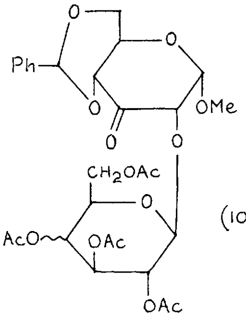
References to the use of 3- and 4-ulosides in the synthesis of deoxy- and branched-chain sugars are made in Chapters 11 and 13, respectively. Compounds (7)-(9) deactivate a bacteriophage, probably by generation of superoxide radicals[6] which cause the ketones to undergo autoxidation. Sodium borohydride reduction of the disaccharide ketones (10) gives mainly D-allo-products with about 4:1 selectivity.[7]



(7) R = Bz

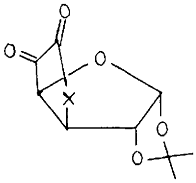
(8) R = Ts

(9) R = Bn



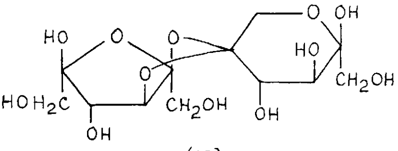
(10)

A new paper on 4'-methoxyadenosine is referred to in Chapter 19; such compounds are formally derivatives of D-erythro-pentos-4-ulose. Oxidation of 1,2-O-isopropylidene-α-D-glucofuranose and the 3-acetamido-3-deoxy analogue with pyridinium dichromate gave compounds



(11) X = O

(12) X = NAc



(13)

(11) and (12) respectively; in the former case, some selective reaction occurred at C-6.[8]

D-threo-2,5-Hexodiulose exists in the crystal as the dimer (13) and the similarity of its ^{13}C spectra in the solid and in DMSO indicates that this form persists in this solvent also.[9]

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15

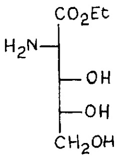
Sugar Acids and Lactones

1 Aldonic Acids

^{1}H And ^{13}C n.m.r. methods have been used to determine the preferred conformations of the four D-pentono-1,4 lactones[1] and D-glucono-, D-mannono-, D-gulono- and D-galactono-1,4-lactone.[2] The kinetics of hydrolysis of D-glucono-1,4-lactone have been examined in detail,[3] and calcium D-arabinonate has been shown to epimerize to a mixture containing 80% of the D-ribo-isomer at 137°C in the presence of calcium hydroxide.[4]

Two reports have appeared on the kinetics of oxidation of D-glucose to D-gluconic acid by immobilized D-glucose oxidase and catalase,[5,6] and a non-specific photochemical oxidation by hydroxyl radicals produced from hydrogen peroxide has been studied.[7] A further kinetic examination was concerned with the degradation of D-fructose to D-arabinonic acid by use of chloramine-T.[8]

References to the use of sugar aldehydes in chain-extending syntheses of unsaturated acids are given in Chapter 12. 2,3-O-Isopropylidene-D-glyceraldehyde continues to find use in this context, being employed for the synthesis of the amino-aldonic acid derivatives (1) and (2), prepared via ethyl isocyanoacetate and oxazoline intermediates; (analogous results were obtained with 2,3-O-isopropylidene-D-erythrose).[9] Various C-2 branched-chain acids, e.g., (3), result from using β-dicarbonyl compounds,[10] and the 2,2-dichloropentonic acid derivatives (4) are formed by use of methyl dichloroacetate magnesium enolate. The last products provide suitable means of preparing 2-halogenated pentonolactones.[11]



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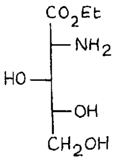

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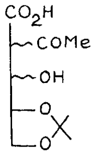

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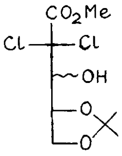
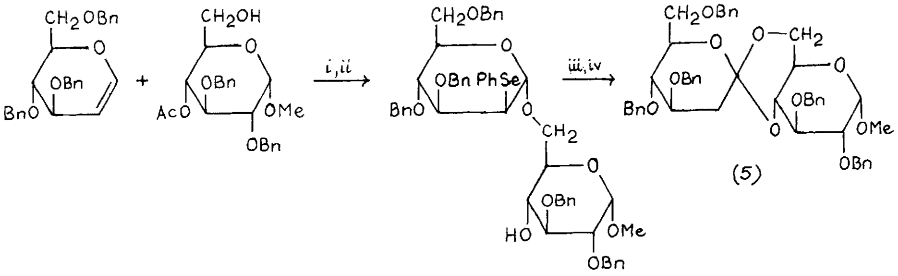


(4)

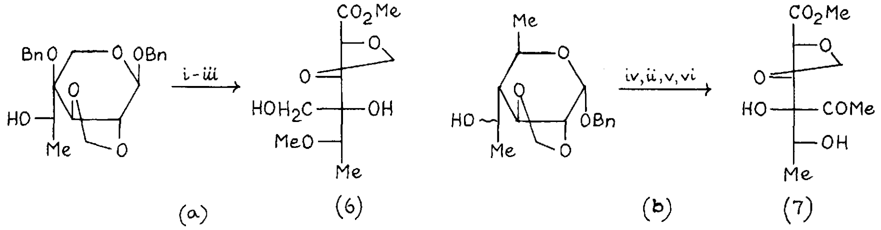
The direct conversion of tri-O-acetyl-D-glucal into the 2,3-unsaturated 1,5-lactone diacetate is reported in Chapter 12 and its use in the synthesis of the disaccharide lactone acetal (5) is outlined in Scheme 1. The key step was glycosyloxyselenation which was followed by oxidative elimination via the selenoxide and a spontaneous interunit cycloaddition process.[12] A general route to lactone acetals related to (5) involves the use of 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone with trimethylsilylated alcohols or diols and catalytic trimethylsilyl triflate.[13]



Reagents: i, glycosyloxyselenation; ii, MeO^-; iii, $NaIO_4$; iv, Δ-Pr^i_2NH

Scheme 1

Branched-chain aldonic acids have received attention (see also saccharinic acids). The synthesis of the L-idonate and D-galactonate derivatives (6) and (7) as shown in Schemes 2 and 2b served to confirm the structures of the branched-chain 2,3-O-methylene-aldonolactones present in everninomicin B and C and in flambamycin and avilamycin A, respectively.[14] Further work in this area by Yoshimura's group is noted in Chapter 13.



Reagents: i, MeI-NaH-DMF; ii, H_2-Pd; iii, Br_2-MeOH; iv, NCS-Me_2S; v, Br_2-H_2O-$BaCO_3$; vi, MeOH-H^+

Scheme 2

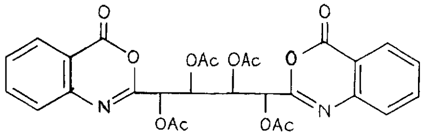
Work from Pedersen's laboratory on the treatment of pentonic acid salts with hydrogen bromide in acetic acid and reactions of the dibromo products is referred to in Chapter 7, and reference to 6-amino-6-deoxyheptonic acids is made in Chapter 8.

2 Aldaric Acids

^{1}H And ^{13}C n.m.r. have been used to determine the preferred solution conformations of D-glucaric acid, its 1,4- and 6,3-lactones and its 1,4:6,3-dilactone, and to monitor its lactonization in water.[15]

Cestric acid, isolated from *Cestrum evanthes* is an equilibrated mixture of the four positional isomers of *O*-caffeylglucaric acid,[16] and L-idaro-1,4-lactone is an inhibitor of α-L-idosiduronase.[17]

Galactaric acid chloride tetra-acetate, condensed with anthranilic acid followed by dehydration, gave the oxazinone (8),[18]



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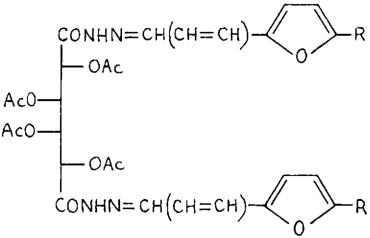
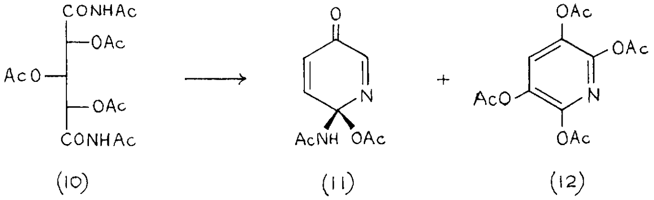


(9)

and with hydrazine it gave the dihydrazide which, with appropriate aldehydes afforded the series of compounds (9).[19] Treatment of the xylaric acid (10) (or the *ribo*-isomer) with sodium acetate in acetic anhydride gave the heterocyclic compounds (11) and (12) (Scheme 3).[20]



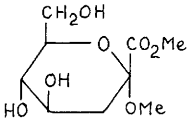
Scheme 3

3 Saccharinic Acids

The identity of the first naturally occurring saccharinic acid lactone to be detected (de Pascual Teresa *et al.*, *Tetrahedron Lett.*, 1980, **21**, 1359) has been confirmed as 2-*C*-methyl-D-*erythrono*-1,4-lactone by synthesis from 1,2-*O*-isopropylidene-3-*C*-methyl-D-allofuranose.[21]

4 Ulosonic Acids

Methyl (methyl 3-deoxy-α-D-*arabino*-2-heptulopyranosid)onate (13) has been synthesized from the free aldulosonic acid and characterized by X-ray diffraction analysis.[22] The acid-catalysed reactions of methyl 3-deoxy-β-D-*erythro*-2-hexulopyranosidonic acids carrying



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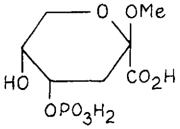
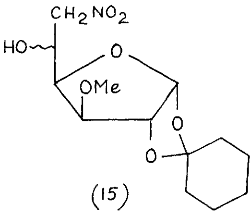


(14)

a phosphate and a β-D-glucopyranosyl substituent at *O*-4 have been closely examined; at pH 3-6 phosphate is released from the former (14) faster than at pH 0-1 and by an elimination procedure.[23]

Oxidation of the nitro-compound (15) with potassium permanganate in water-benzene in the presence of a phase transfer catalyst gave the ulosonic acid derivative (16), and analogous compounds having



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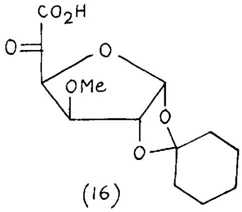
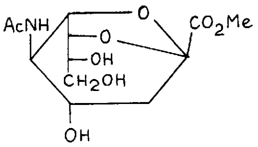


(16)

tertiary hydroxyl groups were converted into the corresponding hydroxyacids.[24] Chromium trioxide oxidation of acetylated 3-amino-3,6-dideoxy-L-hexopyranosides proceeds only with compounds having equatorial aglycones; the α-L-*gluco*-isomer is thus resistant, but the β-L-*gluco*- and α-L-*talo*-compounds are oxidized to the corresponding 5-aldulosonates[25] (S.J. Angyal and K. James, *Aust. J. Chem.*, 1970, *23*, 1209).

The synthesis of 3-deoxy-D-*manno*-octulosonic acid-1-^{14}C of high specific activity has been effected from 2-deoxy-D-*manno*-heptose by use of labelled potassium cyanide,[26] and $^{3}J_{C-1,H-3a}$ values of *ca* 5 Hz have been used to establish the β-anomeric configuration of the acid glycosidically bonded in polysaccharides and model compounds.[27]

An updating review has been published on the chemistry, metabolism and biological function of the sialic acids.[28] Methanolysis of N-acetylneuraminic acid gives, in addition to the methyl ester methyl β-glycoside, about 15% of the 2,7-anhydride (17), and the related compound (18) was obtained on methanolysis of a carboxyl-reduced meningococcal polysaccharide.[29] The synthesis of a courmarin glycoside of N-acetylneuraminic acid is reported in Chapter 3. In the course of this work a glycal-like byproduct formed by elimination of hydrogen chloride from a glycosyl chloride was described; further reference is made to such compounds in Chapter 12. Various specific silyl ethers of the methyl ester methyl glycoside of N-acetylneuraminic acid are reported in Chapter 4, and some consequently produced azido-derivatives are referred to in Chapter 9.



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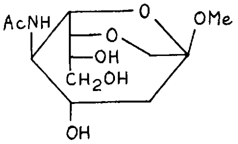

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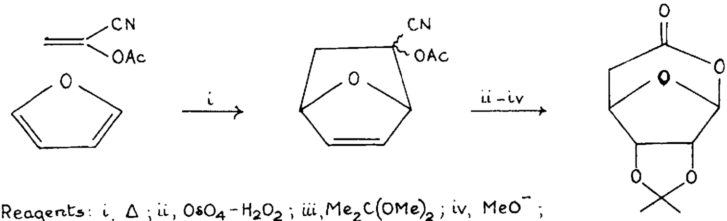
5 Uronic Acids

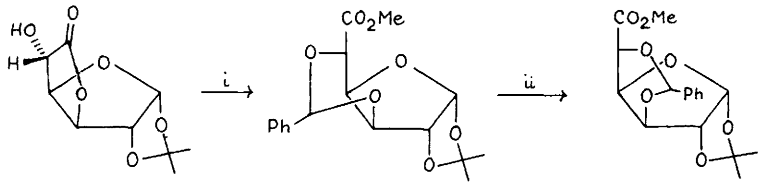
Considerable work continues in this area, Scheme 4 outlining a synthesis of racemic 5-deoxyhexuronic acid derivatives.[30]



Reagents: i, Δ; ii, OsO_4-H_2O_2; iii, $Me_2C(OMe)_2$; iv, MeO^-; v, MCPBA

Scheme 4

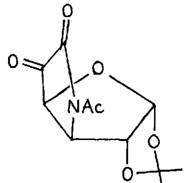
A specific epimerization of a D-glucuronic acid compound gives simple access to L-iduronic acid (Scheme 5).[31]



Reagents: i, $PhCH(OMe)_2$; ii, MeO^-

Scheme 5

The lactam (19) was synthesized directly from compound (20) by pyridinium dichromate oxidation in DMF. Similar reaction of 1,2-O-isopropylidene-α-D-glucofuranose gave the corresponding ulosonic



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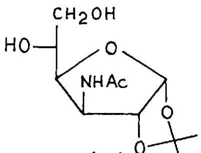

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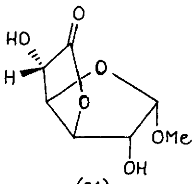
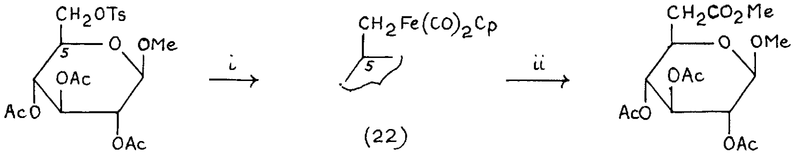


(21)

acid lactone (with degradation) together with 1,2-O-isopropylidene-D-glucofuranurono-6,3-lactone.[32] Fenton's reagent (H_2O_2, ^-OH, Fe^{2+}) reacts slowly with methyl α-D-glucopyranoside to give the corresponding uronic acid derivative which, on dehydration under mild conditions (acidic resin, concentration of solution), underwent ring contraction to give mainly the furanoid lactone (21) which hydrolysed spontaneously to give D-glucofuranurono-6,3-lactone. Methyl α-D-mannopyranoside behaved in analogous fashion.[33]

A carbonyl-insertion reaction of the dicarbonylcyclopentadienyliron compound (22) provides a route to 6-deoxyhepturonic acid derivatives (Scheme 6).[34]



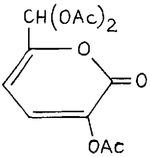
(22)

Reagents: i, $NaFe(CO)_2Cp$; ii, Br_2-MeOH

Scheme 6

Specific syntheses of all the possible mono-,[35] di- and tri-methyl ethers of methyl (methyl α-D-galactopyranosid)uronate[36] have been reported. Preparation of 2-amino-2-deoxy- and 4-C-methyl-derivatives of D-glucofuranurono-6,3-lactone are noted in Chapters 8 and 13, respectively.

Treatment of D-glucuronolactone triacetate or the D-*manno*-isomer with potassium acetate in acetic anhydride at 60°C in the presence of 18-Crown-16 gave 60% of the pyranose (23) which, with acetic anhydride and triethylamine, is reported to afford the acyclic dienoic acid derivative (24) although this implies a hydrolytic step.[37]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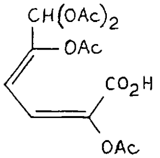
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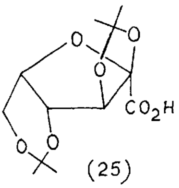

(25)

6 Ascorbic Acids

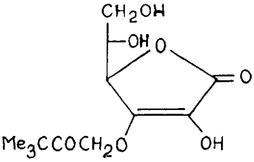
An important *Adv. Chem. Ser.* issue covers many aspects of ascorbic acid chemistry and biochemistry including synthesis,[38] derivatives,[39,40] derived radicals,[41] and dehydroascorbic acid.[42] A separate review deals with products of reaction with polyphosphoric acid.[43]

A further study of the oxidation with oxygen on platinum of 2,3:4,6-di-*O*-isopropylidene-L-sorbose to the L-ascorbic acid precursor (25) (Reichstein route) has been reported.[44]

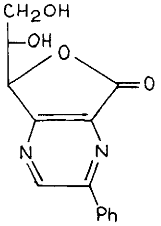
Additional papers on the oxidation of L-ascorbic acid have appeared as follows: with the peroxodisulphate ion ($S_2O_8^{2-}$) catalysed by copper(II),[45] with mercury(II) acetate in aqueous acetic acid,[46] with cobalt and ruthenium complexes,[47] and with a series of transition metal ions.[48] Metal complexes are involved in most of the above reactions, and in the photochemical reaction with mercury(II) salts a paramagnetic intermediate believed to be the ion pair involving the ascorbate radical ion and Hg^{2+} is involved.[49]

The reaction of 1,1-dibromopinacolone ($Me_3CCOCHBr_2$) with excess of L-ascorbic acid in aqueous propan-2-ol containing sodium hydrogencarbonate resulted in the formation of the ether (26) rather than the expected 2,3-*O*-acetal. Evidently either the dibromide is partially debrominated by the reducing action of the acid and the product acts as an alkylating agent or these two steps are reversed.[50]

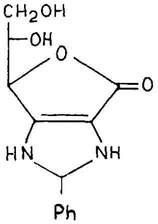
L-Ascorbic acids specifically deuterated at C-6,6′ and at C-1,1′,3,4,5 were prepared from 2,3-*O*-isopropylidene-α-L-sorbofuranose and methyl α-L-sorbopyranoside labelled at these positions by exchange with boiling deuterium oxide in the presence of deuterated Raney nickel.[51]



(26)



(27)



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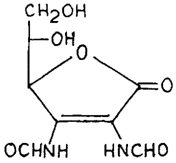

(29)

The derivatives (27)-(29) of 2,3-amino-2,3-dideoxy-L-ascorbic acid have been reported together with their mass spectra.[52] Related nitrogen-containing compounds derived from dehydroascorbic acid are noted in Chapter 9.

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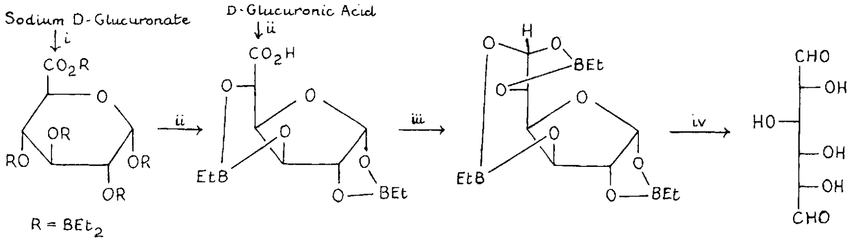
16

Inorganic Derivatives

1 Boron Derivatives

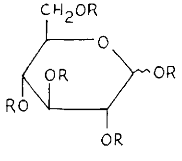
A one-pot procedure for the quantitative conversion of sodium D-glucuronate or D-glucuronic acid to D-gluco-hexodialdose using ethyl boron derivatives is outlined in scheme 1.[1]



Reagents: i, $Et_2BCl-Et_3B$; ii, $EtB(OH)_2-(EtBO)_3$; iii, $Et_2BH-(EtBO)_3$; iv, $MeOH-(CH_2OH)_2$

Scheme 1

A new O-silylation method uses diethylboryl ethers and esters prepared from the sugar with triethylborane; the boryl ether derivatives react with the trimethylsilyl enolate of pentane-2,4-dione to give the corresponding trimethylsilylated sugar, e.g., (1)→(2).[2] An account of ethylboron assisted transformations in carbohydrate chemistry includes protective and directive effects of ethylboranediyl groups in glycosidation procedures.[3]



(1) $R = BEt_2$

(2) $R = SiMe_3$

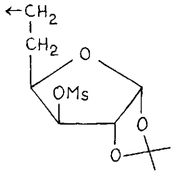
(3) BR_3

(4) $RB(C_6H_{11})_2$

(5) RBr

(6) RI

R =



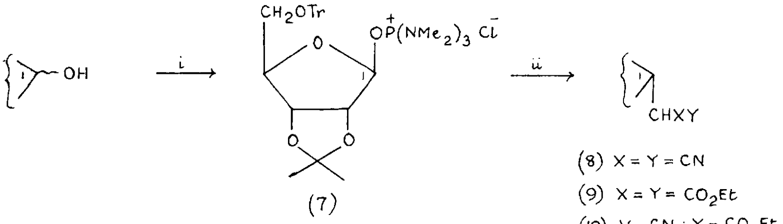
The carbohydrate boranes (3) and (4) have been prepared from the corresponding hex-5-enose derivatives, and used to prepare 5-bromo- and 5-iodo-5,6-dideoxy analogues (5) and (6) respectively.[4]

The chelation of phenylboronic acid with the pentitols and D-mannitol has been studied potentiometrically; only 1:1 chelates were detected.[5]

2 Phosphorus Derivatives

Phosphate Esters are mentioned in chapter 6.

C-Nucleosides have been synthesized from D-ribose by activating the anomeric group via the alkoxytris(dimethylamino) phosphonium salt (7), and condensing this with enolate anions to give corresponding α-C-glycosides (8)-(10), which serve as nucleoside precursors (Scheme 2).[6]



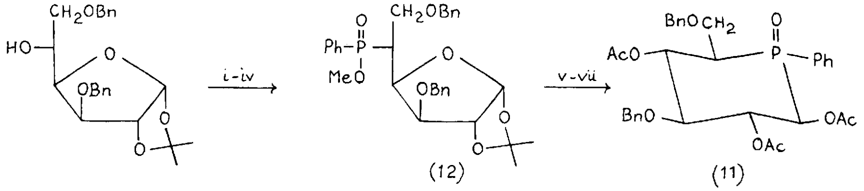
Reagents: i, CCl_4- $P(NMe_2)_3$; ii, NaCHXY

Scheme 2

S-Diethylisopropoxyphosphine-gold 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside has been prepared by a novel alkoxy-interchange reaction.[7]

Phosphono analogues of α- and β-D-glucose 1-phosphate, in which the anomeric oxygen is replaced by methylene, have been synthesized from corresponding bromomethyl C-glycosides using triethylphosphite.[8,9]

The first D-glucopyranose derivative with phosphorus in the ring, compound (11), has been prepared via the 5-C-phosphinyl sugar (12) which was formed by addition of methyl phenylphosphonate to a hydrazone intermediate (Scheme 3). The configuration at phosphorus, carbon-1 and carbon-5 was assigned from the $^2J_{PH}$ coupling constants calculated from the ^1H n.m.r. spectrum of (11), since model compounds showed a relationship between $^2J_{PH}$ values and the O=P-C-H dihedral angle.[10] The same group has also prepared the unsubstituted 5-deoxy-5-C-ethylphosphinyl-D-glucopyranose,[11] and analogous ring phosphinyl derivatives of 6-deoxy-L-ido- and -D-gluco-pyranose,[12,13] and of pentofuranoses,[14] some of

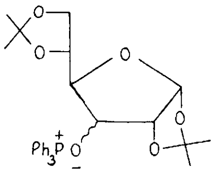


Reagents: i, PCC-mol.sieve; ii, TsNHNH$_2$; PhP(O)(OMe)$_2$-CF$_3$SO$_3$H; iv, NaBH$_4$; v, (MeOCH$_2$CH$_2$O)$_2$AlH$_2$; vi, H$_3$O$^+$; vii, Ac$_2$O-Py

Scheme 3

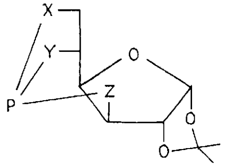
which were characterized by X-ray crystal structure analysis.[12,15] Other C-phosphinyl sugar derivatives have been prepared by displacement of sulphonyloxy or chloro groups with phosphines and sodium dihydrobis(2-methoxyethoxy) aluminate.[16]

Ionic 3-O-phosphonium derivatives (13) of D-glucose and D-allose have been obtained by reaction of the corresponding 3-hydroxy sugars with appropriate phosphorus reagents in presence of DEAD-TPP; the phosphorus-oxy group in these compounds underwent conventional S_N2 displacement with halide and azide ions, the glucose isomer also giving rearranged products.[17]



(13)

X = I, Br,

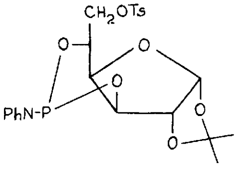


(14) X = S, Y = Z = O

(15) Y = S, X = Z = O

(16) Z = S, X = Y = O

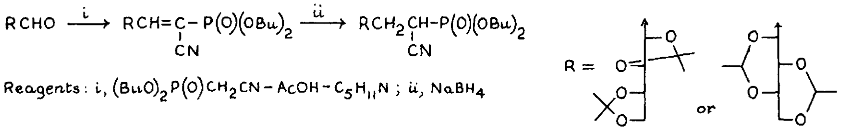
(17) X = NPh, Y = Z = O



(18)

The synthesis and reactions of novel sugar bicyclo-thiophosphites (14)-(16) have been reported.[18] The bicyclophosphoramidite (17) has been obtained by cyclization of the corresponding 6-substituted D-glucofuranose 3,5-cyclophosphoramidite (18).[19] 1,2-Cyclophosphoramidites of 3,5,6-tri-O-methyl-D-glucofuranose and 3,5-di-O-methyl-D-xylofuranose have been prepared conventionally; the former yielded a mixture of exo and endo isomers, whereas the latter only formed an exo product.[20]

Condensation of aldehydo-pentose derivatives with cyanomethylphosphonate esters in a Knoevenagel type reaction led to the corresponding unsaturated and hence the saturated sugar phosphonic acids as outlined in Scheme 4.[21]

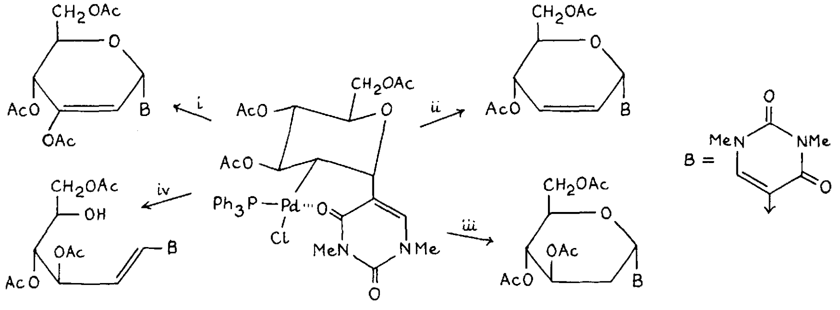


Reagents: i, $(BuO)_2P(O)CH_2CN-AcOH-C_5H_{11}N$; ii, $NaBH_4$

Scheme 4

3 Metal Derivatives

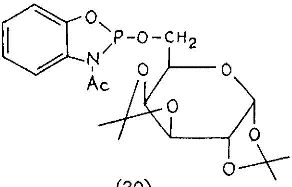
C-Nucleosides have been synthesized from 3,4,6-tri-O-acetyl-D-glucal using N,N-dimethyluracil-5-yl mercuriacetate in presence of a palladium complex to give the palladium derivative (19), which could be used to prepare a range of C-nucleosides, each in high yield, as indicated in Scheme 5.[22] The galactose 6-phosphoramidite (20) forms a complex with π-allyl palladium chloride which is a highly active catalyst for the hydrogenation of alkenes, being more stable than previously investigated catalysts of this type.[23] Methoxymercuration of the appropriate exocyclic unsaturated sugars with 0.5 molar equivalents of mercury(II) acetate gave the epimeric bis(heptulosid-1-yl)mercury derivatives (21) and (22).[24]



(19)

Reagents: i, Δ(PhMe) ; ii, HCO_3^- ; iii, H_2 ; iv, H_3O^+

Scheme 5



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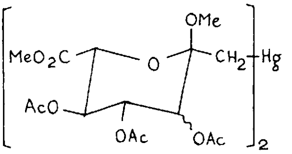
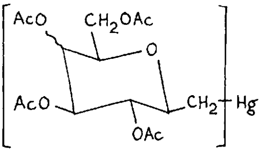


(21)



(22)

4 Metal Chelates

The chelation of metal ions (Cu^{2+}, Zn^{2+}, Co^{2+}) with Schiff's bases prepared from 2-amino-2-deoxy-D-glucose derivatives and aromatic aldehydes has been investigated using standard spectroscopic and magnetic moment measurements.[25] N.m.r. measurements, including ^{119}Sn data, on methyl α-L-rhamnopyranoside in the presence of tin(II)chloride indicate that the latter forms a 2,3-cyclic complex by comparison with results using the 2-, 3-, and 4-O-monomethyl derivatives of the glycoside, the first two of which fail to form a complex.[26] The complexing of various metal ions with methyl α- and β-D-ribo- and α-D-lyxo-furanoside has been studied by calorimetry. While Ca^{2+}, Sr^{2+}, and Ba^{2+} form 1:1 complexes, Cu^{2+} and Mg^{2+} revealed little interaction, whereas Pb^{2+} appears to interact with two sugar ligands. The lyxofuranoside complexed most strongly with yttrium(III) and lanthanum(III) ions.[27] The binding of the paramagnetic ions Gd^{3+} and Mn^{2+} to N-acetyl-2-O-methyl-α-neuraminic acid and its methyl ester has been studied; in both cases, binding involved the glyceryl side chain and the acetamido group, and in addition the free acid complexes at the carboxyl group.[28] The complex formed between fructose or sorbose and ferric ion has been shown to be polymeric both in aqueous solution and in the solid by Mossbauer spectroscopy and molecular weight studies.[29]

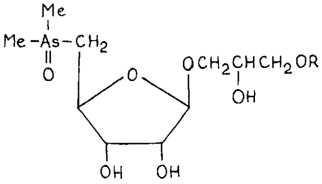
Magnesium alkoxides prepared from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose and 1,6-dideoxy-3,4-O-isopropylidene-2,5-di-C-methyl-L-*threo*-hexitol have been reported to form chiral complexes with Grignard reagents, leading to enantioselective Grignard reactions. The stereochemical results of such reactions were discussed.[30]

5 Miscellaneous Derivatives

Calcium glucoheptonate has been labelled with technecium (using Na $^{99}TcO_4$) to provide a useful brain-scanning agent.[31]

The formation and properties of sugar arsenate esters, particularly D-glucose 6-arsenate and 6-O-arsenyl-D-gluconate, have been investigated, since such esters are good analogues for phosphate esters in reactions with enzymes. The spontaneous formation of the arsenate esters occurred ~10^5 times more rapidly than for the corresponding phosphate; the mono-anion was more reactive than the di-anion, like mono-alkyl phosphates, but unlike glucose 6-phosphate.[32]

The dimethylarsinyl derivatives (23) of ribose have been isolated from the kidney of the giant clam, Tridacna maxima, the sulphate being identified by X-ray crystal structure analysis.[33]



(23) R = H or SO_3H

Chapter 4 includes references to the regioselective alkylation of sugars via trialkylstannylation (ref. 10) and copper(II) chelates (ref. 9), and the use of dicarbonylcyclopentadienyl-iron derivatives for the synthesis of uronic acids is covered in Chapter 15 (ref. 34).

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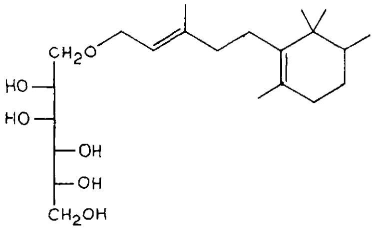
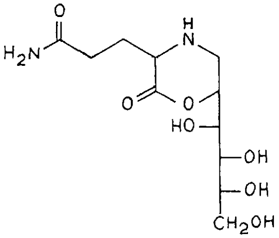
17
Alditols and cyclitols

1 Alditols

D-Glucitol has been found primarily in the endosperm of maize seeds.[1] Chalmicrin (1), a methylated monocyclofarnesyl ether of D-mannitol, has been isolated from the fungus Chalara microspora.[2] Agropine, a crown-gall tumour product, has been shown to have structure (2) rather than that reported previously (Vol.14, p.71), by its synthesis from D-mannose involving reductive amination with L-glutamine ($NaBH_3CN$-H^+-resin) and lactonization [$(CF_3CO)_2O$].[3] Further 1-C-aryl-D-glucitol derivatives such as (3), described as C-glucosidic ellagitannins, have been isolated from plant sources.[4]



(1)



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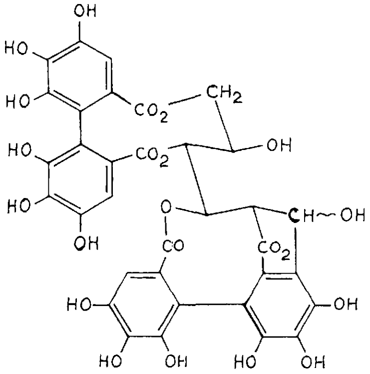

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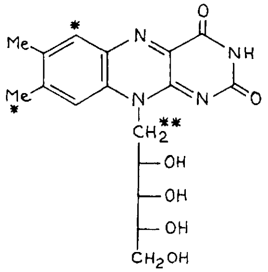
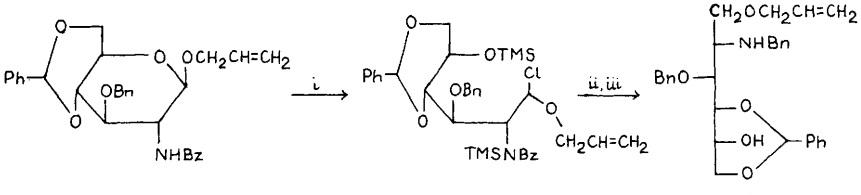


(4)

Biosynthesis of riboflavin (4) using D-[1-^{13}C]ribose revealed labels mainly as indicated.[5]

The effect of pressure on the hydrogenation of glucose in 80% aqueous isopropanol over Raney nickel has been investigated,[6] while the reaction kinetics of a three-phase slurry, catalytic hydrogenation of glucose have been reported.[7] In connection with the recovery of xylitol as a byproduct in the manufacture of D-glucitol, the solubility parameters of these alditols in aqueous ethanol have been determined, and a procedure for recovering xylitol given.[8] Factors effecting the diastereoselectivity of ketose hydrogenations with supported copper and nickel catalysts have been investigated. With D-fructose, the selectivity of copper catalysts for D-mannitol production was enhanced by halide ions, while sulphate doping of nickel catalysts gave a high selectivity for D-glucitol production.[9]

Cello-oligosaccharide derivatives with a ^{3}H-label have been obtained by partial hydrolysis of cellulose, borotritide reduction, and chromatographic isolation of individual products.[10] 2-Benzylamino-2-deoxy-D-glucitols (e.g., 5) were obtained in high yield by opening of the pyranoside ring of 2-benzamido-2-deoxy-D-glucopyranosides (e.g., 6) with trimethylsilyl chloride at reflux temperatures, and reduction of the intermediate chloro-ether (7) with concomitant reduction of the tertiary amide at C-2 (Scheme 1).[11]

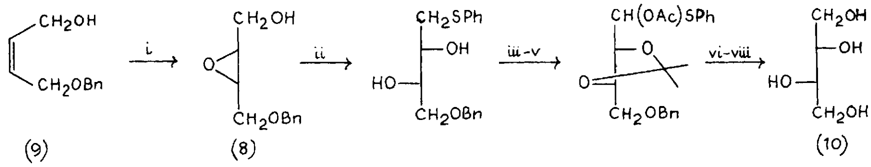


(6) (7) (5)

Reagents: i, TMSCl-NaH-THF ; ii, LiAlH$_4$; iii, H$_2$O

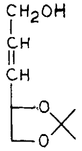
Scheme 1

Sharpless has extended his (+) or (-)dialkyltartrate mediated asymmetric epoxidation procedure to synthesize alditols. Thus epoxide (8), obtained in high enantiomeric excess from the Z-enitol (9), was subjected to a specific epoxide opening reaction to provide threitol (10) (Scheme 2). Erythritol was similarly synthesized from the E-isomer of (9), while all the possible D-pentitols and -hexitols were obtained from the E- and Z-isomers of (11) and (12) respectively.[12] Kishi et. al., synthesized D-pentitols, 2-deoxy-D-pentitols, and 2-amino-2-deoxy-D-pentitols by the same asymmetric



Reagents: i, $Ti(OPr^i)_4$-Bu^tO_2H-(−)-diethyl tartrate; ii, NaOH-PhSH; iii, Me_2CO-H^+; iv, MCPBA, v, Ac_2O-NaOAc; vi, $LiAlH_4$; vii, H^+; viii, H_2-Pd/C

Scheme 2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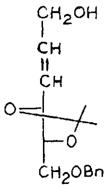
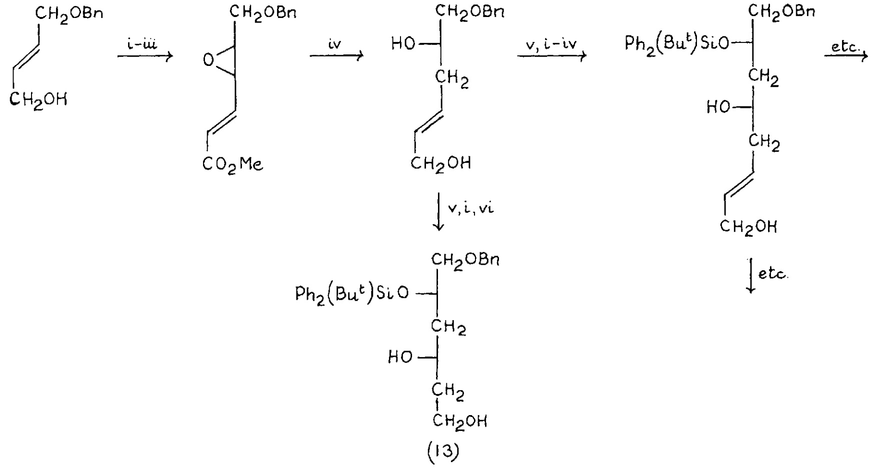

(12)

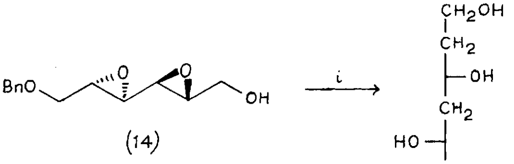
epoxidation of the allylic alcohols (11), followed by specific opening of the epoxide ring at *C*-2 through the use of *O*-1 benzylcarbonates, REDAL [$NaAlH_2(OCH_2CH_2OMe)_2$] reduction, and *O*-1 benzylurethanes respectively.[13] Nicolaou and Uenishi have coupled the Sharpless asymmetric epoxidation procedure with regioselective REDAL



Reagents: i, $Ti(OPr^i)_4$-Bu^tO_2H-(−)-diethyl tartrate; ii, DMSO-$(COCl)_2$; iii, $Ph_3P{=}CHCO_2Me$; iv, $(Bu^i)_2AlH$; v, Bu^tCOCl-Py, then $Ph_2(Bu^t)SiCl$-imidazole, then $(Bu^i)_2AlH$; vi, REDAL

Scheme 3

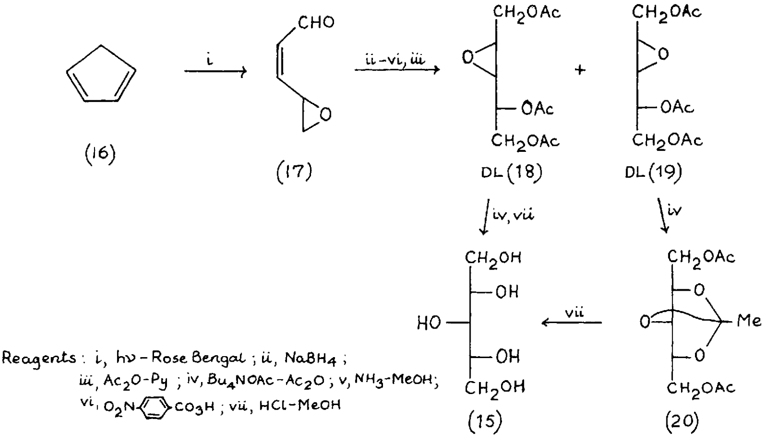
reduction of the resulting hydroxyperoxide in an iterative procedure for synthesizing chiral 1,3,5,...(2n+1) polyols (e.g., 13) as outlined in Scheme 3.[14] Sharpless and co-workers have reported related syntheses of such deoxyalditols, one of which included the reduction of the diepoxide (14) as shown in Scheme 4.[15]



Reagent: i, REDAL

Scheme 4

A stereoselective synthesis of xylitol (15) from cyclopentadiene (16) via the known photolysis product (17) (Scheme 5) involved

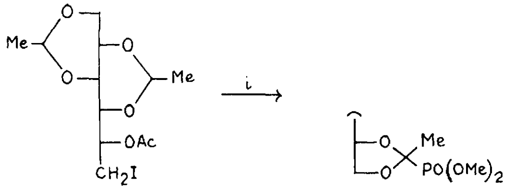


Reagents: i, hν - Rose Bengal; ii, NaBH$_4$; iii, Ac$_2$O-Py; iv, Bu$_4$NOAc-Ac$_2$O; v, NH$_3$-MeOH; vi, O$_2$N-C$_6$H$_4$-CO$_3$H; vii, HCl-MeOH

Scheme 5

acetolysis of a mixture of racemic epoxides (18, major) and (19, minor) to give primarily products with the xylo-configuration; epoxide (19) in particular, gave xylitol (15) in >98% yield via the bicyclic orthoester (20).[16] A re-examination of the epoxidation-hydrolysis of divinylmethanol (Vol.11, p.143) has revealed that although DL-arabinitol, xylitol, and ribitol were obtained, the diastereoselectivities characterizing the epoxidation step, and the regioselectivities governing the epoxide ring-opening, were not sufficiently high to make this an attractive synthesis of any one of them.[17]

3-O-Allyl- and -benzyl-D-mannitol have been synthesized from a partially protected D-mannitol derivative, while 1,2,3,5,6-penta-O-benzoyl-D-mannitol was prepared by partial esterification of the 1,2,5,6-tetrabenzoate.[18] 2-O-Octanoyl, -palmitoyl, -lauroyl, and myristoyl-D-mannitols have been conventionally synthesized from 1,3:4,6-di-O-benzylidene-D-mannitol, while the 3-O-acyl analogues were obtained from 1,2:5,6-di-O-isopropylidene-D-mannitol.[19] The conformations adopted by a variety of D-mannitol derivatives have been probed by ^{1}H-n.m.r. studies.[20] New derivatives of 1,3:2,4-diethylidene-D-glucitol bearing mesyloxy, bromine or iodine substituents at C-5 and C-6 have been reported, as has the conversion shown in Scheme 6.[21]

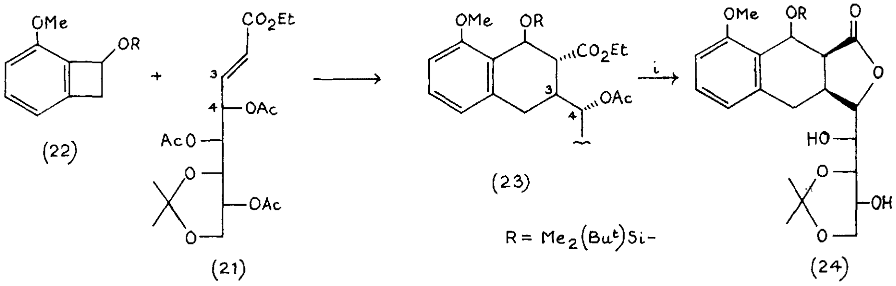


Reagent: i, $P(OMe)_3$

Scheme 6

Hydrolysis of 1,6-dibromo-1,6-dideoxygalactitol and 1,2:5,6-dianhydrogalactitol, two bifunctional alkylating agents which show cytostatic activity, has been examined in detail; 3,6-anhydro-1-bromo-1-deoxy-DL-galactitol was the main product from the former, while the latter gave 1,5-anhydro-DL-galactitol, 2,5-anhydro-DL-altritol, and galactitol as end products.[22]

Diels-Alder addition of sugar enone (21) and the diene generated from the cyclobutabenzene (22) led mainly to the pentitol-1-ylated derivative (23), from which lactone (24) was prepared by epimerization-lactonization (Scheme 7); related reactions of unsaturated sugar derivatives were also described.[23]



Reagents: i, K_2CO_3-MeOH

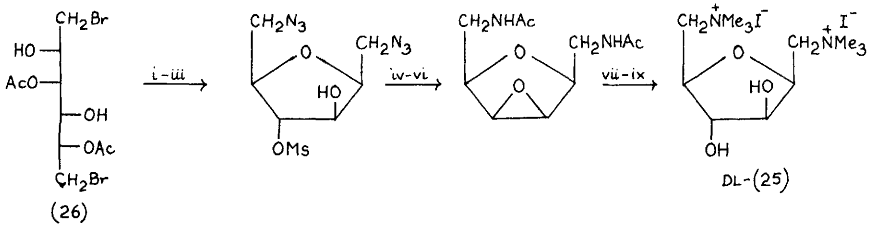
Scheme 7

The alkylation of partially tetrahydropyranylated alditols and the chemistry of chiral crown ether derivatives incorporating alditol moieties are covered in Chapter 4.

Aldoses and ketohexoses were the primary products of indirect anodic oxidation of D-glucitol and of D-mannitol in aqueous calcium iodide; aldoses were degraded to the next lower aldose by conversion to the aldosulose and *C*-1 oxidation-decarboxylation.[24] 2-And 3-uloses and hex-2,5-diuloses were the major products of bromine oxidation in the presence of excess calcium carbonate of pentitols and hexitols, the product mixtures being examined by g.l.c.-m.s. of the trifluoroacetylated *O*-alkyloxime derivatives.[25,26] The branched-chain sugars obtained from periodate oxidation-intramolecular aldol condensation of 2,5-*O*-ethylidene-D-mannitol are covered in Chapter 13.

Osmotic and activity coefficients for sorbitol in aqueous sodium or potassium chloride have been redetermined.[27] Spectral studies of 1-deoxy-1-nitroheptitols are mentioned in Chapter 21, and borate complexation of polyhydroxy compounds is covered in Chapter 16.

2,5-Anhydro-1-deoxy-D-lyxitol, -mannitol, and -talitol have been synthesized and examined as substrates and inhibitors of hexokinase and fructokinase,[28] while 2,5-anhydro-D-mannitol and its 1,6-di-*O*-tosyl, 1,6-di-*O*-trityl, 1,6-dideoxy, 1-deoxy-1,1-difluoro, and several other derivatives have also been synthesized and examined as potential β-D-fructofuranoside inhibitors.[29] The formation of anhydro-derivatives from D-glucitol and D-mannitol in hot aqueous acid has been monitored by ^{13}C-n.m.r. methods, and rate constants for the various reactions were determined; formation of 1,4:3,6-dianhydro-D-mannitol was shown to involve inversion at *C*-1, since (1*S*)-[1-^{2}*H*]-D-mannitol gave the (1*R*)-[1-^{2}*H*]-dianhydride.[30] 2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-galactitol, -glucitol, and -mannitol were synthesized by tributyltin hydride dehalogenation



Reagents: i, NaN$_3$; ii, MsCl-Py; iii, H$^+$; iv H$_2$S; v, Ac$_2$O-Py; vi NaOMe-MeOH; vii, H$_3$O$^+$; viii, H$_2$CO-HCO$_2$H; ix, MeI

Scheme 8

of the corresponding acetylated glycosyl bromides, and the method was considered to be a general, convenient procedure.[31] The "double-headed" muscarine analogue (25) and other derivatives of 1,6-diamino-2,5-anhydro-1,6-dideoxy-DL-glucitol have been synthesized from the 1,6-dibromide (26) (Scheme 8).[32]

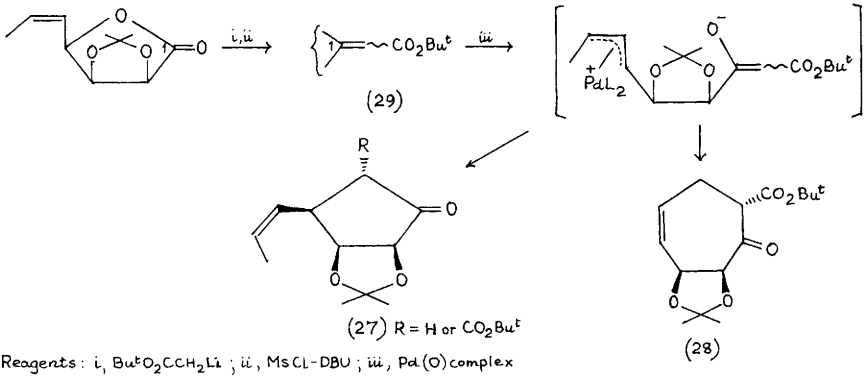
2 Cyclitols

The biosynthesis of inositols from D-glucose has been reviewed, and refinements in the mechanism of carbocyclic ring formation proposed.[33] Under conditions of water-stress, the level of O-methyl-scyllo-inositol in the leaves of some Vigna species, or of ononitol (1-D-4-O-methyl-myo-inositol) in other species, is markedly increased, and these plants appear to be good sources of these rare O-methyl-inositols.[34] Two L-inositol and two myo-inositol tetra-O-angelates were isolated from aerial parts of Inula cappa.[35]

5-O-Caffeoylshikimic acid was shown to be the major constituent of the acutely toxic fraction of bracken fern.[36] Neosurugatoxin, which contains an O-(β-D-xylopyranosyl)-myo-inositol moiety esterified by a complex pentacyclic heterocycle, has been shown to be the causative agent present in toxic Japanese ivory shellfish.[37]

Cyclopentanone and cycloheptanone derivatives, (27) and (28) respectively, have been synthesized from D-mannose via palladium (0) catalysed isomerization of the 5-vinyl-2-alkylidene furanoid derivatives (29) (Scheme 9); the yields of each of the three products shown can be good by selection of suitable conditions.[38]

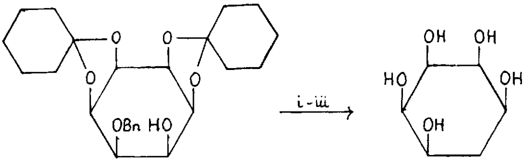
Single free hydroxy groups in otherwise protected inositols can



Reagents: i, $Bu^tO_2CCH_2Li$; ii, MsCl-DBU ; iii, Pd(0)complex

Scheme 9

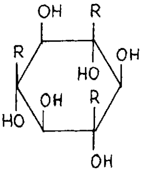
be removed by the deoxygenation procedure of Barton and McCombie, in which an S-methyl dithiocarbonate derivative is treated with tributyltin hydride; in this way a number of cyclohexanepentols were synthesized, as exemplified by the transformation shown in Scheme 10.[39]



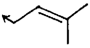
Reagents: i, CS_2-MeI-NaH; ii, Bu_3SnH; iii, H_3O^+

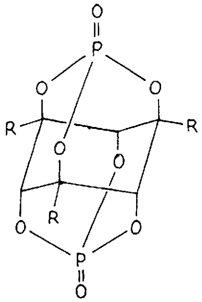
Scheme 10

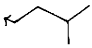
The reduced derivative (30) of muellitol (31), a tri-C-alkenyl-scyllo-inositol, formed a borate complex, and gave mono-orthophosphate (with $POCl_3$) and bis-orthophosphate (32) (with P_2O_5) derivatives. The derivative (33), in contrast, did not complex with borate, but gave a "cage" orthophosphate (with $POCl_3$).[40]

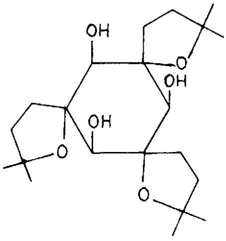


(30) R =


(31) R =


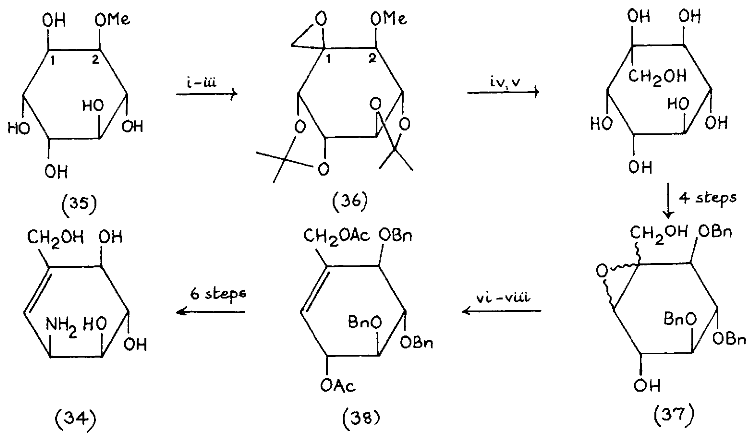


(32) R =




(33)

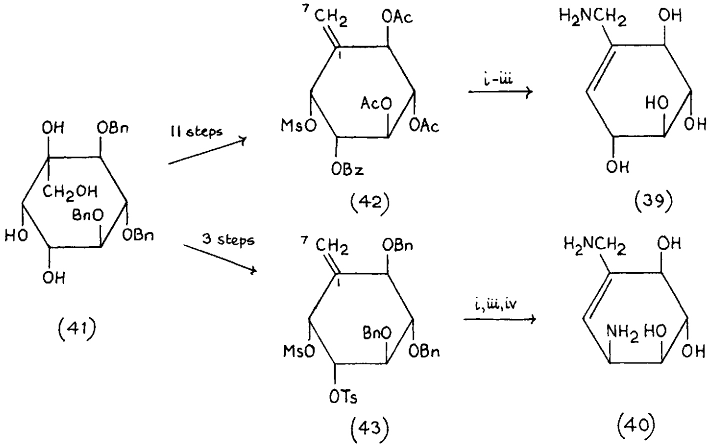
In a complex paper reporting over 86 compounds, Paulsen and Heiker, have reported a twenty-step synthesis of valienamine (34) from quebrachitol (L-2-O-methyl-chiro-inositol) (35) (Scheme 11). Many of the steps involved manipulation of protecting groups, but the major transformations were: a) addition of diazomethane to a 1-ulose to give a mixture of epoxide (36) and its C-1 epimer; b) demethylation at O-2; c) formation of epoxides (37) by sulphonate displacement; d) synthesis of alkene (38) by conversion of these epoxides to iodohydrins and elimination ($POCl_3$-py); and e) displacement of an allylic hydroxy group by azide using the DEAD-TPP reagent



Reagents: i, $Me_2C(OMe)_2$-H^+; ii, RuO_4-$NaIO_4$; iii, CH_2N_2; iv, KOH; v, BBr_3; vi, Ac_2O-Py; vii, NaI; viii, $POCl_3$-Py

Scheme 11

system. Studies modelling these latter two transformations in unbranched cyclitol derivatives were included.[41] These same authors have also synthesized the valienamine isomer (39) and 7-aminovalienamine (40) from the L-chiro-inositol derivative (41) (Scheme 12). The exocyclic alkenes (42) and (43) were obtained by way of 1,7-spiroepoxide derivatives, which were deoxygenated with

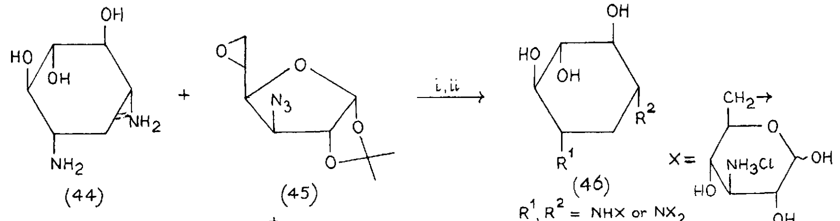


Reagents: i, NaN_3; ii NaOMe-MeOH; iii, NH_3-MeOH-Ph_3P; iv Na-NH_3

Scheme 12

either sodium diethyltellurophosphate, or selenoxobenzothiazole-trifluoroacetic acid. On treatment with sodium azide, these allylic sulphonates (42) and (43) underwent displacement reactions followed by facile [3.3]-sigmatropic rearrangements to give the thermodynamically more stable endocyclic alkenes, the latter compound undergoing a second sulphonate displacement to provide the diaminated product (40).[42] Syntheses of a pseudotrisaccharide and of DL-validosylamines A and B, which contain valienamine moieties, are covered in Chapters 3 (and 8) and 18 respectively.

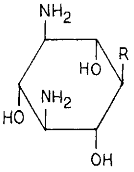
Controlled condensation of 2-deoxystreptamine (44) with two, three, or four molecules of 5,6-epoxide (45) provided the secondary and tertiary amine derivatives (46) (Scheme 13); by using a different epoxide, analogues incorporating other sugar moieties were obtained.[43]



Reagents: i, H_2-Pd/C ; ii, H_3O^+

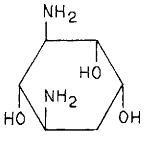
Scheme 13

A series of racemic 1,3-inosadiamines, including streptamine (47), 5-deoxystreptamine (48), and 2,4-diamino-1,2,4-trideoxy-DL-chiro-inositol (49) have been synthesized from "cis-benzene trioxide" via compound (50).[44]



(47) R = OH

(48) R = H



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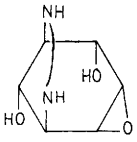
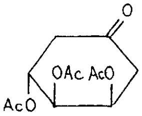
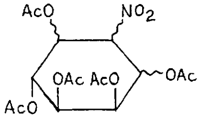


DL-(50)

The ketocyclitol triacetate (51) was obtained via reductive elimination ($NaBH_4$) of the β-acetoxy-groups from the nitrocyclitol (52) (obtained from D-mannose); compound (51) has previously been employed in a synthesis of (-)shikimic acid. An analogous strategy led to the synthesis of 2-deoxystreptamine pentaacetate from N-acetyl-D-glucosamine.[45]



(51)



(52)

^{13}C-N.m.r. studies on inositols and cyclohexanepentols are covered in Chapter 20.

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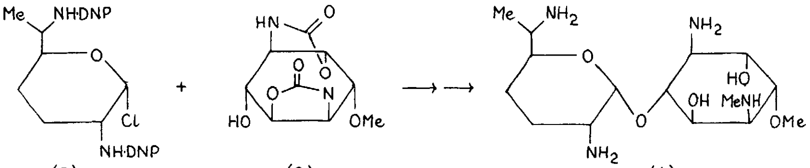
18
Antibiotics

1 Aminoglycoside Antibiotics

Total synthesis of fortimicin B (1) has been achieved. The key steps involved condensation of the α-sugar chloride (2) with the biscarbamate cyclitol (3).[1,2] Several derivatives of lysinomycin (4), a fortimicin analogue, have been prepared, which include 4-N-glycyl and lysyl derivatives. The derivatives were found to be less active than the parent lysinomycin.[3] 1-Deamino-2-deoxyfortimicins A (5) and B (6), the 1,2-di-epi-fortimicins (7), and the 1,2-regio-isomeric fortimicins (8) and (9) have been synthesized from fortimicin B by standard conversions involving 1,2-unsaturated and 1,2-anhydro derivatives.[4] 2-Deoxy-3-demethoxyfortimicin A has been synthesized from 1,2',6'-tri-N-benzyloxycarbonyl-3-O-demethylfortimicin B, using the



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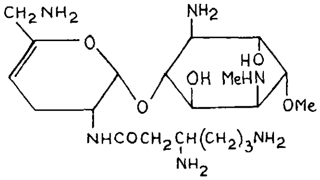
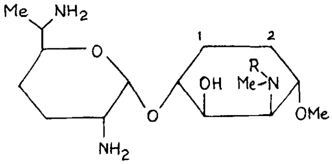
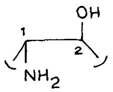


(4)



(5) R = $COCH_2NH_2$

(6) R = H



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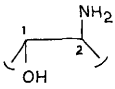

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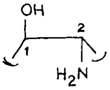
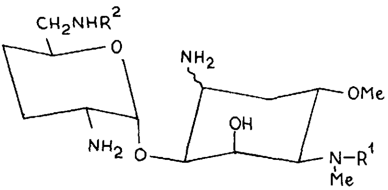


(9)

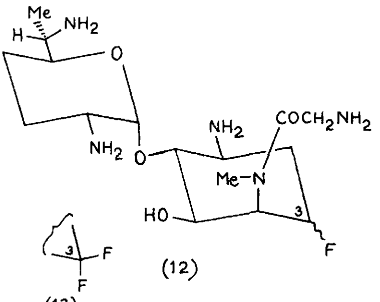
Tipson-Cohen procedure to prepare a 2,3-unsaturated intermediate from a 4,5-oxazolidine-2,3-dimesylate derivative. The in vitro antibiotic activity of this deoxy analogue was approximately twice that of fortimicin A.[5] The conversion of fortimicin B to dactimicin (see Vol. 15, p.176), which contains a N-2" formimino group, has been reported. N-Butyloxycarbonyl and benzyloxycarbonyl groups were used to achieve selective formimidation of this 2"-amino group in the sequence -NHMe -> $N(Me)COCH_2NH_2$ -> $N(Me)COCH_2NHCH = NH$. A similar sequence has been used to convert istamycin A_0 and B_0 to the newly isolated component (10) of the istamycin complex which also carry N-formimino glycinyl residues.[7] Several other istamycin components (11) have been isolated from S.tenymariensis, and characterized by ^{13}C- and ^1H-n.m.r.[8]



(10) $R^1 = COCH_2NHCH{=}NH$, $R^2 = H$

(11) $R^1 = H, COCH_2NHR^3$, $R^2 = Me, Et$

$R^3 = H, CHO, CONH_2$



(12)

(13)

Synthesis of the 3-demethoxy-3-fluoro-sporaricin A analogues (12) from sporaricin B has been achieved using diethylaminosulphur trifluoride (DAST) as the fluorinating reagent on intermediate 3-hydroxyepimines. The difluoro analogue (13) was similarly obtained from a 3-keto precursor.[9] The 3-O-methyl group of sporaricin A has been replaced by an allyl group leading to 3-O-(3-amino-2-hydroxypropyl)-3-O-(4-amino-2-hydroxypropyl)-sporaricin A derivatives. These compounds show high activity against bacteria resistant to sporaricin A.[10] Sporaricin E, another component of the sporaricin complex (see Vol. 13, p.157; Vol. 15, p.176), has been identified; it is identical to 2-deoxyfortimicin B, showing only very weak antibiotic activity.[11]

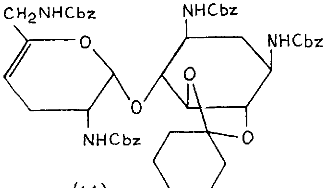
6-Deoxydihydrosteptomycin has been synthesized from dihydrostreptomycin by a standard tosyloxy -> chloro -> deoxy sequence. It was much less active than dihydrostreptomycin.[12] Two related syntheses of 3"-epidihydrostreptomycin from dihydrostreptomycin have been reported, which achieve epimerization by sulphonate ester displacements, either directly or via an oxazoline intermediate formed by neighbouring group participation from the 2"-N-benzyloxycarbonylamino group, which was then reduced and hydrolysed.[17] 3"-Epidihydrostreptomycin is active against resistant bacteria and is as potent as 3"-deoxydihydrostreptomycin.[14]

The biosynthesis of the N-methyl-L-glucosamine moiety of streptomycin from D-glucosamine by S.griseus has been studied. Addition of thymine to the culture medium stimulated formation of streptomycin, and the conversion of D-glucosamine to N-methyl-L-glucosamine. A novel UDP-aminosugar nucleotide intermediate, UDP-N-methyl-D-glucosamine phosphate, has been detected which is formed before maximum production of the antibiotic.[15]

The location of guanidino and ureido groups in bluensomycin has been established by comparison with the ^{13}C-n.m.r. spectra of streptomycin and related compounds.[16]

Structures have been reported for the antibiotics SU-1, SU-2 and SU-3, which are close relatives of gentamicin C_{1a}, produced by a mutant strain of micromonospora sagamiensis KY 11509.[17] 2'-Deoxygentamicin B, 2',3'-dideoxygentamicin B, 2'-desaminogentamicin C_{1a} and 2'-desaminosisomicin have been synthesized from the ψ-disaccharide garamine by glycosylation. The solution conformations of members of this series and their diastereoisomers have been studied by ^{13}C-n.m.r. Using D- and L- glycosides, shielding effects on deoxystreptamine carbons are shown to provide a reliable method of assigning absolute stereochemistry to related glycosides.[18] Synthesis of gentamine C_{1a} from neamine has been reported. An efficient preparation for the key compound, tetra-N-benzyloxycarbonyl-3',4'-dideoxy-3'-ene-5,6-O-cyclohexylideneneamine (14), from the corresponding 3',4'-xanthate by reductive radical elimination has been described.[19]

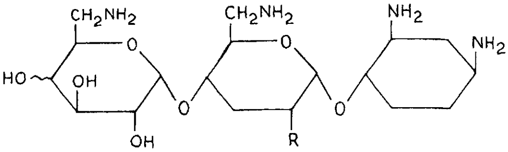
Insertion reactions of acyl nitrenes leading to the amination of the 6"-amino group of gentamicin C_2 have been studied. The study also includes various model systems.[20] Gentamicin C_{1a} has been acylated at N-1 by a cyclic, chiral γ-amino - α -hydroxy acid derived from quinic acid which can be regarded as an analogue of the butanoic acid unit in butirosins.[21]



(14)

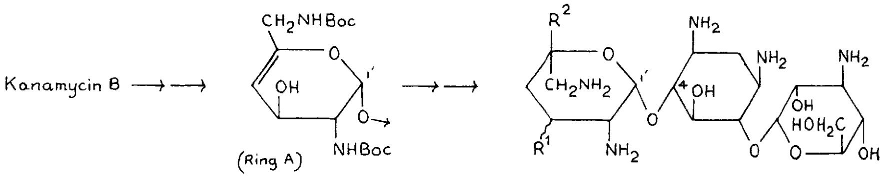
The biosynthesis of sagamicin and related aminoglycoside antibiotics has been studied using blocked mutants of micromonospora sagamiensis which normally produces the close relative gentamicin C_1.[22] Mutational biosynthesis has been used to prepare 2-hydroxy-sagamicin, by feeding streptamine instead of 2-deoxystreptamine to a mutant strain of micromonospora sagamiensis.[23]

Three α-glycosides (15) of 2,5,6-trideoxystreptamine have been prepared using maltal and lactal derivatives by stereospecific α-glycosylation with a chiral ditosyloxy-cyclohexanol followed by conventional amination via azidolysis. These α-disaccharide-2,5,6- trideoxystreptamines, analogues of aminoglycoside antibiotics, showed no antibacterial activity. Since monosaccharide 2,5,6-trideoxystreptamine analogues were active, the absence of a glycoside unit at the C-4' is probably critical for activity.[24] A series of hilrimycins, derived biosynthetically



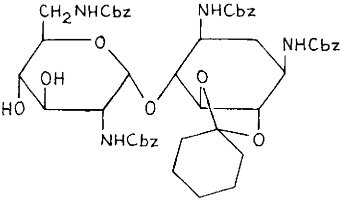
(15) R = H or OH

from deoxystreptamine blocked mutants with streptamine, inosamine and other analogues, and which occur in trace amounts along with related aminoglycosides antibiotics, have been characterized by mass spectrometry, although these substances have not been isolated in pure form.[25] Kanamycin B analogues (16) have been prepared from the Kanamycin B derivative (17) (part structure) by regiospecific methylation and stereospecific hydrogenation procedures, during which the 4-O-glycosidic unit (ring A) is converted from a D- to an L- sugar.[26] O-Substituted derivatives of neamine and 2-deoxystreptamine have been prepared from neamine, giving useful intermediates for modified antibiotics, e.g., compounds (18) and (19).[27]



(17)

(16) $R^1 = Me, R^2 = H$; $R^1 = H, R^2 = Me$



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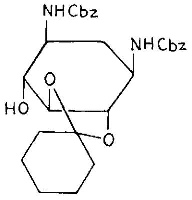
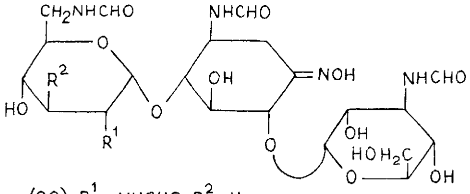
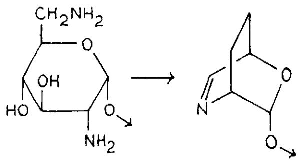


(19)

3',4'-Dideoxykanamycin B (dibekacin) has been synthesized from Kanamycin B by standard methods. It shows good activity against bacteria resistant to kanamycin B.[28] 1-Epitobramycin and 1-epikanamycin have been prepared from the parent antibiotics via electrochemical or catalytic hydrogenation of 1-oxime derivatives (20), and (21), respectively. To achieve C-3 epimerization of tobramycin via the analogous 3-oxime, it was necessary to use sodium cyanoborohydride; hydrolysis of 1-epi- and 3-epi-tobramycin led to the enantiomeric chiro-diaminocyclohexanetriols.[29] Kanamycin B has been modified by converting the neosamine ring to the bicyclo-oxazoctene unit (22).[30]



(20) $R^1 = NHCHO, R^2 = H$
(21) $R^1 = R^2 = OH$

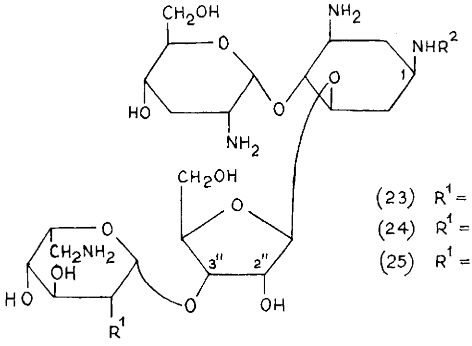


(22)

The regiospecific synthesis of 1-N-[(S)-4-amino-2-hydroxybutanoyl]-2"- deoxykanamycin B from neamine has been achieved.[31] 4"-Epi-deoxyhalogeno and 4"-deoxy derivatives of Kanamycin A have been prepared by conventional methods. Attempts to use the former as substrate for S_N2 reactions invariably resulted in elimination to give the corresponding 4"-ene derivative.[32] 3'-Deoxyamikacin has been used to prepare 3',6"-dideoxy, 5,3'-dideoxy, and 5,3',6"-trideoxy derivatives. 5'-Deoxyamikacin has also been prepared from amikacin.[33] Secondary ion mass spectrometry (SIMS) of Kanamycins A, B and C has been reported.[34]

Paromamine has been synthesized from D-glucosamine using lead tetraacetate decarboxylation and sodium borohydride deacetoxylation as the key steps.[35] Paromomycin has been converted to 3'-eno, 3'-deoxy-4-epi- and 3',4'-dideoxy analogues, all of which are more active than paromomycin itself against organisms producing 4'-adenyl transferase or 3'-phosphotransferase enzymes.[36]

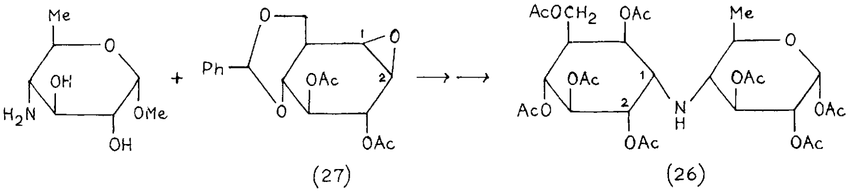
The analogue (23) of lividomycin B (24) and the 2"-substituted regioisomer have been synthesized to test the effect of the N-1 butanoyl substituent on the activity of their N-1 unsubstituted parents; whereas the 2"-isomer was less active, the 3"-isomer showed enhanced activity on substitution.[37] The parent pseudo-tetrasaccharides ((25) and its 2"-regioisomer) were synthesized from a 6-azido-L-idosyl chloride and the appropriate pseudo-trisaccharide.[38]



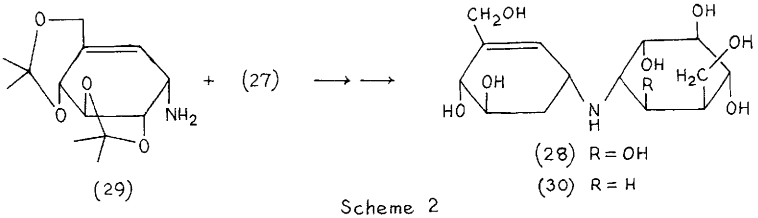
(23) $R^1 = OH, R^2 = -COCH(OH)CH_2CH_2NH_2$
(24) $R^1 = NH_2, R^2 = H$
(25) $R^1 = OH, R^2 = H$

Experiments using [6-^{2}H]-labelled D-glucose to study the biosynthesis of ribostamycin by ^{2}H-n.m.r. have been briefly reviewed.[39] Butirosin A has been used to prepare 3'-deoxy, 5"-amino-3',5"-dideoxy- and 5"-amino-4',5"-dideoxy-butirosin A, which are active against microorganisms resistant to butirosin and other antibiotics by 3'-phosphorylation.[40]

^{13}C-N.m.r. data have been given for the pseudo-trisaccharide antibiotic LL-BM 123 (see Vol. 11 p.154), which contains myo-inositol-2, and the pseudo-disaccharide LL-BM 782 (see Vol. 15, p.182), containing myo-inositol. The n.m.r. data support a ß-linkage from the hexose to cyclitol in both these antibiotics, in contrast to the previous proposals.[41] The peracetyl derivative (26) of the 4-amino-4, 6-dideoxy-D-glucose-inosamine pseudo-disaccharide (a structural unit in oligostatins) has been prepared as indicated in Scheme 1. Analagous reaction of methyl 4-amino-4-deoxy- α -D-glucopyranoside with the racemic 1,2-anhydroinositol (27) gave the four possible isomeric pseudo-disaccharides.[42] DL-Validoxylamine B (28) was similarly prepared from compound (27) and the unsaturated cyclohexylamine (29) (Scheme 2),[43] and the pseudo- disaccharide analogously prepared from (27) and the saturated analogue of (29) could be dehydrated to give DL-validoxylamine A (30)[44] (see also Vol. 15, p. 183).



Scheme 1



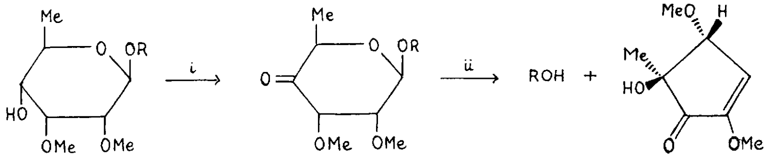
Scheme 2

Partially and fully de-N-methylated spectinomycins have been obtained from spectinomycin by catalytic N-demethylation using oxygen-on-platinum black. The products showed reduced or no biological activity.[45]

The potential of marine microorganisms for antibiotics and enzyme production, including aminoglycoside antibiotics, has been discussed.[46] Aminoglycoside antibiotics have been analysed by chemical ionization mass spectrometry, yielding protonated molecular ions and useful fragment ions caused by glycosidic cleavage.[47] A comprehensive study of the field desorption and secondary ion mass spectra of kanamycin, lividomycin A, dihydrostreptomycin, and minosomycin has been made. The two methods provide complementary information about molecular weight and structure.[48]

2 Macrolide Antibiotics

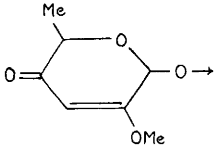
A pathway has been suggested for the latter stages of tylosin biosynthesis, which includes attachment of three glycosidically bound sugars, mycinose, mycaminose and mycarose, to a 16-membered ring macrolide. The study involved sixteen possible biosynthetic precursors.[49] A tylosin aglycone has been released from 5-O-mycaminosyl tylonolide using acetic anhydride-chloroform (modified Polonovski reaction). Mass spectral data of a number of 5-O-mycaminosyl tylonolides have been reported.[50] Mycinose can be selectively cleaved from mycinamicins, which also contain desosamine, under neutral conditions by sequential Moffatt oxidation to the corresponding glucos-4-ulose derivative, and hydrolysis using silica gel in methanol (Scheme 3).[51]



Reagents: i, DMSO-DCC-Py-CF_3CO_2H ; ii, SiO_2-MeOH

Scheme 3

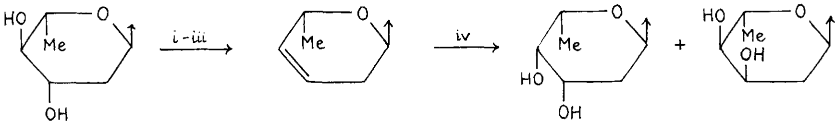
The first total synthesis of tylosin by regio- and stereoselective attachment of the sugar units (4-O-(α -L-mycarosyl)- D-mycaminose and D-mycinose) to the C-5 and C-23 hydroxy groups in the aglycone has been reported.[52] A series of 4"-O-substituted tylosin derivatives have been prepared (mycarose substitution).[53] New macrolide antibiotics produced by mutants of S.fradiae NRRL 2702 have been shown to have structures similar to tylosin, containing 6-deoxy-D-allose (YO-7625) or 2-O-methyl-3,6- dideoxy-hex-2-enopyranos-4-ulose (31) (YO-9010) instead of mycinose.[54] Tylosin has been transformed into 23-O-mycinosyl-12,13-desepoxy-12, 13-didehydro- rosaramicin by degradative removal of



(31)

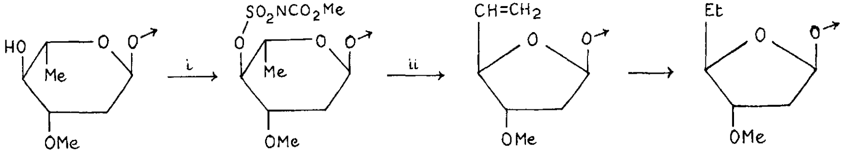
the disaccharide moiety (acetolysis of its N-oxide) followed by microbiological reglycosylation of the resulting free aglycone with desosamine. The product, a hybrid of rosaramicin and mycinamicin, was highly active against gram positive organisms.[55] ^{13}C-Spin-lattice relaxation times for the sugar components of mycinamicin antibiotics have been reported.[56]

The structures of conconamycins B and C closely resemble that of conconamycin A (see Vol. 15, p. 124), containing either an unsubstituted 2-deoxy-ß-D-rhamnopyranosyl unit (C) or the 4-O-carbamoyl derivative of this sugar (B), the latter being also present in conconamycin A.[57,58] Patricin A, B and C, components of the antifungal and antiprotozoal heptaene macrolide antibiotic patricin (produced by S. aureofaciens NRRL 3878), have been characterized, and shown to contain mycosamine.[59] Erythromycin A, labelled with carbon-11 in the desosamine moiety, has been prepared by rapid reductive methylation of N-demethylerythromycin A with [^{11}C]-formaldehyde, giving material useful for biological tracer studies.[60] The 2,6-dideoxy-α-L-*arabino*-hexopyranosyl residue in oleandomycin Y has been isomerized to the corresponding L-*ribo* and L-*lyxo* diastereoisomers by the unsaturation-hydroxylation sequence shown in Scheme 4. These relatives of oleandomycin show enhanced antibiotic activity.[61] Ring contraction of oleandrose residue (32) in oleandomycin has been achieved *in situ* using ((methoxycarbonyl) sulphamoyl) triethyl ammonium hydroxide (Scheme 5). The vinyl group in the product furanose (33) was also hydrogenated to afford the trideoxyhexose unit (34).[62]



Reagents: i, Ac_2O-EtOAc ; ii, imidazole–2,4,5-tri-iodo-imidazole–Ph_3P ; iii, $NaHCO_3$; iv, OsO_4

Scheme 4



(32) (33) (34)

Reagents: i, $Et_3\overset{+}{N}SO_2\overset{-}{N}CO_2Me$; ii, Δ(xylene)

Scheme 5

Further members of the tetrocarcin complex (E_1, E_2, F and F-1) found in the culture broth of *Micromonospora chalcea* KY 1109 have been isolated and characterized. They all contain tetronolide and tetronitrose, and in addition, E_1 and E_2 contain L-digitoxose and F, an uncharacterized 2-deoxy sugar. They show antitumour activity against *B. subtilis* which is proportional to their content of deoxy sugars.[63] Tetronitrose (kijanose) has been confirmed (see Vol. 15, p.193) as a D-series sugar by a synthesis from D-mannose (see also Chapter 13).[64] Tetramycin A and B, tetraene macrolide antibiotics, have been isolated and characterized by n.m.r. spectroscopy. They contain 3-amino-3,6- dideoxy-D-mannopyranose ß-linked as a glycoside.[65] *N*-Aminoacyl derivatives of the polyene macrolide antibiotics, 67-121-C and amphotericin B, which also contain this amino sugar residue, have been prepared; derivatives with some amino-acids appear most promising for further study.[66]

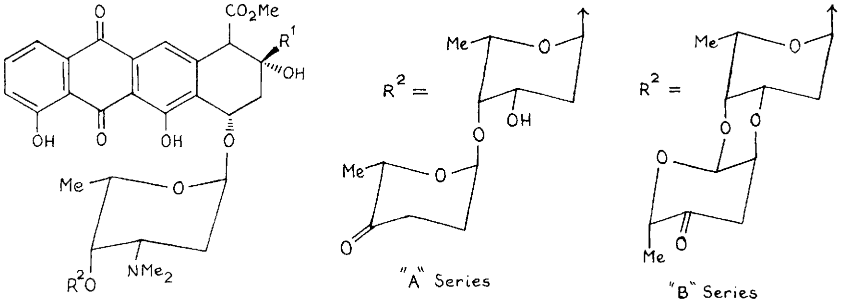
3 Anthracycline Antibiotics

4-*O*-Demethyl-11-deoxydoxorubicin and some analogues have been isolated from *S.peucetius* var. *aureus*. All contain daunosamine.[67]

Several papers report synthesis of 3'-N-alkylated derivatives of anthracycline antibiotics. The 3'-deamino-3'-morpholino analogue of daunorubicin has been shown to be the most potent synthetic anthracycline analogue so far against mouse leukemia P388.[68] Likewise 3'-deamino-3'-morpholino analogues of daunomycin, adriamycin, and carminomycin have been reported.[69] N-Monoethyl derivatives of carminomycin and rubomycin have been prepared by treatment with acetaldehyde in the presence of sodium borohydride. The corresponding N,N-diethyl derivatives were also formed. As compared to parent compounds, all derivatives showed reduced antibacterial activity.[70] Israel's group has reported the synthesis of daunorubicin and adriamycin,[71] 3-amino-3,5-dideoxy-D-ribofuranosyl α- and ß-glycosides of daunomycinone,[72] and ß-D-glucosaminyl derivatives of daunomycinone and adriamycinone.[73] Whereas methylation of the hydroxy groups in the aglycone of daunorubicin and analogues resulted in complete loss of neoplasm-inhibiting activity, methylation of the amino-sugar 4'-hydroxy group of 11-deoxydaunorubicin and 11-deoxydoxorubicin increased their effectiveness against P.388 leukemia in mice.[74] A complete molecular mechanism optimization of daunomycin has been described. The two different D ring puckers are of comparable energy, consistent with the n.m.r. data, although only one has been observed by X-ray crystallography.[75] 7-O-[3-Amino-2,3,6-trideoxy-4-O-(2,6-dideoxy-α-L-lyxo-hexopyranosyl)-α-L-lyxo-hexopyranosyl] daunomycinone has been synthesized by standard $SnCl_4$-catalysed glycosylation of daunomycinone with an appropriate disaccharide 1-acetate, whose synthesis is referred to in Chapter 3.[76]

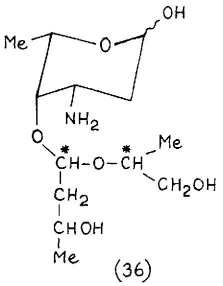
A review (in Russian) has appeared on actinomycin A.[77] (See Vol, 13, p.162). The isolation and characterization of new anthracyline antibiotics, auromycins and sulphurmycins, obtained from culture of streptomyces galileus strain OBB-111, has been reported. They contain new aglycones auromycinone and sulphurmycinone, the sugar residue being the same as in aclacinomycin A and B, as shown in structure (35).[78] The minor components of these auromycin and sulphurmycin antibiotics have been characterized. All contain L-rhodosamine together with variable amounts of 2-deoxy-L-fucose, L-amicetose and L-rhodinose, contained in mono- to tetra-saccharide chains.[79]

The monoacetyl trisaccharide which can be obtained from tri-O-acetyl aclacinomycin A by hydrogenolysis has been used to form α-glycosides from various aglycones (aklavinone, daunomycinone, adriamycinone and carminomycinone) in a one-pot reaction using trifluoromethanesulphonyl anhydride, N-tetrabutyl ammonium bromide and 2,4,6-collidine. Some 3"-O-acyl derivatives of these modified anthracyclines showed marked antitumour activity against mouse leukemia L 1210. N-Monomethyl and N,N-didemethyl derivatives were also prepared by photolysis in sunlight.[80] The spatial configuration of carbohydrate part of carminomycins II and III has been studied. The difference between them is in the configuration at the acetal and glycol carbon atoms indicated in structure (36).[81]



Auramycin, R^1 = Me
Aclacinomycin, R^1 = Et
Sulphurmycin, R^1 = CH_2COMe

(35)

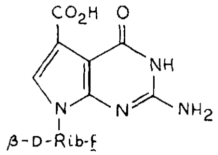


(36)

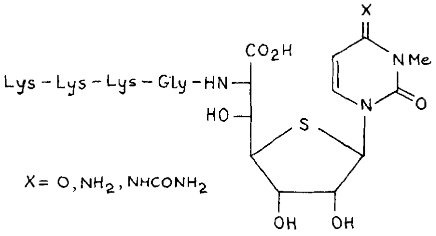
Chemical ionization mass spectrometry of ten anthracycline antibiotics, including nogalamycin and aclacinomycin A, has been studied. Compounds give few but intense negative ions, not including any glycosidic ions, whereas a great variety of ions were obtained in positive ion spectra, including several from the sugar unit.[82]

4 Nucleoside Antibiotics

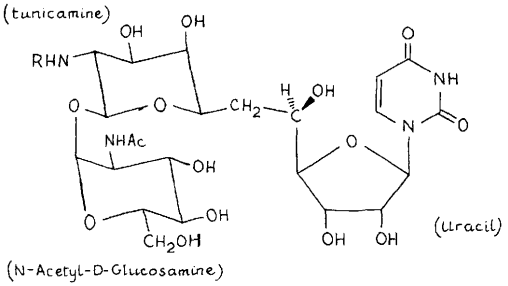
A new antitumour antibiotic, cadeguomycin, occurring along with tubercidin in a strain of S.hygroscopicus has been identified as 7-carboxy-7-deazaguanosine (37).[83] 5'-Sulphamoyl-2-chloro-adenosine, an antibacterial antibiotic closely related to the sulphamoyl- fluronucleoside nucleocidin (see Vol.3, p.3 or Vol. 13, p.64) has been obtained from an S.rishiriensis subspecies.[84] Psicofuranine together with its α-anomer have been prepared by standard methods from perbenzoylated sugar and silylated base.[85] The deferriform of the thionucleoside antibiotics albomycins δ_1, δ_2 and ϵ has been shown to have structure (38), established by chemical and spectroscopic



(37)



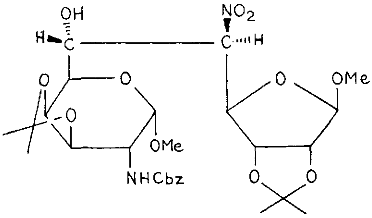
(38)



(39) R = C_{14}-C_{20} Acyl (Sat., αβ-unsat., β-hydroxy)

methods.[86] Corynetoxins, which cause ryegrass toxicity, have been identified as new members of the tunicamycin group of antibiotics (39) differing only in the particular N-acyl substituent.[87] The nitro pseudo-disaccharide (40) (an intermediate for tunicamycin synthesis) has been synthesized by condensation of the corresponding 5-nitropentose and dialdohexose units. The configuration of (40) was established by X-ray analysis.[88]

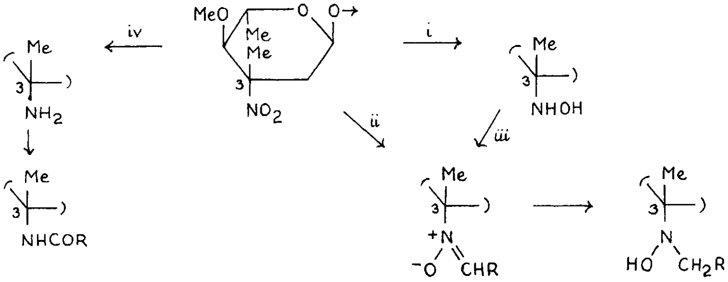
The chemistry and biochemistry of tunicamycin has been reviewed.[89]



(40)

5 Miscellaneous Antibiotics

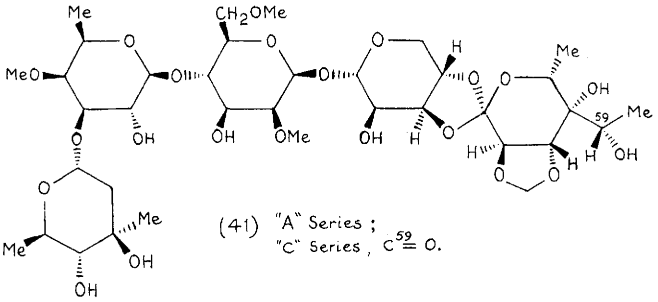
Everninomicin D has been chemically converted into new biologically active derivatives by reduction of the nitro group of the evernitrose residue to hydroxyamino and amino sugar analogues (Scheme 6).[90] The stereochemistry and structure of avilamycins



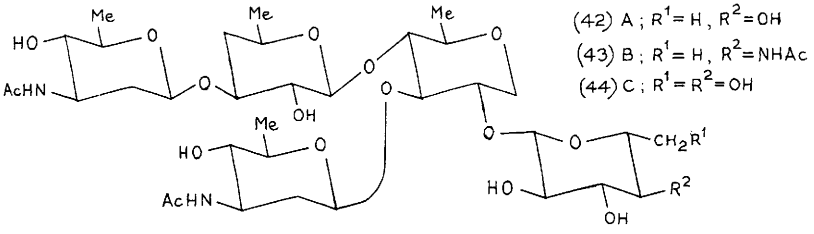
Reagents: i, e^- (Electrode) ; ii, Zn-RCHO ; iii, RCHO ; iv, H_2-Cat.

Scheme 6

A and C have been established by chemical degradation to avileurekanose C (41) whose acetate was analysed by n.m.r., and X-ray crystallography. Apart from the configuration at C-16 (ring C ortho ester), all the remaining centres in avilamycin A and C have been defined.[91]


(41) "A" Series ; "C" Series , $C \overset{59}{=} O$.

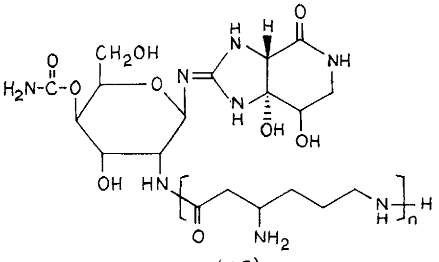
The structures of the heteropentasaccharide components of the sporaviridin complex, viridopentaoses A, B and C, have been revised (see Vol. 13, p. 158) to the structures (42) - (44) on the basis of further chemical degradation and ^{1}H-n.m.r. evidence.[92] These structures have been confirmed by matrix-assisted molecular secondary ion mass spectral (SIMS) results, considered to be a valuable technique for the analysis of polar molecules,[93] and CD measurements on benzoylated derivatives.[94]


(42) A ; $R^1 = H$, $R^2 = OH$
(43) B ; $R^1 = H$, $R^2 = NHAc$
(44) C ; $R^1 = R^2 = OH$

The first total synthesis of streptothricin F (45) has been achieved starting from D-glucosamine,[95] confirming its structure (see also Vol. 15, p.193), for which further evidence has been given.[96, 97]

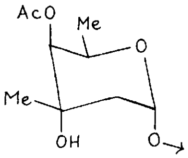
The antibiotics chrysomycin A and B$_1$, have been shown to contain 3-C-methyl-6-deoxy-L-gulopyranose instead of the

6-deoxyhexofuranose present in the related gilvocarcin complex.[98]

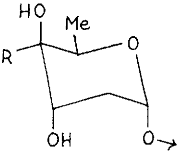


(45)

The structures of the anti-tumour antibiotics trioxacarcins A-C have been elucidated. They contain branched-chain sugars (46) and (47) glycosidically α -linked to a complex polycyclic aglycone.[99]



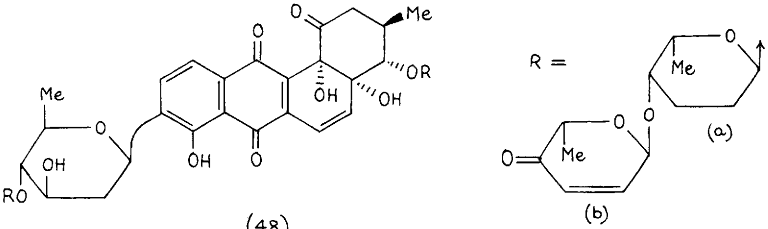
(46)



(47) R = CH(OH)Me or Ac

The relative configuration of the oxiran groups present in the side chain of the aglycone in hedamycin (see Vol. 13 p.172) and pluramycin A have been deduced by spectroscopic comparison with model compounds.[100]

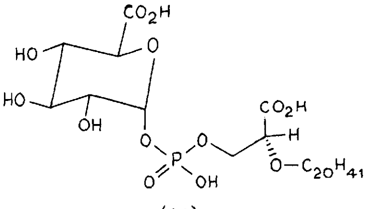
The absolute configuration of the antitumour antibiotic vireomycin A_1 (48) has been established by characterization of its O-glycosidic components, α -L-rhodinose (2,3,6-trideoxy-L-



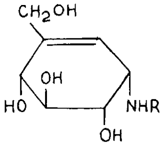
(48)

threo-hexopyranose) [unit a] and α-L-aculose(2,3,6-trideoxy-L-*glycero*-hex-2-enopyranos-4-ulose) [unit b], and by comparison of the data with previous X-ray crystal structure data (see Vol. 15, p.234, ref. 65). The sugar residues were hydrogenated prior to methanolysis, giving a 4-ulose and a completely saturated product.[101] Vineomycin B contains the same carbohydrate chains as vineomycin A$_1$.[102]

The structural analogues (49) of moenomycin A have been synthesized by condensation of chiral glyceric acid derivatives with peracetyl-D-glucose-1-phosphate.[103]



(49)



(50)

R = Alkyl or Aralkyl

A series (24 compounds) of *N*-substituted valienamines (50), which are α-glycosidase inhibitor analogues of valienamine (50, R=H), have been synthesized. *N*-Alkyl and *N*-aralkyl derivatives all showed inhibitory activity, some more than the parent compound. By contrast *N*-acyl derivatives either lack activity or are very weak inhibitors, suggesting that the antibiotic works by interacting with the acidic proton on the enzyme.[104]

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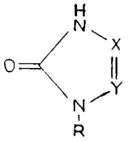
19
Nucleosides

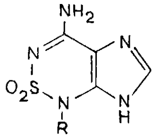
Reviews have appeared on the chemistry and biological properties of aza- and deaza- nucleosides,[1] the use of organometallic intermediates in the synthesis of nucleoside analogues,[2] potential antiviral nucleosides,[3] and nucleosides, nucleotides and nucleic acids.[4]

1 Synthesis

Standard procedures involving the condensation of glycosyl esters or halides with heterocyclic bases have been employed to prepare *N*-(β-D-ribofuranosyl) derivatives of azolinones (1),[5] 5-mercaptouracil,[6] 6-aza-3-deaza analogues of uracil and cytosine,[7] 1-H-imidazo[4,5-b]pyridine (including β-D-xylofuranosyl and α-L-rhamnopyranosyl derivatives),[8] quinoxalin-2-one and quinoxaline-2,3-dione,[9] 3-hydroxypyrazole,[10] 1,2,6-thiadiazine-1,1-dioxide derivatives (2) (and its 8-oxa analogue),[11] pyrazolo[3,4-d]pyrimidine derivatives,[12] 4-ethoxycarbonylamino-5-methylimidazole (ribose attached to either ring nitrogen),[13] and the quinazolinone-pyrazole bases (3) and (4).[14]



(1) X,Y = CH or N



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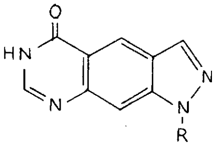

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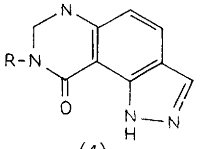


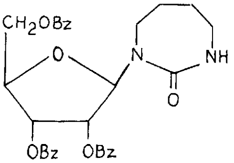
(4)

R = β-D-Rib-*f*

Mercury (II) oxide catalysed the formation of the *O*-glycoside from a silylated cyclic urea, which rearranged to the more stable *N*-glycoside (5) in the presence of mercury (II) bromide.[15] A phase transfer procedure has been used to prepare the α- and β-anomers of 7-deazaguanosine, the former being predominant using 50% aqueous sodium hydroxide.[16]

The synthesis of nucleosides using iodotrimethylsilane has been modified to a 'one-pot' procedure with a mixture of chlorotrimethylsilane and sodium iodide; uracil derivatives of D-ribose and D-xylose were conveniently prepared.[17]

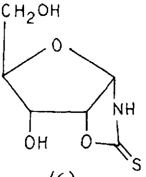
The synthesis of 1-β-D-arabinofuranosylcytosine and some derivatives has been reviewed.[18] Syntheses reported for other ara-nucleosides include spongo-uridine,[19] ara-tubercidin,[20] and the α- and β-anomers of ara-7-deazaguanosine prepared by phase-transfer catalysis.[21,22] Conventional methods have been used to prepare D-glucofuranose derivatives of uracil and thymine,[23] a β-D-glucopyranosyl derivative of nicotine,[24] and 9-(3,4-anhydro-6-deoxy-α-L-talopyranosyl)-6-benzoyl-adenine from L-rhamnose.[25]



(5)

The synthesis of pyrimidine nucleosides from glycosyl bromides having the 2-hydroxy group unsubstituted gave 1,2-<u>trans</u> products stereospecifically; the mechanism of the reaction was discussed.[26]

The ribofuranosyl-oxazolidine thione(6) has been used as a source of α-ribofuranosyl imidazole derivatives leading to purine and 2-azapurine α-nucleosides.[27] D-Arabinose or D-ribose reacts with cyanamide to yield isomeric 2-amino-1,2-oxazolines (7), which are useful intermediates for nucleoside synthesis.[28] The P-N ylide (8) has been used to prepare tetrazole nucleosides by conversion to the diimide (9) with isocyanate and subsequent azide cyclo addition.[29] Conversely, glycosyl azides undergo cyclo-



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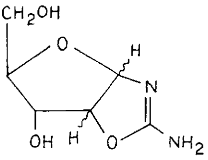

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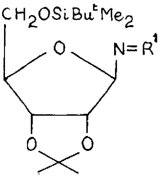
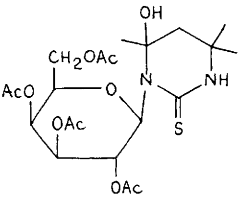


(8) $R^1 = PPh_3$

(9) $R^1 = C{=}NR^2$



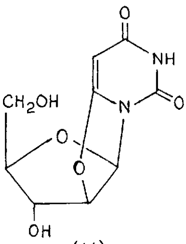
(10)

addition with acetylene derivatives to give triazole nucleoside analogues (see Vol. 5, p. 77, ref. 358); derivatives of allose, arabinose, mannose, and ribose were prepared in an improved procedure.[30] Glycosylation of tetra-*O*-acetyl-β-D-galactopyranosyl isothiocyanate with 4-amino-4-methyl-2-pentanone yielded the β-ureido nucleoside (10).[31] Similarly a D-ribosyl isothiocyanate yielded a urea derivative with 1-amino-2,2-diethoxyethane which could be cyclized to the imidazole-2-thione nucleoside.[32]

Condensation of 5,6-diamino-1,3-dimethyl-uracil with D-xylose yielded an acyclic Schiff-base of the sugar which on acetylation yielded the corresponding xylopyranosylamine which in turn was further elaborated to give 7-xylopyranosylxanthine.[33]

2 Anhydro- and Cyclo-Nucleosides

The rate of formation of 6,2'-anhydro-β-D-arabino-, 6,3'-anhydro-β-D-xylo-, and 6,5'-anhydro-β-D-ribo-furanosyluridines, (11)-(13) respectively, on treatment of the corresponding 5-iodouracil nucleosides with sodium methoxide has been found to be in the order of (11)>>(12)>(13), corresponding to the ease of formation of 5,6 and 7-membered rings, respectively. The ease of acid hydrolysis was in the reverse order. The same relative ease of cyclization has been observed with the cytidine nucleoside analogues. The 6,3'-anhydride (12) and its cytidine analogue (14) are the first examples of this class of cyclopyrimidine nucleoside.[34]



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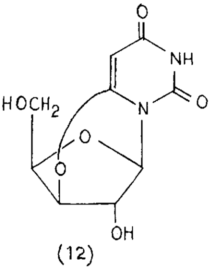

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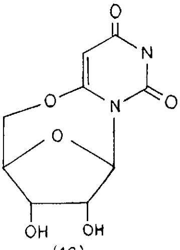

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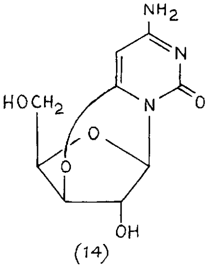
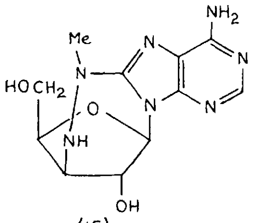


(14)

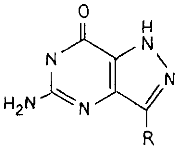
Treatment of 5-fluorocytidine with acetylsalicyloyl chloride yielded *O*^{2},2'-cyclo-β-D-arabinofuranosyl-5-fluorocytosine, which on hydrolysis afforded β-D-arabinofuranosylcytosine.[35] A general procedure for the synthesis of specifically labelled pyrimidine ribonucleosides, including [5'-^{18}O] and [*O*-2,5'-$^{18}O_2$]-uridine, utilizes *O*-2,5'-anhydro-2',3'-*O*-isopropylideneuridine with [^{18}O] sodium hydroxide.[36,37] 6,5'-Cyclo-5'-deoxyuridine has been prepared from 2',3'-di-*O*-isopropylidene-5-chlorouridine by sequential bromination at the C-5' position, 6,5'-cyclization with tributylstannane, dehydrochlorination, and deacetonation.[38,39] The cyclization of a 8-methylhydrazinyl-adenosine 3'-sulphonate yielded the N-cyclo-nucleoside analogue (15).[40]



(15)

3 C-Nucleosides

An efficient conversion of formycin to 5-amino-formycin B (16) via the pyrazole intermediate (17) has been described,[41] a ribosyl thiophen derivative has been converted to the inosine isostere (18),[42] and the pyrazole C-nucleoside (19) has been prepared



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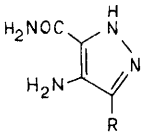

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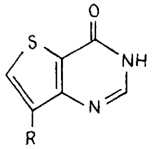

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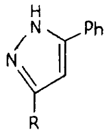


(19)

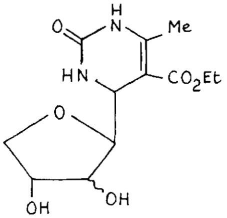
R = β-D-Rib*f*

from 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose by sequential phenylethynylation, oxidation, and cyclization of the resulting ynone with hydrazine.[43]

Other 2,5-anhydro-aldehydo-sugars have been used to prepare *threo*- and *erythro*-*C*-glycosides of dihydrouracil, *e.g.*, (20),[44,45] and the α-dihydrouracil *C*-glycoside of D-arabinose (21) from a dithioacetal of 2,5-anhydro-D-mannose prepared from D-glucosamine.[46]

The synthesis of pyrazofurin A (the 4-hydroxy analogue of (17)) and its α-anomer pyrazofurin B by a Wittig condensation on a ribose derivative is mentioned in Chapter 3 (ref. 183). Further references to antibiotic C-nucleosides occur in Chapter 18. C-Nucleosides of indoles have been prepared by glycosylation using ribosyl chloride derivatives.[47]

An improved procedure for the synthesis of 2'-deoxy-*C*-nucleosides for the corresponding *C*-ribonucleosides involves sequential 3',5'-



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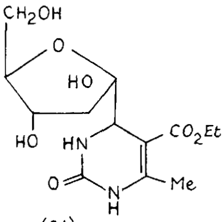
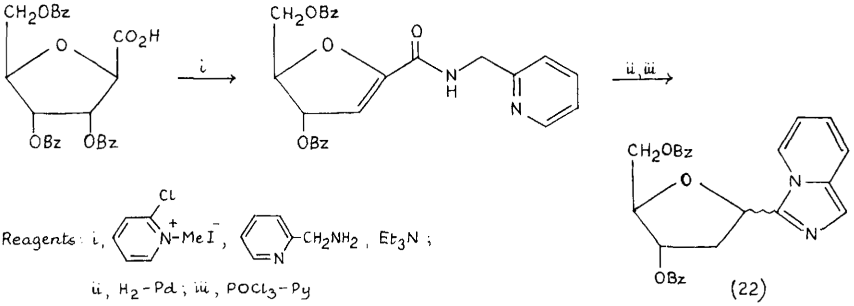


(21)

protection using the tetraisopropylsiloxanyl group, conversion to the 2'-*O*-[(imidazol-1-yl)thiocarbonyl] ester, and reduction with tributylstannane.[48,49] 2'-Deoxyribo-*C*-nucleosides, *e.g.*, (22), have been synthesized from 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid, using the elimination-reduction sequence outlined in Scheme 1. Other heterocyclic methylamines were used to prepare tri- and tetra-aza analogues of (22).[50]



Scheme 1

The reactions of glycals with [1,3-dimethyl-2,4(1H,3H) pyrimidinedion-5-yl] mercuric acetate in the presence of a stoichiometric amount of $LiPd(OAc)_4Cl_2$ results in regio- and stereospecific C-C bond formation between C-5 of the pyrimidine and C-1 of the sugar. The regiospecificity derives from exclusive approach of the metallopyrimidine to the face opposite that bearing the allylic acetate group.[51,52]

4 Amino- and Azido-Sugar Nucleosides

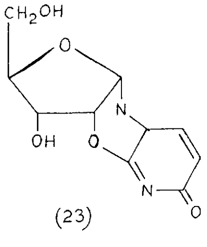
Several azido- and amino-sugar nucleosides have been shown to exhibit antiviral and antitumour properties, which has triggered interest in their synthesis. In general, aminosugar nucleosides have been prepared from their corresponding azido derivatives. Synthetic approaches to 6-substituted 9-(3-azido-3,4-dideoxy-β-DL-erythro-pentopyranosyl) purines have been described.[53] A mixture of 3'-amino-3'-deoxyguanosine and its α-anomer (α:β, 1:3) has been obtained from 3'-amino-3'-deoxyadenosine by exchange of the base moiety through an acetolysis-N-glycosylation sequence.[54] 5'-Azido- and 5'-amino-5-fluorouridine, among other derivatives, have been prepared by standard sulphonate-displacement procedures.[55,56] Analogues of (E)-5-(2-bromovinyl)-2'-deoxyuridine modified in the 2'-, 3'- or 5'-position with halo-, azido- or amino- groups have been synthesized, and similar modifications were carried out on ara-uridine. (E)-5-(2-Bromovinyl)-3'-amino-2',3'-dideoxyuridine showed the greatest potency as an antiherpes agent in vitro.[57]

5'-Azido-5'-deoxy-nucleosides and 5'-azido-2',5'-dideoxy nucleosides have been prepared by a polymer support method, using polystyrenesulphonyl chloride reagent in conjunction with lithium azide,[58] which on triphenylphosphine reduction yielded the corresponding amino-sugar nucleosides.[59]

Disaccharide nucleosides have been prepared in which neuraminic acid is glycosidically 5'-linked (by Königs-Knorr procedures) to 5-fluorouridine or inosine, giving derivatives with useful immunological activity.[60,61] The 2-nitroimidazole N-glycoside of neuraminic acid has also been reported.[62]

5 Halo- and Deoxy-nucleosides

The synthesis of a series of 2'-fluoro-5-substituted arabinofuranosyl-cytosines and -uracils has been described. 5-Methyluracil and 5-iodocytosine derivatives were the most effective against herpes simplex virus. The arabino configuration was essential for antibiotic activity, and corresponding chloro and bromo analogues were less effective.[63] 5'-Bromo-, 5'-fluoro-, and 5'-iodo-derivatives of 5-fluorouracil have been prepared conventionally.[55] The α-anomer of 5'-fluoro-5'-deoxyuridine has been synthesized from a 1,2-oxazoline derivative of 5-deoxy-5-fluoro-D-ribose, in turn prepared by a sulphonate displacement using pyridinium fluoride.[64] Treatment of 1-(α-D-arabinofuranosyl)-uracil with diphenylcarbonate yielded the 1,4-oxazin derivative (23) which yielded the 2'-chloro-2'-deoxy-arabino-α-nucleoside (24) on chlorination; this was then reduced to the 2'-deoxy analogue (25).[65] 5-Fluorouridine has been conv converted to 5'-deoxy-5-fluorouridine via a 5'-iodo-intermediate.[66]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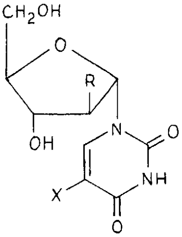
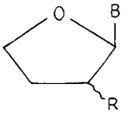
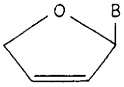

(24) R=Cl
(25) R=H

There have been many reports of syntheses of deoxy nucleosides by standard sugar-base condensation reactions. These include 5'-deoxy-ribo nucleosides and 5'-mono- or 5",5-di-deuterated analogues, as well as derivatives of 5-deoxy-D-xylose and 5-deoxy-D-glucose,[67] 5-alkylated thymidine derivatives,[68] 2'-deoxy-6-methyl-5-azacytidine and its α-anomer,[69] the thymidine analogue 4-(2-deoxy-β-D-*erythro*-pento-furanosyl)-6-methyl-1,2,4-triazine 3(HH)-one-1-oxide,[70,71] 6-aza-3-deaza analogues of 2'-deoxycytidine and 2'-deoxyuridine,[7] 3'-deoxycytidine from a 3-deoxyribofuranose obtained from a fermentation broth producing the 3'-deoxy nucleoside antibiotic, cordycepin,[72] 4-deoxy-DL-*threo*-pentopyranosyl pyrimidine nucleosides,[73] and 5'-*C*-methyluridines derived from 6-deoxy-D-allose and 6-deoxy-D-talose.[74] [75] A range of 1-(tetrahydro-2-furanyl)-5-fluorouracils, variously substituted in the furan ring, *e.g.*, (26), have been synthesized and tested for antitumour activity; the glycal (27) showed the greatest activity.[76]


(26) R=H,OH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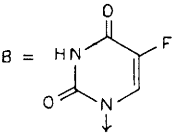
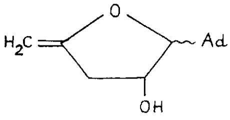


6 Unsaturated Nucleosides

3',5'-Dideoxy-5'-iodoadenosine has been converted to the corresponding 4'-eno derivative (28) by treatment with DBU in DMF; an earlier reported synthesis from the same laboratory is corrected (the product now shown to have been cordycepin).[77] Glycosylation of N^4-benzoylcytosine with 3,4-di-*O*-acetyl-L-*erythro*- and -D-*threo*-pent-1-enopyranoses led to the expected 4-*O*-acetyl-L and D-*glycero*



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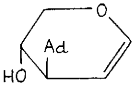

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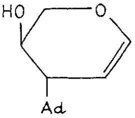


(30)

Ad = Adenin-9-yl

pent-2-enopyranosyl nucleosides, whereas glycosylation of benzoyladenine with the above glycals gave the C-3 nucleosides (29) and (30) in which the 4-hydroxy group and base are trans-related.[78]

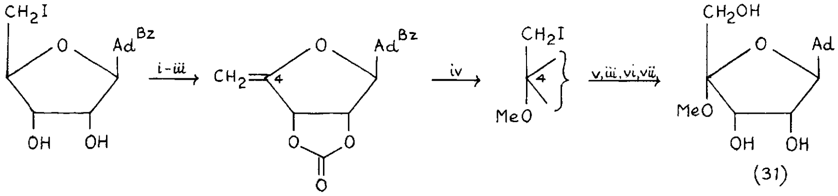
7 Branched-chain Sugar Nucleosides

A general route to 3'-C-alkyl nucleosides from readily available 1,2:5,6-di-O-isopropylidene-3-C-alkyl-α-D-allofuranose has been developed.[79]

8 Keto-sugar and Uronic Acid Nucleosides

The 5'-Carboxylic acid derivative of 5-fluorouridine has been described.[56] The glucuronide methyl esters of 2-hydroxy- and 2-mercapto-pyrimidine, and of 4-hydroxy- and 4-mercapto-pyrimidine have been prepared by standard methods using pyrimidinols with appropriate sugar derivatives.[80]

Scheme 2 outlines the synthesis of the glycosulose nucleoside derivative, 4'-methoxyadenosine (31), involving stereospecific addition of methoxy-iodine to a 4',5'-unsaturated nucleoside intermediate; other 5'-substituted analogues of (31) were prepared by standard displacements on the 5'-iodo-precursor.[81]



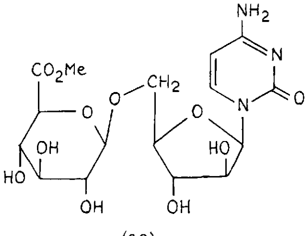
(31)

Reagents: i, $COCl_2$-Py; ii, DBN-Py; iii, BzCl-Py; iv, I_2-MeOH-$PbCO_3$; v, $Ba(OH)_2$; vi, LiOBz-DMSO; vii, NH_3-MeOH

Scheme 2

Some disaccharide derivatives have been reported. 1-(β-D-Arabinofuranosyl)-cytosine 5'-O-glucuronide (32) has been prepared from a 5'-trityl-arabino-nucleoside precursor by standard 5'-

glycosidation with methyl acetobromoglucuronate. By contrast, treatment of an analogous 5'-O-tritylribofuranosyl 1,2,4-triazole-3-carboxylate with this acetobromo sugar in the presence of silver perchlorate gave the simple glucuronyl nucleoside analogue (33).[82]



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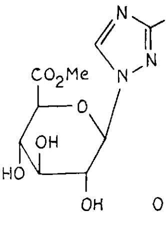

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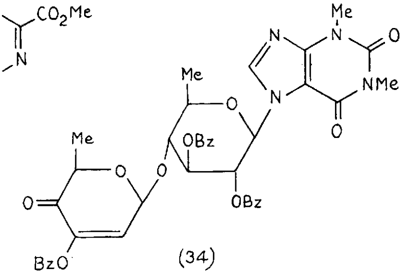


(34)

The keto-disaccharide nucleoside analogue (34) has been synthesized from β-cellobiosyl or β-D-glucopyranosyl derivatives of theophylline. 6'-Deoxygenation of the glucosyl derivative followed by glycosylation to the disaccharide with subsequent standard conversion of the terminal unit to the unsaturated keto sugar was found to be preferable because of the unreactivity of the 6'-hydroxy group in the cellobiose precursor.[83]

9 Ethers and Acetal Nucleosides

The 2'-hydroxy group of adenosine can be selectively blocked as a 4-methoxybenzyl ether, a new protecting group, by treatment with 4-methoxybenzyl bromide and sodium hydride. A mixture of the 2'- and 3'-ethers results if p-methoxyphenyl diazomethane is used in presence of stannous chloride. The ether protecting group was rapidly cleaved with trityl tetrafluoroborate.[84]

Tetrahydrofuranyl derivatives of uridine and 2'-deoxycytidine, either partially or completely O- and/or N-substituted, have been prepared from the nucleoside with dihydrofuran. The protecting group may be removed either by dilute acid or by treatment with microsomal non-specific oxidases.[85] 3'-O-tetrahydrofuranyl-N-benzoyladenosine[86] and a 5'-O-dimethoxytrityl-arabinosyl-adenine derivative[87] have been prepared conventionally for use in ribo-oligonucleotide synthesis.

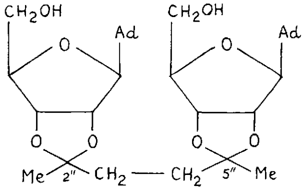
Boron trichloride selectively cleaves benzyl ether groups on the sugar in the presence of 6-methoxy or 6-methylthio substituents in the base moiety of 7-deaza-purine nucleosides.[88]

Good yields of 2'-O-methyl or 2'-O-tertbutyldimethylsilyl derivatives of uridine result on standard sugar-base condensation synthesis of these unsymmetrically substituted nucleosides, β-products forming in spite of the absence of an ester participating group at C-2'.[89]

Selective 2'-O-silylation of ribonucleosides occurs in presence of nitrate or perchlorate ion, whereas 1,4-diazobicyclo[2,2,2]-octane and silver ion lead to selective reaction at O-3'. In this way 2',5' and 3',5'-disilylated nucleosides can be prepared with high selectivity.[90] 2'- and 3'-Mono-tetbutyldimethylsilyl ethers of standard nucleosides have been prepared by partial silylation of 5'-O-(4-methoxytrityl) ether intermediates. These ethers could be isomerized in aqueous pyridine.[91] The selective protection of arabino nucleosides[92] and xylo-adenosine[93] with t-butyldimethyl groups has also been described.

Treatment of 5'-bromo- or 5'-chloro-5'-deoxy-ara-cytosine with basic ion-exchange resin yields the 2',5'-anhydro nucleoside; biochemical studies suggest that the anhydro nucleoside is the effective cause of the biological activity of the halo-nucleoside precursors.[94]

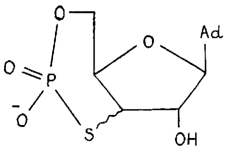
Treatment of adenosine with 2,2,5,5-tetraethoxy-ethane yields diasteomeric forms of the bis-acetal (35) (S,S and R,S on acetal carbon), which were of interest in studying stacking effects and their influence on enzymatic deamination.[95]



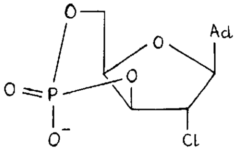
(35)

10 Nucleoside phosphates

As usual, standard syntheses of nucleotides are not included in this survey. 5'-(β-D-Glucopyranosyl) monophosphates of nucleosides and 2'-deoxy-nucleosides have been synthesized by orthoester glycosylation of the 5'-phosphates.[96] Deoxy-nucleoside 5'-monophosphates have been prepared from unprotected nucleosides by treatment with phosphorus oxychloride in trialkylphosphite followed by incubation with nuclease P1, which cleaves the contaminating 3'-monophosphates and 3',5'-diphosphates back to the parent nucleoside and 5'-phosphate. The procedure can be adapted to a wide range of alkylated nucleosides.[97] A simple and rapid method has been described for synthesizing nucleoside 5'-monophosphates enriched with oxygen-17 or oxygen-18 using labelled phosphorus oxychloride.[98] A series of 3',5'- and 2',5'-cyclophosphates (36)-(38) of modified-sugar adenine nucleosides have been prepared by standard methods, the xylo isomer of (36) exhibiting biological activity.[99]



(36)



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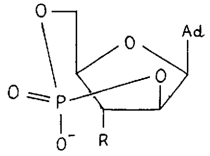
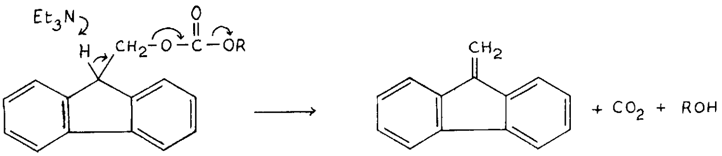


(38) R=Cl, NH_2

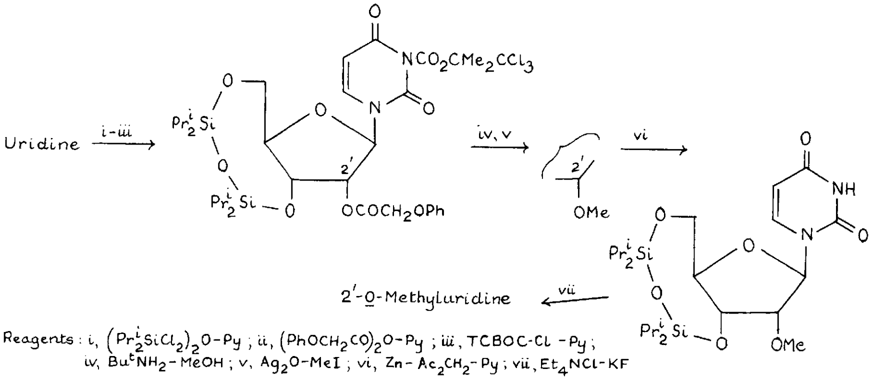
11 Other Ester Derivatives

5'-O-Toluene-p-sulphonyl and 5'-O-methanesulphonyl derivatives of 5-fluorouridine have been prepared and tested chemotherapeutically as prodrugs for 5'-deoxy-5-fluorouridine.[55] The value of the fluoren-9-ylmethoxycarbonyl (FMOC) group for the protection of the 5'-hydroxy group in nucleosides has been demonstrated. It can be removed under sufficiently mild basic conditions (triethylamine-pyridine) to leave other base-labile groups, e.g., laevalinyl, intact. The probable mechanism is shown in Scheme 3. The selective removal of other protecting groups in its presence has also been examined.[100]



Scheme 3

A new protecting group, 2,2,2-trichloro-tert-butyloxycarbonyl (TCBOC) has been employed to protect the imido unit of uracil in a synthesis of 2'-O-methyluridine (Scheme 4), the group being selectively removed using zinc in pentan-2,4-dione/pyridine.[101]



Reagents: i, $(Pr^i_2SiCl_2)_2O$-Py; ii, $(PhOCH_2CO)_2O$-Py; iii, TCBOC-Cl-Py; iv, Bu^tNH_2-MeOH; v, Ag_2O-MeI; vi, Zn-Ac_2CH_2-Py; vii, Et_4NCl-KF

Scheme 4

The 3'-O-formyl ester of 5'-O-(dimethoxytrityl)-2-deoxy-nucleosides has been prepared using formic anhydride and pyridine. The small size of the formyl group together with its ease of removal makes it useful in oligonucleotide synthesis.[102] Adenosine nucleosides have been regiospecifically 3'-O-succinoylated using succinic anhydride in presence of dibutylstannyl chloride and pyridine.[103] Regioselective 2'-carbamoylation of ribonucleosides can be achieved using amines and phenyl isocyanate, the selectivity being greatest with diisopropylethylamine.[104] On the other hand, sequential treatment of ribonucleosides with bis(tributyltin)oxide and phenylisocyanate or phenylisothiocyanate yielded 5'-O-carbonyl derivatives with high regiospecificity.[105]

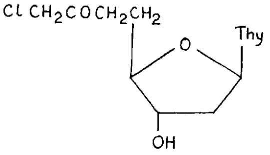
12 Reactions

The rates of hydrolysis of 5'-tri- and -di-phosphates of adenosine and 2'-deoxyadenosine have been compared. Above pH 5, hydrolysis involves mainly or exclusively cleavage of the polyphosphate chain, whereas below pH 4, cleavage of the N-glycosidic bond occurs primarily, although not as rapidly as in 2'-deoxy-purine-nucleoside analogues.[106] An ^{1}H-n.m.r. study of the borohydride reduction of periodate-oxidized nucleotides indicates that the two aldehyde groups are sequentially reduced in the order of 3'>2', the intermediate being the 3'-alcohol, 2'-aldehyde.[107] Periodate oxidation of ATP gives a single product, a potential affinity reagent, which exists in aqueous solution as an equilibrium mixture of three dialdehyde monohydrates and a dihydrate, the former being diastereomeric cyclic hemiacetals. Borohydride reduction gave the expected diol.[108] Treatment of the dialdehyde obtained from lead tetraacetate oxidation of N, O-5'-ditritylated adenosine with Wittig reagents yielded the corresponding acyclic di-alkenes, which however show cytotoxic rather than the desired antiviral activity.[109]

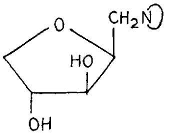
The treatment of nucleosides with N,O-diacetyl-hydroxylamines in water or acetone causes alkylation of the bases, whereas in phosphate buffer at the same pH adenosine and guanosine are acetylated on the ribose units.[110]

13 Miscellaneous Nucleoside Analogues

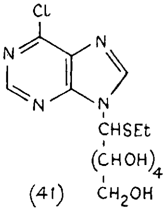
The thymidine analogue (39) has been prepared by a Wittig reaction on 5'-aldehydo-thymidine.[111] Reaction of 5-chloro-5-deoxy-1,4-anhydro-DL-xylitol with nucleoside bases yielded the racemic nucleoside analogues (40).[112,113] Condensation of sugar dithioacetals with 6-chloro-purine yielded the acyclic thio-aldityl-heterocyles (41),[114] the D-glucitol derivatives then being selectively oxidized by Acetobacter suboxydans to yield the ketose nucleoside analogue (42).[115] Michael addition of uracil to 3-O-acryloyl or 6-O-acryloyl derivatives of glucose provides corresponding 3-(uracil-1-yl)propanoyl derivatives of D-glucofuranose (43) which are analogues of anti-tumour nucleosides.[116]



(39)



($\pm$)(40)(N = A,C,U)



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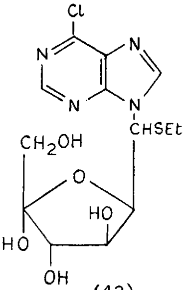
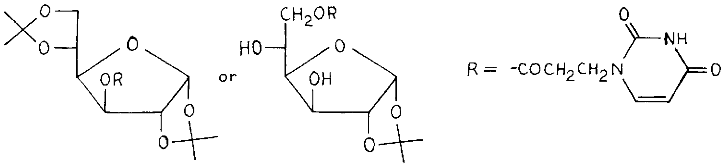


(42)

14 Structure, Conformation, and Spectral Studies

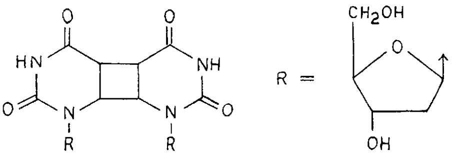
Crystal structures of 67 nucleosides and nucleotides have been examined in connection with calculations of orthogonal coordinates of the bases; the evidence suggests that the mean geometry of each



(43)

base residue is exactly or almost exactly planar.[117]

The crystal structures of pyridin-4-one nucleoside[118] and 5-bromo-2'-deoxycytidine have been reported.[119] The conformation of thymidine 3',5'-cyclopyrophosphate has been studied by ^{1}H- and ^{31}P-n.m.r. and atom-atom potential calculations; agreement with experimental values can be achieved if in aqueous solution the compound exists as an equilibrium mixture of conformers (1:1, ratio) with the sugar ring either in the ^{3}E or $_{1}$E conformation and with a crown cyclodiphosphate ring.[130] An apparent correlation of C-1' chemical shifts with vicinal coupling constants for H-1' and H-2' protons in nucleosides is ascribed to 1,2-eclipsing interactions between the O-2' oxygen and the heterocyclic nitrogen atom in an S-type conformation.[121] Base-sugar conformations of a number of adenosine derivatives have been studied by n.m.r. and c.d. measurements, confirming previous assignments; the significance of these for chemical properties such as the formation of 5',8-cyclo derivatives is discussed.[122] An exception to the Imbach rule for determining the anomeric configuration of 2',3'-O-isopropylidene-ribofuranosyl nucleosides has been reported. The rule suggests that the chemical shift difference between the isopropylidene methyl proton resonances is$<$0.15 p.p.m. for α- and $>$0.15 p.p.m. for β-nucleosides. However, for β-uridine derivatives bearing an anisotropic substituent on C-6 (base), e.g., nicotinyl, values of $\Delta\delta$ can be $<$0.15 p.p.m. The rule is founded on the anisotropic effect of the aglycone in the α-nucleosides, and evidently the C-6 substituent can fulfil a similar role in these β-nucleosides.[123] The ^{13}C-n.m.r. spectrum of 2'-fluoro-2'-deoxyadenosine 3',5'-cyclophosphate has been unambiguously assigned utilizing ^{13}C-^{19}F coupling constants, allowing a definitive solution to the disputed assignment of C-3' and C-4' signals in other 3',5'-cyclophosphates.[124] Two-dimensional ^{1}H-n.m.r. of *cis-syn*-mesocyclobutadi-2'-deoxyuridine (44) has been studied.[125] The solid ^{13}C-n.m.r. spectra of cytidine, uridine, adenosine and



(44)

guanosine have been measured by using the combined techniques of high-power proton decoupling, cross-polarization and magic angle spinning. Well resolved spectra were obtained at 50 MHz. Those for uridine and guanosine revealed two distinct conformations for the sugar ring.[126] ^{1}H-n.m.r. and chemical evidence has been presented to show that the major products of the β-galactosidase-induced transfer of galactosyl residues from *o*-nitrophenyl β-D-galactoside to uridine, inosine and adenosine are the 3'-*O*-(galactopyranosyl)-ribonucleosides.[127]

The influence of metals on the ^{13}C-n.m.r. spectrum of guanosine and inosine in DMSO has been studied.[128] The effect of metal (Zn^{2+}, Ba^{2+}, Hg^{2+}) ion complexing with adenosine, cytidine and guanosine has been investigated by ^{15}N-n.m.r. spectroscopy; metallated nitrogens are shielded.[129]

The mass spectra of TMS derivatives of nucleosides selectively labelled with deuterium and oxygen-18 have been recorded.[130] The position of chlorine atoms in the carbohydrate ring of chloro-deoxy-nucleosides can be established from their mass spectrum.[131] The desolvation of nucleoside hydrates in the crystal proceeds along a direction corresponding to one of the crystallographic axes.[132] Ultrasonic methods have been used to study hydration of pyrimidine nucleosides and of D-ribose itself in aqueous-ethanolic solution. Variations in ultrasonic wave velocity with alcohol concentration could be related to the extent of interaction of the sugar hydroxy groups with water.[133]

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N. M. R. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

The use of n.m.r. spectroscopy in the study of mono- and oligosaccharides, covering both ^{1}H and ^{13}C data, as well as data from other nuclei has been reviewed.[1]

A comparison of theoretical M.O. methods for the calculation of carbohydrate conformations has led to the conclusion that CNDO/2 is the most reliable. The energies of the conformers of α- and β-D-glucose and α- and β-D-idose were calculated.[2] D-Glucitol, D-mannitol and galactitol have been subjected to a theoretical study and shown to prefer a planar zig-zag conformation in the absence of other effects. The energy difference between the bent chain and straight chain conformations is less for D-glucitol than for the other two alditols and solvent accessibilty studies suggest that the bent chain is adopted whereas D-mannitol and galactitol prefer straight chains. Since the energy difference is small, the lattice energy plays a large part in the favoured conformation in the solid state.[3] PCILO Semi-empirical quantum mechanical calculations on the disaccharide moiety of bacterial peptidoglucan have been reported, using chitobiose and glucosaminobiose as models to determine the side chain conformations and mutual orientation of the pyranose rings. In general, PCILO predicts similar results to other empirical methods, e.g., PCILO calculations suggest that a chitin-like structure is not adopted by the glycan moiety of the peptidoglycan, and removal of the N-acetyl group does not affect the relative orientation of the two sugar rings.[4]

Ab initio quantum mechanical methods have been used to compare the anomeric effects of thiosugars with their oxygen counterparts. The lower anomeric effect in sulphur systems was attributed to lower dipolar contributions to the total energy when compared with the oxygen systems.[5,6] N.m.r. spectroscopy has also been used to evaluate anomeric effects. An assessment of the generalized exo-anomeric effect used ^{13}C chemical shifts, ^{13}C-^{1}H couplings and n.O.e. studies of substituted 2-methoxy-1,3-dioxans.[7] By analysis of the ^{13}C-n.m.r. spectrum of 2-methoxytetrahydropyran in the range 143 - 165K, it was shown that ΔH^{o} is ca. 0 and ΔS^{o} is -2.7 calK^{-1} mol^{-1} for the conversion of the axial (α) conformer to the equatorial (β) conformer in an 85:15 mixture of trichlorofluoromethane-trichlorodeuteromethane.[8] Conformational energies of C-2 carbon-substituted tetrahydropyrans form the basis of an important paper on the conformational analysis of such compounds. The values obtained will be of use in the field of C-glycosides.[9] An exception to the Imbach criteria for determining the anomeric configuration of D-ribofuranosyl nucleosides has been reported (see also Chapter 19).[10]

An analysis based on the approach to the catalyst surface of various configurational isomers in the Koch and Stuart deuterium exchange for hydrogen at carbon atoms using Raney nickel and heavy water (see Vol. 12, ch. 2, p. 4, ref. 8) has elicited the criteria for the reaction; these include the requirement that at least two hydroxy groups must be present, that equatorial hydrogens are exchanged more rapidly than axial ones, and that the isomerization is kinetically controlled.[11]

Statistical calculations have been carried out to test different potential energy estimates of furanose pseudorotation. The furanose rings of ribonucleosides and their phosphates are shown to be more rigid than those of their 2'-deoxy counterparts, and it was suggested that this could account for the difference in flexibility between RNA and DNA.[12] Further calculations were carried out on these systems incorporating an additional "gauche" energy term to allow for the interactions of groups at C-4 and nitrogen functions at the anomeric centre.[13] The H-bonding system in the α-D-galactopyranose crystal and oxygen to hydrogen H-bond lengths have been the subjects of a theoretical calculation. Theory agrees completely with the system described by Ohanessian and Gillier-Pandraud (1976); however, values of torsion angles differ between theory and experiment, the discrepancy being greatest for the O-4-H group. This was attributed to inaccurate co-ordinates for the hydrogen atom of this group. The H-bonding system of Sheldrick (1976) could not be reproduced with a reasonable energy.[14]

Interactive computer programmes for the establishment and maintenance of an ^{1}H-n.m.r. data base, the prediction of ^{1}H-n.m.r. shifts, and the rank-ordering of structural candidates based on observed and predicted spectra, have been devised. The programmes take into account the configurations at chiral centres and at double bonds, as well as diastereotropy.[15] Further work using 2D-J spectroscopy has been published. The method has been applied to glucose, maltose, maltotriose, α-cyclodextrin, β-cyclodextrin and a dextran, and led to some reassignments of the ^{13}C-n.m.r. spectra of maltose and maltotriose.[16] Two new 2D-J spectroscopic techniques, COSY (2D correlation spectroscopy) and SECSY (spin-echo correlated spectroscopy), have been applied to trideuteromethyl 2,3,4,6-tetra-O-(trideuteroacetyl)-α-D-glucopyranoside as a simple example. These methods, employing non-selective two-pulse sequences, and requiring considerable data-handling capacity, produce two-dimensional plots to allow identification of coupled protons.[17] Deuterated and ^{13}C-selectively-enriched sugar derivatives have been studied by 2D-J spectroscopy in the ^{1}H and ^{13}C-n.m.r. experiments; the technique was shown to be suitable for separating chemical shifts and coupling constants into different frequency axes and has potential for the elucidation of biosynthetic pathways as well as structure determination. The compounds investigated were 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose, methyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside, 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose, and galactitol peracetate.[18] A new n.m.r. coupling constant-torsion angle relationship has been used for the conformational analysis of β-D-*ribo*-, β-D-deoxy-*ribo*-, β-D-*arabino*-, β-D-*xylo*-, and β-D-*lyxo*-nucleosides.[19]

An extension of a previously published procedure for determining ring-sizes and positions of isopropylidene acetals (see Vol.14, p.200, ref.56) has been reported.[20]

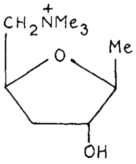
The metabolic fate *in vivo* of [U-^{13}C]glucose has been monitored by ^{13}C-n.m.r. spectroscopy.[21]

Sugars at very high concentrations have been examined by ^{1}H-n.m.r. and their anomeric resonances found to show additional temperature and concentration dependent lines which are assignable to anomeric protons of incompletely hydrated species. Solvation was deemed to be incomplete at concentrations of molar ratio greater than 1:2 (sugar:water).[22] Natural abundance one bond ^{13}C-^{13}C coupling constants for twelve free sugars, sucrose, and glycopyranosides have been measured; $J_{1,2}$ and $J_{5,6}$ values fell in the ranges 47.4 - 42.5 and 44.6 - 40.5 Hz respectively, whereas $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$, values were found between 41.0 and 37.4 Hz. Other correlations with configuration were found.[23]

D-Threose has been shown to contain 51% α-furanose, 38% β-furanose, 0.7 - 4.7% aldehyde and 10.2 - 7.1% aldehyde hydrate at equlibrium depending on temperature. By determination of ^{1}H and ^{13}C-saturation transfer n.m.r. spectra of [1-^{13}C]-D-threose and [1-^{13}C]-D-erythrose, unidirectional rate constants for interconversions of the species present were obtained.[24] Assignments of the signals of D-psicose in solution, in which both furanose and pyranose species are present, have been made by using differential isotope-shift measurements.[25]

2 Furanose Systems

The orientation of C1-O-H of 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose has been determined by measurement of ^{13}C-^{1}H coupling constants, n.O.e., spin-lattice relaxation rates for the relevant protons, and ^{13}C-relaxation times. The O-H bond was shown to be *anti* with respect to C-2 and forms an angle of *ca* 40° with C_1-H_1.[26] A paper recording ^{1}H-n.m.r. spectra of many D-fructofuranoside derivatives and their inferred conformations has appeared.[27] The conformation of (+)-muscarine (1) in solution has been determined using ^{1}H-n.m.r. Coupling constant values correspond to an equilibrium 71% in favour of the C_4-*endo* conformation in which the sterically demanding interaction of the trimethylamino group with the ring is minimized by making it pseudoequatorial.[28]



(1)

The conformations adopted in solution by 8-bromo-9-β-D-xylofuranosyladenine as determined by ^{1}H-n.m.r. using a modified Karplus equation has been compared with that found in the solid state by *X*-ray crystallography.[29] Solid state ^{13}C-n.m.r. spectra of cytidine, uridine, adenosine, and guanosine at 50 MHz gave well resolved signals; uridine and guanosine were found to exist in two distinct conformations for the sugar ring.[30] The base-sugar conformations of a number of adenosine derivatives have been confirmed by n.m.r. and c.d. measurements. The implications of the conformations for certain chemical properties, such as the formation of 5',8-cyclo-derivatives were discussed.[31]

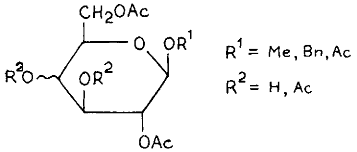
3 Pyranose Systems

The high field n.m.r. spectra of the hydroxy protons of twenty-three aldo- and keto-pyranose derivatives at 250 MHz in DMSO-d_6 have been reported, and the stereochemical dependence of *vic* *H*CO*H* and long-range coupling constants determined.[32]

It has been demonstrated that the use of ordinary, partially relaxed pulsed Fourier transform ^{13}C-n.m.r. data allows determination of tautomeric compositions with an accuracy comparable to those obtained by more sophisticated n.m.r. procedures. The method was applied to D-ribose, D-glucose, D-mannose, and D-fructose.[33] The spin-lattice relaxation rates of the ring protons of all eight D-pentopyranose tetra-acetates and of methyl α-D-xylopyranoside triacetate have been reported. These values are of qualitative utility in assigning configuration and conformation, since they are related to interatomic H-H distances by a reciprocal sixth power.[34] The ^{1}H- and ^{13}C-n.m.r. spectra of methyl mono-, di-, and tri-*O*-acetyl-α- and -β-D-xylopyranosides have been fully assigned. The effect of a single acetate substituent was to deshield the carbon by 0.4 - 2.1 p.p.m. and the proton by 1.2 - 1.6 p.p.m. at the site of attachment, to weakly deshield vicinal protons by 0.08 - 0.26 p.p.m., but to strongly shield vicinal carbons by 2.0 - 3.7 p.p.m. That these effects were additive was demonstrated by prediction of the spectra for the di- and tri-acetates. The effect on one-bond ^{13}C-^{1}H coupling was also invest- igated.[35] The ^{13}C-n.m.r. data for all the methyl mono-*O*-acetyl-α- and -β-D-xylopyranosides have been reported with the conclusion that the shift effects of individual acetyl groups are not additive in this series.[36]

^{1}H And ^{13}C-n.m.r. chemical shift data for the fully acetylated and all the acetylated mono-hydroxy glucose and galactose derivatives (2) have been recorded, and, with the aid of Eu(fod)$_3$, shifts were fully assigned.[37] 1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-gluco- and -manno-pyranose have been shown to adopt the $^{4}H_{5}$ conformation by ^{1}H- and ^{13}C-n.m.r. studies, the spectra being completely assigned.[38] The ^{1}H n.m.r. spectra of 2-*O*-tosyl-, 4-*O*-tosyl-, and 2,4-di-*O*-tosyl-derivatives of 1,6-anhydro-β-D-glucopyranose have been reported.[39]

The anomeric effect in 5-amino-D-glucopyranose (nojirimycin) in water has been found to be *ca.* 3 kJ mol^{-1} greater than in D-glucopyranose. This is in agreement with the predictions of qualitative perturbational MO theory.[40] ^{1}H- and ^{13}C-n.m.r. spectra of benzyl 2-acetamido-2,6-dideoxy- and 2,4-diacetamido-2,4,6-trideoxy-α-D-*gluco*- and -*galacto*-pyranoside derivatives have been fully analyzed.[41] The conformation of the oxazoline (3) earlier reported (Nashed *et al*, *Carbohydr. Res.*, 1980, *82*, 237) to be $^{O}S_{2}$, has been shown by ^{1}H-n.m.r. studies to have a distorted $^{4}H_{5}$ shape.[42] Based on a ^{1}H- and ^{13}C-n.m.r. study, the structures and conformations of the *N*-benzoyl



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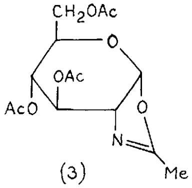
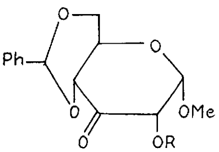


(3)

derivatives of the biologically important 3-amino-2,3,6-trideoxy-L-hexoses have been shown to be as follows: the L-*xylo*- and L-*arabino*-hexoses exist as mixtures of the α- and β-pyranoses, whereas the L-*ribo*- and L-*lyxo*-hexoses are mixtures of the anomeric pyranoses and furanoses; all the pyranoses adopt the $^{1}C_{4}$ (L) conformation exclusively except the L-*lyxo* which contains 15% $^{4}C_{1}$ (L); the α-L-*ribo*-furanose adopts the $^{1}T_{2}$ conformation while the β-L-*ribo*-furanose was found to take up the $^{2}T_{1}$ conformation.[43]

An analysis of the ^{13}C-n.m.r. spectra of the oxo-sugars of general formula (4) and (5) has been achieved by correlations with the spectra of the parent diols.[44] The regio- and stereochemistry of 3,4,6-trideoxy-3,4,6-trifluoro-α-D-galactopyranosyl fluoride (6) has been established by detailed multinuclear n.m.r. experiments.[45]



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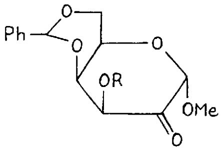

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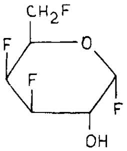
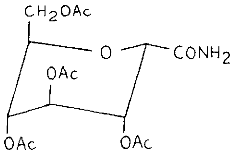


(6)

The ^{13}C-n.m.r. spectral characteristics, including T_1 and n.O.e. values, for methyl 3,4-*O*-(1-carboxyethylidene)-β-D-fuco- and -galacto-pyranosides have been recorded and compared with those of 4,6-*O*-(1-carboxyethylidene)-analogues. The acetal carbon resonance in the pyruvate acetal moiety is at 107 - 109.5 p.p.m. for 5-membered acetals, and 100.5 - 102.4 p.p.m. for 6-membered acetals. The chemical shifts of C-3 and of the pyruvate methyl protons are sensitive to the configuration of the 3,4-(1-carboxyethylidene) acetal.[46]

^{13}C-N.m.r. $^{3}J_{(C\text{-}1\ -\ H\text{-}3a)}$ values (*ca* 5 Hz) have been used to prove the β-anomeric configuration of (3-deoxy-D-*manno*-2-octulopyranosyl)ono (KDO) residues; spin-lattice relaxation times support the structure assignments.[47]

Conformations of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*ido*- (7) and -L-*gluco*- (8) heptonamides have been shown to be $^{2}C_{5}$ by *X*-ray crystallography.[48]



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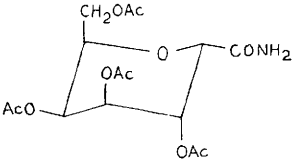


(8)

4 Acids and Lactones

Pilot experiments to enable an n.m.r. study of the process of lactonization of sugar acids in solution have been carried out.[49-52] Solution conformations of D-glucaric acid have been shown by ^{1}H- and ^{13}C-n.m.r. to consist of an equilibrium between the zig-zag and two sickle forms; D-glucaro-1,4-lactone adopts the $^{3}E \rightleftharpoons E_{3}$, D-glucaro-6,3-lactone the $^{4}E \rightleftharpoons E_{4}$, and D-glucaro-1,4:6,3-dilactone the ^{3}E:E_{4} conformation.[49] Similar analysis has shown that all four D-pentano-1,4-lactones exist as an equilibrium between ^{3}E and E_{3} conformations in which the C-2 hydroxy group is quasi-equatorial.[50] Preference for such an arrangement was also shown by D-mannono-, D-gulono-, and D-galactono-1,4-lactones, *i.e.*, equilibria between ^{3}E and E_{3} were displayed. The exception was D-glucono-1,4-lactone in which the C-2 hydroxy group prefers the quasi-axial arrangement.[51]

D-Glucono-, and D-mannono-1,5-lactone adopt the $^{4}\underline{H}_{3}$ and $\underline{B}_{2,5}$ conformations in aqueous solution respectively.[52] 2,3,4,6-Tetra-$\underline{O}$-acetyl-D-glucono-1,5-lactone also adopts the $^{4}\underline{H}_{3}$ conformation.[53]

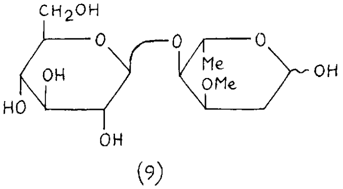
5 Oligosaccharides

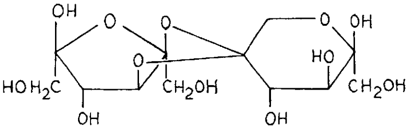
A review in Japanese on the ^{13}C-n.m.r. spectra of cellulose and related carbohydrates has been published.[54]

A graphical procedure based on ^{13}C-^{13}C coupling connectivity plots has been used to determine positions of glycosidic linkages. Cellobiose was used in the model to demonstrate the potential of the method.[55] An elegant ^{1}H-n.m.r. method for sequencing oligosaccharides uses a combination of 1D and 2D coupling analysis to identify the component monosacharides, and n.O.e. methods to determine the sequence.[56]

The structures of a number of oligosaccharides having L-arabinose at the reducing end have been studied by ^{1}H- and ^{13}C-n.m.r. spectroscopy.[57] A series of synthetic methyl β-glycosides of (1→4)-β-D-xylo-oligosaccharides of D.P. = 2-6 together with variously substituted derivatives have been used in ^{13}C-n.m.r. investigations.[58] Conformations of the alditol moieties in 6-$\underline{O}$-(α-D-glucopyranosyl)-D-mannitol, isomaltitol (whose crystal structure was determined), and their (1→4)-linked analogues have been compared, and the principles for predicting the preferred conformations in glycosylalditols generally were elaborated.[59] A study of n.m.r. spectra has suggested that a disagreement exists between predicted conformational stabilities and chemical shift data for α,α-linked disaccharides.[60] ^{1}H-N.m.r. data at 270 MHz have been reported for hepta-$\underline{O}$-benzoyl-derivatives of β-cellobiose, β-lactose and β-maltose in benzene.[61] Conformational analysis of gentiobiose octa-acetate has been carried out using proton J-values, relaxation data, and n.O.e. measurements and by hard-sphere calculations. The results were in accord with data for the solid state conformation of gentiobiose. In addition, ^{2}H-n.m.r. relaxation data have been used to estimate the relative motional correlation time of deuterated derivatives of glucose penta-acetate and gentiobiose octa-acetate in various solvents.[62] Sixteen synthetic methyl manno-oligosaccharides have been used in ^{1}H- and ^{13}C-n.m.r. investigations and the signals for the anomeric protons and anomeric carbon atoms in branched manno-penta-osides and

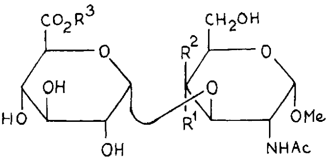
-hexa-osides assigned, based on data for methyl manno-biosides and -triosides. The correlations are thus of use in determining the branching patterns in mannans and manno-glycoproteins.[63] In connection with their use as model compounds for glycopeptides, the complete assignments of ^{1}H-n.m.r. spectra of synthetic methyl 3,6-di-O-(α-D-mannopyranosyl)-α-D-mannopyranosides and methyl 3-O- and 6-O-(α-D-mannopyranosyl)-α-D-mannopyranoside were made.[64] The ^{13}C-n.m.r. spectra of the four linkage isomers of methyl O-D-galactopyranosyl-β-D-galactopyranose and related D-galactobioses have been examined as models for D-galactopyranans. In the case of the β-linked biosides the glycosyloxylated carbon atoms have chemical shift values characteristic of the linkage position but limited variation was observed in C-1' chemical shift; for the α-linked counterparts, C-1' was sensitive to linkage position while the glycosyloxylated carbon chemical shift varied but little.[65] The structure of a new disaccharide, glaucobiose (9), from a Chinese drug, "Pai-Ch'ien", has been established on the basis of its ^{13}C-n.m.r. spectra and those of its methyl α- and β-glycosides.[66]


(9)


(10)

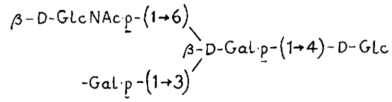
^{13}C-N.m.r. chemical shifts of methyl β-lactoside have been verified and its ^{1}H-n.m.r. spectrum fully assigned with the aid of specifically deuterated and/or ^{13}C-enriched samples. This disaccharide has a similar conformation in aqueous solution to that found in the crystal.[67] The conformational properties of sucrose have been studied by both detailed ^{1}H- and ^{13}C-n.m.r. studies and hard-sphere, exo-anomeric effect molecular modelling. Sucrose is a rather rigid molecule showing similar conformational preference about the glycosidic linkage and in intramolecular hydrogen bonding between O-1 and O-2 to that found in the crystalline state, even in dilute solution. This result is in contradiction of that reported by Mathlouthi et al from i.r. studies (see Vol.14, p.202, refs. 7,9 and Vol. 15, p. 12, ref. 54). The hydrophilic topography was compared with that of 1-chloro-1-deoxy-sucrose and saccharin in connection with sweetness studies.[68] Chapter 2 (ref.48) contains a description of the use of deuterium-induced differential isotope-shift experiments for determining tautomeric distributions in 4-*O*-glycosyl-fructose species. Eighteen free and substituted 1,6-anhydro-derivatives of reducing di- and tri-saccharides in deuterium oxide and deuteropyridine have been subjected to ^{13}C-n.m.r. analysis.[69] The magic-angle spinning, cross-polarization ^{13}C-n.m.r. spectrum of D-*threo*-2,5-hexodiulose in the solid state gave results which could be directly correlated with atomic positions previously found in an *X*-ray crystallographic analysis. The compound is a dimer (10), a structure which n.m.r. shows to be the predominant form in DMSO.[70]

All the ^{1}H-n.m.r. signals of a number of disaccharides related to hyaluronic acid and chondroitin sulphate in DMSO-d$_6$ solution have been assigned, including those of hydroxy and amino-groups. Evidence of inter-residue OH-4 and O-5' hydrogen bonding was obtained for the hyalobiuronate (11), but was absent in the chondrosinate (12), consistent with observations made on their polymers. Intra-residue hydrogen bonding of OH-4' and the uronate residue was also observed.[71] The influence of lone *O*-acetate and *O*-formate groups on the ^{1}H- and ^{13}C-n.m.r. spectra of carbohydrates was investigated during the study of the acylated oligosaccharides released from *Klebsiella* K63 extracellular polysaccharide by hydrolytic or bacteriophage depolymerization.[72]



(11) R^1=OH, R^2=R^3=H

(12) R^1=H, R^2=OH, R^3=Na



$$\begin{matrix} \beta\text{-D-GlcNAc}p\text{-}(1\to6) & \\ & \beta\text{-D-Gal}p\text{-}(1\to4)\text{-D-Glc} \\ \text{-Gal}p\text{-}(1\to3) & \end{matrix}$$

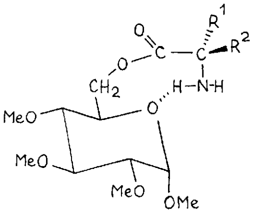
(13)

Preferred conformations of α-L-Fuc-(1→2)-α-D-Gal-(1→3)-β-D-Gal and α-L-Rha-(1→2)-[α-L-Rha-(1→3)]$_2$-β-D-GlcNHAc have been calculated on the basis of hard-sphere, exo-anomeric effect molecular models. The predicted energy minima were in good agreement with those from n.m.r. methods.[73] A 270 MHz ^{1}H-n.m.r. study of β-D-GalNAc-(1→3)-α-D-Gal-(1→4)-β-D-Gal(1→4)-β-D-Glc, a component of mammalian glycosphingolipids and a receptor for a pathogenic *E. coli*, has been carried out.[74]

The ^{13}C-n.m.r. spectrum of the branched tetrasaccharide (13), isolated from the milk of the tammar wallaby, has been reported along with those of related model compounds.[75] Evidence for a revised structure of viridopenta-oses A, B, and C, components of sporaviridin antibiotics has been obtained from 360 MHz ^{1}H-n.m.r spectra and chemical degradations.[76] Primary structures of fourteen neutral oligosaccharides from bronchial mucus glycoproteins have been determined by Vliegenthart's group using 500 MHz ^{1}H-n.m.r. spectroscopy. The same group has reported the characterization of the primary structure and microheterogeneity of oligosaccharide chains from porcine Blood-Group H substance using a similar technique.[78]

6 Glycopeptides

The ^{13}C-n.m.r. spectra of 3-O-α- and -β-D-xylopyranosyl L-serine and L-threonine, models for such residues in glycoproteins, have been reported.[79] ^{1}H- and ^{13}C-N.m.r. studies of methyl 2,3,4-tri-O-methyl-6-O-(L-phenylalanyl)-α-D-glucopyranoside (14) and methyl 2,3,4-tri-O-methyl-6-O-(D-phenylalanyl)-α-D-glucopyranoside (15), revealed that the LD-compound (14) is more flexible than its DD counterpart (15), which probably assumes a folded conformation.[80] A ^{13}C-n.m.r. study of mono- and di-O-α- and -β-D-galactosylated dipeptides of L-threonine and glycine has conclusively shown that peptide bond formation does not affect the chemical shifts of the attached carbon atoms of the carbohydrate. In the cases of the di-O-glycosylated compounds, no carbohydrate-carbohydrate interactions could be observed, suggesting that this is not the main influence on the conformation adopted by the peptide.[81] The ^{13}C-n.m.r. spectrum of the glycopeptide (16), obtained by lysozyme digestion of linear, non-crosslinked peptidoglycan polymer from culture fluids of penicillin-treated Brevibacterium divaricatum, has been reported.[82] Free and

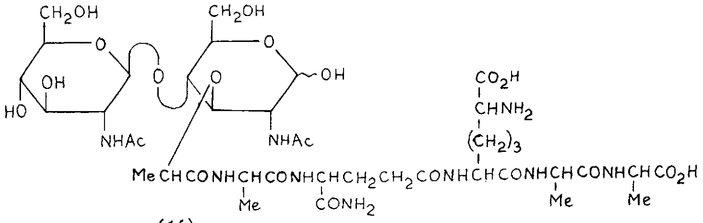


(14) R^1=H, R^2=Ph

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

glycosidically-linked O-acetylated sialic acids have been studied by 360 MHz ^{1}H-n.m.r spectroscopy as models for glycoconjugates.[83]

Several fragments of the carbohydrate-protein linkage region commonly occurring in proteoglycans have been investigated by 500 MHz ^{1}H-n.m.r. spectroscopy.[84]



(16)

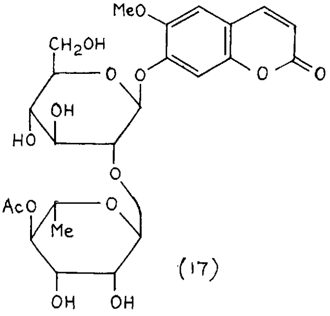
7 Inositols, Glycosides, and Sugar-containing Macromolecules

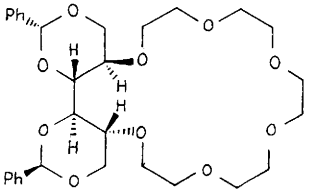
All the resonances in the ^{13}C-n.m.r. spectra of the eight diastereomeric inositols and the ten diastereomeric cyclohexanepentols have been assigned. The additive empirical constants used to correlate the configuration of hydroxy groups with ^{13}C chemical shifts were considerably different between the two series, and it was concluded that the shift rules are a rather unsatisfactory method for assigning configuration.[85]

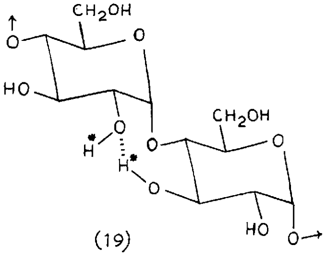
Structures of avilamycins A and C have been established by n.m.r. and X-ray methods.[86] Tetramycin A and B, tetraene macrolide antibiotics, have been separated and their ^{1}H- and ^{13}C-n.m.r. spectra at 400 MHz completely assigned.[87] An usually high glycosylation shift of +11.8 p.p.m. has been observed for C-2 of the glucosyl moiety in the saponin, chikusaikoside-I, which was established to be the 3-O-β-xylopyranosyl-(1→2)-β-glucopyranosyl-(1→3)-β-fucopyranoside of saikogenin F. Normally glycosylation at such a site would result in ca. 8 p.p.m. deshielding.[88] The application of ^{13}C-n.m.r. spectroscopy to structure elucidation of flavonoid O- and C-glycosides has been reviewed.[89] An n.m.r. spectroscopic analysis of the per-trimethylsilylated derivative of haploperoside B (17) has been made.[90]

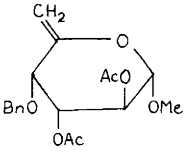
The conformation of the 20-crown-6 derivative (18) and of its molecular complex with benzylammonium cation has been examined by variable temperature ^{1}H-n.m.r. spectroscopy.[91]

^{1}H-N.m.r. studies at 400 MHz in DMSO-d_6 of cyclodextrins, in which hydroxy protons were partially exchanged for deuterium, revealed novel isotope shifts for H-2 and H-3, and for OH-2 and OH-3. This was ascribed to the presence of deuterium as one of the asterisked hydroxy protons in the structure (19), showing the dominant inter-residue hydrogen bond between OH-2 and OH-3[92] (c.f. the situation in sucrose[68]).


(17)


(18)


(19)


(20)

8 N.m.r. of Nuclei other than ^{1}H and ^{13}C

Catalytic tritiation of compounds containing vinylic protons under both heterogeneous and homogeneous conditions has been studied using ^{3}H-n.m.r. spectroscopy. Reduction of the hex-5-enoside (20) was shown to lead to product with more than 95% of tritium at the terminal methyl position.[93]

A review of ^{31}P-n.m.r. spectra of chair-twist conformational equilibria for diastereoisomeric phosphorus derivatives of thymidine cyclic 3',5'-monophosphate has appeared.[94]

Natural abundance ^{17}O-n.m.r. spectra of D-glucose, D-galactose, D-mannose and some methyl derivatives of D-glucose in aqueous solution have been reported. Although chemical shifts for monosaccharides were found generally to parallel the sequence for simple primary and secondary alcohols and ethers, several exceptions were noted, and these were discussed in terms of steric and electrostatic repulsive forces between oxygen atoms.[95]

Complex formation between tin(II) chloride and methyl α-L-rhamnopyranoside was demonstrated by means of ^{119}Sn-n.m.r. spectroscopic measurements together with ^{1}H- and ^{13}C-n.m.r. spectra. Analogous complexation with its 4-O-methyl ether but not with its 2- or 3-O-methyl ether analogues established that complexation occurred *via* the 2,3-diol system.[96]

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21
Other Physical Methods

1 I.r. and Raman Spectroscopy

Complete i.r. and Raman spectra for crystalline α- and β-D-glucose have been reported; characteristic differences were noted, and hydrogen bonding was considered responsible for low frequency differences between the two forms.[1] Laser Raman spectroscopy has been used to investigate structural changes in mono- and oligosaccharides in solution induced by pH change; all showed enhanced band intensities at lower pH.[2] Techniques of multiple internal reflection i.r. spectroscopy coupled with f.d. mass spectrometry have been applied to the structural elucidation of ginsenosides isolated by h.p.l.c.[3] The structure of nucleosides and nucleotides adsorbed at a silver electrode have been investigated from their surface-enhanced Raman spectra.[4]

Hydrogen-bonding studies on methyl tetrofuranosides in dilute carbon tetrachloride solution have been reported.[5]

2 Mass Spectrometry

A review of some recent applications of f.i./f.d. mass spectrometry in organic chemistry include examples of sugars, glycolipids, nucleosides, and macrolide antibiotics.[6]

A new method for measuring the e.i. mass spectra of labile compounds of low volatility involves rapid heating of the sample using a conventional f.d./c.i. probe in the absence of a reactant gas; (M + 1) ions are observed, as shown by sucrose.[7] The laser desorption mass spectrum of sucrose has also been studied as a function of substrate temperature, suggesting that gas phase cationization was the major ionization process.[8] Unprotected methyl glycopyranosides analysed by isobutane c.i. mass spectrometry showed $[M_2H]^+$, $[M_2H - MeOH]^+$, and $[M_2H - 2MeOH]^+$ ions, and others resulting from ion-molecule reactions; ion-source reactions are proposed to account for these ions.[9]

Fast atom bombardment (FAB) mass spectra of some simple monosaccharides have been recorded, examining negative-ions; intense

$(M-H)^-$ ions were observed, together with analytically useful fragment ions.[10] Xenon and argon induced mass spectra have been measured for sucrose, raffinose and stachyose.[11] C.i. and e.i. mass spectra of dianhydrohexopyranoses have been studied; c.i. spectra showed significant differences for both regio- and stereo-isomers, whereas there was little difference in their e.i. spectra. Acetyl derivatives of these dianhydro sugars only gave stable $[M + C_4H_9]^+$ ions when an oxiran was trans to an acetate, attributed to acetate participation in oxiran ring opening.[12]

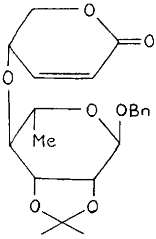
Matrix assisted molecular secondary ion mass spectra of viridopentaoses have been described, illustrating a valuable technique for the structural analysis of polar compounds.[13] Mass spectral study of antibiotics is also referred to in Chapter 18.

The fragmentation of derivatized neuraminic acid has been elucidated using nitrogen-15 and trideuteriomethyl labelled compounds.[14] E.i. mass spectra of fully methylated (1→4) linked xylo-oligosaccharides (d.p. 2-6) and a branched aldopentao-uronic acid have been used for sequence analysis.[15] Conventional (e.i. or c.i.) mass spectra have been reported for peracetylated galacturonosyl-galactose and rhamnose derivatives,[16] peracetylated mono-saccharide mono-formates,[17] and polyhydroxyalkyl-benzimidazoles.[18] Mass spectra of partially-methylated[19] and trideuterio-acetylated[20] 3-amino-3,6-dideoxy-L-glucitol have been reported, and differences between spectra for 3-amino and 3-acetamido-derivatives in the latter case used to probe the extent of N-deacetylation during acid hydrolysis of polysaccharides containing 3-acetamido-3,6-dideoxy-L-glucose units.[20] FD mass spectrometry is a valuable method for identifying oligosaccharide di- and tri-saponins, especially when applied to chromatographically separated samples prior to conventional techniques.[21]

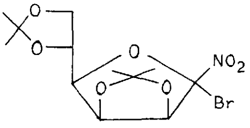
GC-MS has been widely used in the analysis of carbohydrate materials. The photosynthetic incorporation of $^{13}CO_2$ into carbohydrates by corn and soyabean plants can be conveniently monitored by this technique using trimethylsilylated oxime derivatives,[22] and a capillary GC-CI MS procedure has been used to analyse mixtures of pentoses[23] and hexoses[24] via trifluoro-acetylated oxime derivatives. GC-MS data have also been recorded for the products of the formose reaction,[25] permethylated trisaccharide alditols derived from sialic acid-containing glycopeptides,[26] cytokinin ribonucleosides,[27] methylated and acetylated glycosides of hexoses and *N*-acetylglucosamine,^{28} various aldoses, ketoses, sugar acids, polyols and *N*-acetylated amino-sugars,^{29} partially methylated D-galactonitrile acetates,^{30} deoxy-aldonic acids and 2-*C*-hydroxymethyl analogues,^{31} and desulpho-glucosinolates.^{32,33}

3 X-Ray and Neutron Diffraction Crystallography

The following specific crystal structures have been reported:
Free Sugars.- Melezitose,^{34} and lactose^{35} (includes study of degree of crystallinity and the disorder parameter).
Glycosides.- *p*-Nitrophenyl α-D-glucopyranoside,^{36} maltitol (4-*O*-α-D-glucopyranosyl-D-glucitol),^{37} isomaltitol (6-*O*-α-D-glucopyranosyl-D-glucitol),^{38} methyl 2,3,4,5-tetra-*O*-acetyl-β-D-alloheptanoside,^{39} *cis*-2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside 1-spiro-2^1-(3^1-methyl-3^1-tetrahydrofuranol),^{40} heptyl 1-thio-α-D-mannopyranoside,^{41} and 5-(β-D-galacto-thiopyranosyl)-6-azauracil.^{42}
Ethers and Anhydro-sugars.- 1,6-Anhydro-β-D-mannopyranose,^{43} di-D-fructose anhydride III,^{44} 1,2-*O*-(2,2,2-trichloroethylidene)-α-D-glucofuranose (α-D-chloralose),^{45} 1,6,2,5-dianhydro-α-L gulofuranose,^{46} 2,3,5-*O*-orthoacetyl-1,6-anhydro-α-L-gulo furanose,^{47} and the rhamnosyl dihydropyrone ether (1).^{48}



(1)



(2)

Ester derivatives.- 1,2,3,4-Tetra-*O*-acetyl-β-DL-ribopyranose.^{49}
Halogen- and Nitrogen- containing Compounds.- The glucfuranosyl orthoacid derivative (2),^{50} 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl fluoride,^{51} *N*-acetyl-α-D-muramic acid,^{52} methyl 5-acetamido-7,8-anhydro-4,9-bis-*O*-(tert-butyldimethylsilyl)-3,5-dideoxy-L-*glycero*-β-D-*galacto*-2-nonulopyranosidonic acid methyl ester,^{53} 1-*O*-acetyl-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-3-nitro-L-*arabino*-hexose (evernitrose 1-acetate),^{54} 1-*N*,2-*O*-thiocarbonyl β-D-lyxopyranosyl-

amine,[55] 1-*N*-acetyl-β-D-glucopyranosylamine,[56] methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-[2-(methoxycarbonyl) phenylamino]-3-nitro-β-D-mannopyranoside,[57] and (*Z*)-2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranosyl-*O*,*N*,*N*-azoxy-2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranoside.[58]

Deoxy and Branched-Chain Sugars.- Methyl 7-deoxy-β-D-*glycero*-D-*galacto*-heptopyranoside and methyl 7-deoxy-α-L-*glycero*-D-*galacto*-hepto-pyranoside,[59] derivatives of 1,2-*O*-isopropylidene-3-*C*-pyridin-2-yl-β-D-psicopyranose,[60] methyl 4,6-bis-*O*-(*p*-chlorobenzoyl)-2,3-dideoxy-3-*C*-(methoxycarbonylmethyl)-α-D-*ribo*-hexopyranoside,[61] and ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-4',5'-dihydro-3'-phenyl-α-D-*manno*-hexopyranosid [2,3-*d*]isoxazole.[62]

Diulose and Acid derivatives.- D-threo-hexo-2,5-diulose dimer (full report; see Vol. 10, p. 108),[63] galactaric acid,[64] L-ascorbic acid 2-*O*-phosphate,[65] D-erythronic acid 3,4-carbonate,[66] and methyl (methyl 3-deoxy-D-*arabino*-2-heptulopyranosid) onate.[67] Single crystal X-ray analysis has been used to study the dehydration of crystalline D-glucuronamide hydrate.[68]

Phosphorus Derivatives.- Monobarium β-D-glucopyranose 6-phosphate,[69] 2-*O*-[bis(diethylamido)thionophosphate]-3,4-*O*,*O*-(diethylamidothionophosphate)-1,6-anhydro-β-D-glucopyranose,[70] and 2,5-*O*-(*N*-diethylamidothionophosphate)-1,3;4,6-di-*O*-methylene-D-mannitol.[71]

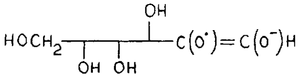
Alditols.- 3,6-Anhydro-1-bromo-1-deoxy-DL-galactitol, 1,5-anhydro-DL-galactitol, 2,5-anhydro-1,6-di-*O*-trityl-DL-altritol, and 2,6-anhydro-1,5-di-*O*-trityl-DL-galactitol.[72] 1,2;5,6-Di-anhydrogalactitol and its 3,4-diacetate.[73]

Nucleosides and Nucleoside Analogues.- Kinetin ribonucleoside,[74] 1,N^6-etheno-adenosine,[75] 2'-deoxy-2'-fluoro-cytidine and 2'-deoxy-2'-fluoro-uridine,[76] 2,2'-cyclocytidine hydrochloride,[77] 5-(prop-2-ynyloxy)-2'-deoxy-uridine,[78] 4-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methyl-1,24-triazin- 3(HH)one 1-oxide,[79] 5'-deoxy-5',6-epithio-5,6-dihydro-2',3'-*O*-isopropylidene-3-methyluridine,[80] disodium guanosine 5'-phosphate,[81] inosine 3',5'-cyclicphosphate,[82] 5-acetyl-1-(3,5-*O*-isopropylidene-β-D-xylofuranosyl)uracil,[83] 8-bromo-9-β-D-xylofuranosyladenine,[84] 2,2'-anhydro-1-β-D-arabinofuranosyl-thymine,[85] 8,2'-anhydro-8-mercapto-9-β-D-arabinofuranosyl adenine 3'-monophosphate,[86] and *S*-8-azaadenos-5-yl-L-homocysteine.[87]

The crystal structures of 67 nucleosides and nucleotides have been surveyed with respect to calculations of base co-ordinates,[88] and formulae were developed for inferring protonation states of the bases and phosphate groups.[89] Crystal structures have also been determined for an olefinic cyclic trimer formed by self-condensation of levoglucosenone (see also Chapter 12),[90] and for 20-crown-6 derivatives prepared from D-mannitol 1,3;4,6-diacetals and ethane-1,2-diol pentamer.[91]

4 E.s.r. Spectroscopy

The rearrangements of radicals produced by proton abstraction by hydroxy radicals on a series of simple sugars have been investigated. The semi-diones (3) and (4) were detected from D-glucose, and two pathways for the radical-induced based-catalysed decomposition of carbohydrates were proposed, involving carbon-oxygen or carbon-carbon bond cleavage of C-2 and C-5 radicals respectively.[92] A similar carbon-oxygen cleavage leadsto the structures (5) proposed for the radicals detected on ball milling α-lactose and α-D-glucose monohydrates, which were studied by e.s.r. and spin trapping experiments.[93]

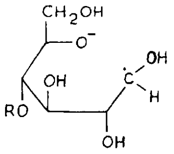


$HOCH_2\underset{OH}{-}\underset{OH}{-}\overset{OH}{-}C(O^{\bullet})=C(O^{-})H$

(3)

$HOCH_2-C(O^{\bullet})=C(O^{-})H$

(4)



(5) R = H or D-Gal

5 Polarimetry and Circular Dichroism Studies

A review on the importance and realization of defined wavelengths in saccharimetry has appeared.[94]

The c.d. of over forty bis-, tris, and tetrakis p-bromobenzoates of methyl pyranosides have been recorded. The amplitudes of the maxima at 235 and 253 nm were additive, based on diester pairs, allowing stereochemical relationships to be determined. This formed the basis for an ingenious method for determining oligosaccharide structures on a microscale (See Vol. 15, p.237, ref.

108),[95] and was also applied to complex carbohydrate antibiotics, allowing the position of glycosidic linkages in deoxy sugars to be assessed.[96]

A strong Cotton effect shown by aryl 1-thio-α and β-glycopyranosides has been studied by a new chiroptical technique involving calculations based on o.r.d. observations, giving results agreeing with c.d. studies; rotational strengths and signs reflect the anomeric configurations and conformations, and the ring oxygen helicity rule for corresponding alkyl glycosides and thioglycosides also applies to the aryl derivatives.[97,98] Furanosides show similar behaviour.[99]

The linear relationship $[M]_D = m\Sigma R_D + 1$, where m and I are constants, has been proposed between molecular rotation and bond refraction for α-aldopyaranose derivatives, including O- and S-glycosides and acetyl or benzoyl ester derivatives; the results can be used to assess probable conformational preferences.[100]

C.d., o.r.d., and u.v. spectra have been recorded for 1-deoxy-1-nitro-heptitols.[101]

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22
Separatory and Analytical Methods

1 Chromatographic Methods

Gas-Liquid Chromatography.- There have been several reports on the separation of enantiomeric sugars using capillary g.l.c. Diastereoisomeric dithioacetals, from seven aldoses with (+)-1-phenylethanethiol-trifluoroacetic acid, were separated as their peracetylated or pertrimethylsilylated derivatives.[1] Trifluoroacetylated O-(-)-menthyloxime derivatives were useful for the separation of several aldose enantiomers, but not those of glucose or xylose,[2] while trimethylsilylated (R)-2-butyl glycoside derivatives were used to confirm that fucose units in brown seaweed polysaccharides have the L-configuration.[3] On chiral stationary phases (copolymers of organosiloxanes and chiral dipeptide moieties), racemic trifluoroacetylated pentoses and 6-deoxyhexoses[4] and per(heptafluorobutanoyl)-ated aldoses and chiro-inositol[5] were resolved; the enantiomers of glucose, however were best resolved as 6-O-trimethylsilyl-α-glucofuranose 1,2:3,5-bis(methaneboronates), while those of myo-inositol 1-phosphate were resolved as trimethylsilylated methyl esters, the L-isomer being shown to be synthesized in bovine testis.[5]

A useful strategy for rapidly acquiring a library of reference data in conjuction with methylation analysis of polysaccharides involves partial methylation of methyl glycosides[6] or alditols,[7] following which a mixture containing virtually all possible partially methylated alditol acetates of a given sugar can be derived, and can be separated and identified by capillary g.l.c.-m.s. Over 50 such derivatives are detailed in one report, including a method for obtaining reproducible retention coefficients using two internal standards,[6] and another paper describes over 242 such derivatives from eight alditols.[7] The suitability of a variety of stationary phases for capillary separation of alditol acetates and their partially methylated analogues derived from neutral[8-10] and amino-sugars[10,11] has been investigated, while the separation of such compounds on packed columns has also been reported.[12] Preparative g.l.c. separations of mono- and di-*O*-methyl ethers of methyl α-D-glucopyranoside have been described.[13]

Permethylation-g.l.c.-m.s. analyses of trimetozine glucuronides in urine,[14] and of trisaccharide alditols produced by sequential *N*-deacetylation, nitrous acid deamination, and reduction of sialic acid-containing glycopeptides,[15] have been described.

The preparation of peracetylated aldononitriles from neutral and aminosugars using *N*-methylimidazole as catalyst and solvent has been further detailed.[16]

By methanolysis-trifluoroacetylation, all the ordinary monosaccharides and fatty acid constituents of lipopolysaccharides, including glucosamine, heptoses, and KDO (3-deoxy-D-*manno*-oct-2-ulosonic acid) were suitably derivatized for capillary g.l.c. analysis; the degradation of 3,6-dideoxyhexoses and the stability of sugar-phosphate linkages under these conditions were noted.[17] Trifluoroacetylation and capillary g.l.c. with electron capture detection was suitable for the analysis of various cytokinins including ribonucleosides, the structure of the derivatives being investigated by g.l.c.-m.s.[18]

Schweer and co-workers have reported extensively on *O*-methyl-, *O*-*n*-butyl-, and *O*-*t*-butyl-oximation-trifluoroacetylation for derivatizing tetroses,[19] pentoses,[19,20] hexoses,[21,22] hex-2-uloses,[22] C_3-C_6 alditols,[19] the bromine oxidation products of pentitols and hexitols,[23] and the products of the formose reaction (including 3-uloses and branched-chain species)[24] for capillary g.l.c.-chemical ionization m.s. The capillary g.l.c.-m.s. (with selected ion monitoring) analysis of some 35 sugars, including aldoses, ketoses, polyols, sugar acids, and *N*-acetylated aminosugars as their trimethylsilylated *O*-methyloxime derivatives, led to complete separation of peaks from many of the commonly encountered sugars.[25] A procedure has been described for converting *N*-acetyl- and *N*-glycolyl-neuraminic acids into their methyl or ethyl esters and then to trimethylsilylated, acyclic *O*-methyl-, *O*-benzyl-, or *O*-trimethylsilyl-ketoximes, suitable for g.l.c.-m.s. analysis.[26]

Methylated ribonucleosides and "hypermodified" adenosines (*i.e.*, modified isopentenyladenosines),[27] the *cis*- and *trans*-forms of nine hydroxycinnamoyl quinic acids in plant extracts,[28] and the *mono*- and di-*O*-pentyloxymethyl positional isomers formed on reaction of methyl α-D-glucopyranoside with pentyloxymethylchloride (of interest as non-ionic surfactants)[29] have all been analysed as their TMS ethers, while trimethylsilylation-g.l.c.-m.s. has been used to determine the level of deoxyaldonic acids and various 2-C-hydroxymethyl analogues in diseased human hearts.[30]

A new method for determining the reducing moiety in disaccharides involved conversion of the reducing unit to a 1-deoxy-1-ethoxycarbonylaminoalditol and the non-reducing unit to its methyl glycosides by sequential O-methyloximation, borane reduction, methanolysis, and treatment with ethyl chloroformate; these two types of products were then readily separated by trimethylsilylation-g.l.c. analysis.[31]

Pyrolysis-capillary g.l.c. has been used for qualitative analysis of carbohydrates.[32]

Column Chromatography.- The gel chromatography of (1→3)-, (1→4)-, and mixed (1→3)(1→4)-linked β-D-glucooligosaccharides on polyacrylamide, and the effect of complexation by boric acid in the eluent has been reported,[33] while analytical and preparative separations of gluco- and xylo-oligosaccharides (D.P. 1-60) on the same medium have been achieved.[34] Cellooligosaccharides (D.P. 1-5)[35] and peracetylated gluco- and xylo-oligosaccharides[36] have been separated on Sephadex LH-20 eluted with DMF. Synthetic acetylated β-(1→6)-linked disaccharides, obtained by Koenigs-Knorr procedures, were well separated from acetylated monosaccharide contaminants on Sephadex LH-20, and could thus be isolated crystalline in improved yields.[37]

Nucleosides and nucleotides could be separated preparatively (up to 50 mg) on a non-ionic TSK-gel with volatile buffer as eluent,[38] while purines, pyrimidines, and their nucleosides could be separated from salts using XAD-4 resin (styrene-divinylbenzene copolymer).[39]

Monoterpene glycosides in grape juice and wine were concentrated by a factor of 20,000 by a single pass of the aqueous sample through a reversed phase (C_{18}) absorbent and elution of the desired glycosides with methanol.[40]

The partial separation of the borate complex of D-glucose from those of various tritium-labelled, as well as [U-^{14}C]-labelled, D-glucoses during anion-exchange chromatography has now been quantified; tritium at positions 2,3,5 and particularly 6 resulted in earlier elution of the complex.[41] A calcium-ion cation-exchange resin has been used in the separation of D-psicose from base-isomerized D-fructose.[42] Hexosamines have been determined with an automated, dual cation-exchange resin column and amino acid analyzer. The eluent contained borate to form complexes with the hexosamines, which were detected at 570 nm following post-column treatment with ninhydrin.[43]

Paper Chromatography.- A new method for detecting carbohydrate and other organic compounds, with high sample recovery, involved heating the chromatogram directly with a domestic iron (∿230°C), the components being visualized as dark spots, or as fluorescent spots with the aid of u.v.-light. The latter visualization allowed greater sensitivity, or better recoveries - up to 98% with $[^{14}C]$-glucose.[44]

Thin Layer Chromatography.- The first separation of all the constituent sugars (seven neutral, two acidic) of plant cell-wall polysaccharides on a single chromatogram was achieved by two-dimensional t.l.c. on cellulose.[45] The R_f values for 12 sugars in 15 solvent systems on silica gel, Kieselgühr, and cellulose have been recorded.[46] Quantitative analysis of sugars, sugar acids, and polyalcohols on high-performance silica gel plates was achieved using in situ reaction with lead tetraacetate then 2,7-dichlorofluorescein to render them fluorescent.[47] Detection of glucose and methylated glucoses on silica gel plates by thermal treatment (135-140°) then visualization as fluorescent spots under u.v.-light, permitted useful sample recovery (ca. 87% in the case of $[^{14}C]$-glucose).[48] For the quantitative analysis of maltooligosaccharides, such as those in starch hydrolysates, high-performance t.l.c. on silica gel, colourimetic detection, and densitometric assay was found to be the method of choice.[49] Water soluble vitamins, including L-ascorbic acid, were separated on silica gel, and quantified by pyrolysis-g.l.c. of the separated zones.[50]

Aminosugars have been examined by high-performance t.l.c. on reversed phase plates (C_{18}-silica gel) impregnated with dodecylbenzenesulphonic acid, and on ammonium tungstophosphate layers,[51] while their separation on silica gel plates and fluorimetric analysis using a fluorescamine spray-reagent has also been reported.[52] The reaction of aminoglycoside antibiotics in the gentamicin C complex with ninhydrin was optimized to permit a quantitative densitometric assay following separation on silica gel,[53] while 21 aminoglycoside antibiotics were chromatographed on silica gel or silica gel impregnated with Carbomer, a polycarboxylic acid resin which acts as an ion-exchanger.[54]

A separation of nucleotides from nucleosides and bases in trichloroacetic acid extracts of cells, using polyethyleneimine-cellulose plates has been described.[55] A thin-layer densitomeric analysis was used to determine the kinetics of the acid-hydrolysis of modified nucleosides.[56] In a study of the charge-transfer t.l.c. behaviour of various biochemicals, adenosine showed little interaction with riboflavin bound to silica gel.[57]

High Pressure Liquid Chromatography.- A novel chemiluminescence detector has been described which selectively detects oxygen-containing compounds (examples included fructose and sucrose). It relies upon anthraquinonedisulphonate-sensitized photooxygenation to produce hydrogen peroxide which is then quantitated by way of a cobalt(II)-luminol chemiluminescence reaction, and it is as sensitive as a refractive index detector.[58] The application of polarimetric detection for carbohydrates has been described in a review on specific detectors,[59] while combined refractometric-polarimetric detection has been employed to estimate partially methylated glucoses, galactoses, and their corresponding alditols after reversed phase chromatography.[60]

Important contributions on the chromatography of sugars on amine-modified silica columns have appeared. It has been conclusively demonstrated that significant or even total removal of aldoses by the column occurs under conditions of optimum column performance, whether the amine function is chemically bound (*e.g.*, γ-aminopropyl groups) or is present in the eluent (*e.g.*, diethylenetriamine). This problem, considered to be due to the formation of glycosylamines by reaction with primary amino-functions, was eliminated by using a phosphate-buffered mobile phase (pH 5.9) under which conditions the glycosylamines, if they are formed at all, are rapidly hydrolyzed.[61] Two groups have independently demonstrated that the retention of sugars on amine-modified silica columns is due to the stationary liquid phase (about the amine) being richer in water than the acetonitrile-water eluent;[62,63] triamino-functionality was shown to bind more stationary liquid, thereby permitting more water in the eluent and facilitating solute solubility.[63] The sugars in cantaloupe melon juice (fructose, glucose, and sucrose) were analyzed on both amine-bonded silica and silica modified by tetraethylenepentamine in the solvent,[64] while semi-preparative separation of a complex mixture of over seventeen *N*-acetylglucosamine-rich, branched, reduced oligosaccharides from hydrazinolysis-borohydride reduction of hen ovomucoid was achieved on primary amine-bonded silica.[65] Aminosugars were retained and at least partially resolved on amine-bonded silica with a metal-ion modified mobile phase containing cadmium sulphate, neutral sugars eluting with the solvent front.[66]

A novel paired-ion chromatographic system for monosaccharides involved a reversed phase column eluted with a methanol-aqueous borate buffer containing methylene blue; sugars at submicrogram levels (especially fructose) form ionic complexes with borate which then pair with the dye, resulting in improved separation and detection.[67]

Reducing sugars have been converted to N-(p-methoxyphenyl)-glycosylamines and separated by reversed-phase h.p.l.c.; advantages included the co-elution of the ring-size and anomeric configurational isomers from each aldose and the sensitivity afforded by u.v.-detection, while problems associated with the fact that formation and gradual degradation of the glycosylamines occurred at different rates for each aldose were minimized through appropriate choice of conditions.[68] More details have been published on the resolution of enantiomeric aldoses as their 1-(N-acetyl-α-methylbenzylamino)-1-deoxy-alditol acetates, prepared by reductive amination.[69] Perbenzoylated O-benzyloxime derivatives have been used to separate the monosaccharide constituents of brown algal polysaccharides using amine-bonded silica, especially L-fucose and D-xylose,[70] while dansyl hydrazone derivatives have been shown to permit excellent separation (on silica) of reducing sugars with fluorimetric detection limits of 3-20 pmol.[71]

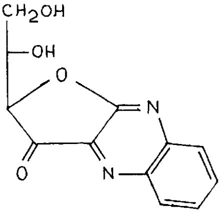
Monosaccharides and cellooligosaccharides (D.P. up to 6) were separated by anion-exchange chromatography on triethylammoniumethyl-spheron 1000 resin,[72] while an improved separation of gluco-oligosaccharides including the cyclodextrins was achieved on a strong cation-exchange resin (Ca^{2+}-form) by using both calcium ethylenediaminetetraacetate in the aqueous eluent to eliminate interference from metal ions leaching from the stainless steel equipment, and wider bore columns (9.0 vs 6.2 mn) which gave significantly improved column efficiency.[73] The exclusion chromatographic behaviour of mono- through to polysaccharides was used to determine the pore size distribution of polystyrene- and silica-based cation-exchange resins.[74] Aldohexoses, their 6-deoxy-analogues, and a series of maltooligosaccharides were studied on an Hitachi 3013-N column, and it was shown that partition chromatography operated with >30% acetonitrile in the aqueous buffer eluent, while exclusion (i.e., gel filtration) chromatography operated with pure aqueous buffer eluent.[75]

The separation of steroid conjugates, including glycosides and glucuronides has been reviewed,[76] and the characteristics of 17 cardiac glycosides on diphenylsilyl-modified silica have been reported.[77] Naturally occurring glucosinolates were analysed by enzymic desulphation and reversed phase chromatography of the derived desulphoglucosinolates, with isolated peak material being identified by trimethylsilylation-g.l.c.-m.s.[78] Analyses of crocetin glycosyl esters from saffron extracts (on silica),[79] hydroxycinnamoyl quinic acids in plant extracts (by reversed phase),[28] and the antitumour drug 1-(2-chloroethyl)-3-(β-D-glucopyranosyl)-1-nitrosourea in blood and urine (by reversed phase)[80] have also appeared.

Hexuronic acids[81] and neuraminic acid derivatives[82] were analysed on strong anion-exchange resins. Glucuronic and iduronic acids were released by methanolic hydrogen chloride treatment of glycosaminoglycans as their methyl glycoside-methyl esters, and were then analysed either on a reversed phase column, or, after de-esterification, on a silica-based, weak anion-exchanger.[83] Non-sulphated hex-4-enuronosyl-glucosamines and -galactosamines released by enzymic degradation of hyaluronic acid and chondroitin sulphate respectively,[84] and the analogous disulphated disaccharides from the latter polymer,[85] were also analysed on this weak anion-exchanger. Oligogalacturonic acids and analogues with 4,5-unsaturation in the non-reducing terminal unit, from enzymic degradation of pectic acid, were separated by three different systems: strong and weak anion-exchange chromatography, and tetrabutylammonium ion-pairing on a reversed phase column.[81] Isomers of glycyrrhizinic acid, a diglucuronosylated triterpenoid, present in liquorice, were analysed on cyanopropyl silica,[86] while an ion-pair reversed phase separation of p-nitrophenyl glucuronide, uridine-5'-diphosphoglucuronic acid, and p-nitrophenol, suitable for the assay of the former in rat-liver microsomal incubations, was reported.[87]

Gangliosides, fractionated by the number of sialic acid residues on diethylaminoethyl-silica gel, were then rechromatographed on silica to obtain individual components.[88] α-D-N-Acetylneuraminyl-(2→3)-β-D-galactopyranosyl-(1→4)-1-deoxy-1-[(2-pyridyl)amino]-D-glucitol [i.e., PA-sialyllactose] and the related PA-glucose and PA-lactose were separated on a reversed phase column in connection with the monitoring of sialidase activity.[89]

A sensitive ion-pair reversed phase determination of L-ascorbic and D-isoascorbic acid utilized electrochemical detection,[90] while a similar analysis for ascorbic acid and dehydroascorbic acid utilized derivatization of the latter with 1,2-diaminobenzene to form compound (1) which was then suitably u.v.-absorbing.[91]



(1)

The following aminoglycoside and other antibiotics and related impurities and degradation products have been examined: novobiocin isomers, on normal[92] and micro-bore silica columns;[93] neomycins, on a micro-bore silica column,[93] and as their 2,4-dinitrophenyl derivatives on silica;[94] amikacin (a semi-synthetic kanamycin derivative) as its tetra-N-(2,4-dinitrophenyl) derivative by reversed phase;[95] and gentamicin components after derivatization with o-phthalaldehyde by reversed phase.[96]

General separations of nucleosides and bases,[97] and of ribonucleosides, deoxyribonucleosides and related cyclic nucleotides and free bases in biological material,[98] using reversed phase h.p.l.c. have been reported. Following a study with nine commercially available columns and five mobile phases, a reversed phase separation of all major pyrimidine and fluoropyrimidine base and nucleosides was achieved.[99] Complexation of ribosyl nucleosides of adenine and hypoxanthine with borate in the eluent effected their earlier elution and enhanced their reversed phase separation from their 2'-deoxy-ribosyl and -arabinosyl analogues.[100] Vidarabine and its deaminated analogue, arabinosyl hypoxanthine,[101] and 5-bromo-2'-deoxyuridine and its common metabolites[102] were separated by reversed phase techniques, while nucleosides and nucleotides of 5-fluorouracil and its analogue 5'-deoxy-5-fluorouridine,[103] and S-adenosyl-L-methionine and its analogues[104] were determined by ion-pair, reversed phase methods. 2-Phenylaminoadenosine and its 4-hydroxyphenyl-metabolite were determined fluorimetrically following O-propionylation and h.p.l.c. on silica.[105]

2 Electrophoresis

Paper electrophoresis in borate buffer and silica gel t.l.c. gave distinctive data for variously linked galactobioses and their pyruvylated analogues [i.e., with 3,4- and 4,6-O-(1-carboxyethylidene)acetals].[106] Analytical isotachophoresis has been used to monitor industrial production of arabinonic acid and its acidic process-related byproducts from oxidation of glucose in alkaline solution,[107] and as a rapid assay for aminoglycosides (e.g., spectinomycin, sisomicin, and tobramycin) and lincomycins in pharmaceutical preparations.[108]

3 Other Analytical Methods

Two sensitive chemiluminescence methods for determining D-glucose have appeared. One uses immobilized glucose oxidase to produce hydrogen peroxide, then immobilized peroxidase to catalyse the chemiluminescent reaction of peroxide with luminol in a flow cell apparatus,[109] while the other uses immobilized luminol for the reaction with enzymically produced hydrogen peroxide.[110]

Quantitative determinations of L-ascorbic acid, D-galactose, D-glucose, cellobiose, lactose and sucrose were made with "enzyme-thermistors", in which the heat produced by reaction of a sugar with an immobilized enzyme (e.g., invertase for sucrose) in a small column is monitored by a thermistor placed in the column eluent; the procedure is suitable for discrete samples or continuous monitoring.[111]

2-Deoxy-glucose could be determined in the presence of 2-deoxy-galactose by treatment with galactose oxidase followed by indole-hydrochloric acid, and vice versa using glucose oxidase; alternatively the hydrogen peroxide released enzymically could be determined by reaction with o-dianisidine.[112]

An iodometric analysis of aldoses[113] and a fluorimetric assay of amino-sugars in solution following reaction with fluorescamine[52] have been described.

Modifications to the colourimetric assay of D-glucosamine released from chitin by acid hydrolysis were detailed,[114] and pentoses were detected in the presence of hexoses by the red colour they produce on treatment with an aniline - aqueous acetic acid reagent.[115]

The amperometric detection of simple sugars has been accomplished using a rapid triple-pulse potential waveform, that would be suitable for monitoring flow injection or h.p.l.c. eluent.[116]

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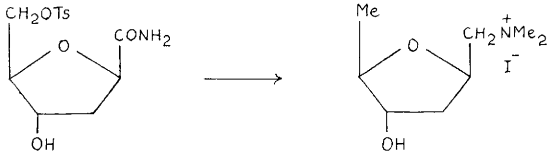
23

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

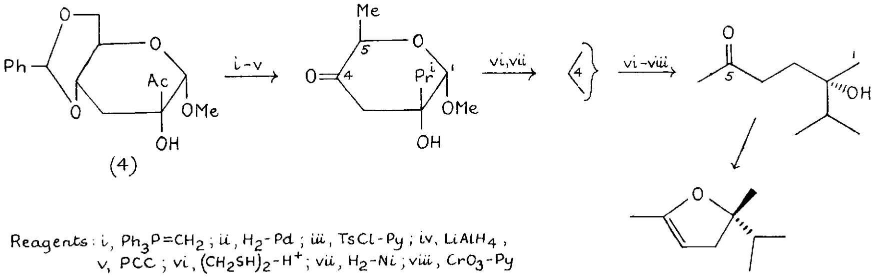
The increasing use of monosaccharides as synthons for chiral compounds is reflected in an extensive review appearing as a conference paper.[1]

1 Tetrahydrofuran Compounds

D-(-)-Muscarine iodide (1) has been prepared from 2-deoxy-D-*erythro* pentose via the acid derivative (2) by sequential lithium aluminium hydride reduction and quaternization. Likewise, L-(+)-allomuscarine was produced from the "α" epimer of (2), and 2-deoxy-L-*erythro*-pentose was used to prepare enantiomers of these compounds.[2] Compound (3), the enantiomer of the pheromone of *Hylecoetus dermestoid*, has been synthesized from D-glucose via the known branched-chain derivative (4) by methods outlined in Scheme 1.[3] The 1,6-dioxaspiro [4,4]nonanes (5), which are aggregation pheromones of *Pityogenes chalcographus*, have been prepared from 3-deoxy-D-glucose by standard deoxygenations to give the dithioacetal (6)(Scheme 2), which provides the ethyl-substituted ring in (5); preliminary



(2) (1)



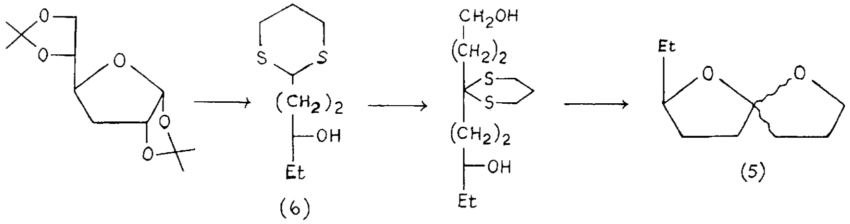
(4)

(3)

Reagents: i, $Ph_3P=CH_2$; ii, H_2-Pd; iii, TsCl-Py; iv, $LiAlH_4$, v, PCC; vi, $(CH_2SH)_2$-H^+; vii, H_2-Ni; viii, CrO_3-Py

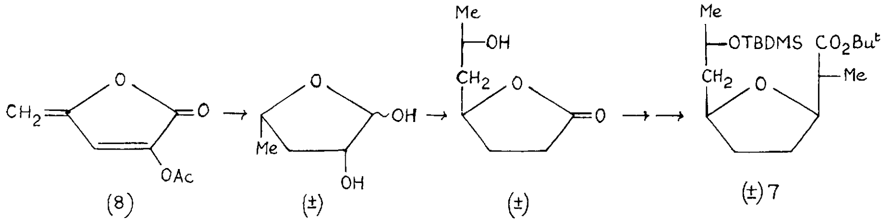
Scheme 1

epimerization of C-4 in the sugar unit led to the enantiomers of (5).[4]



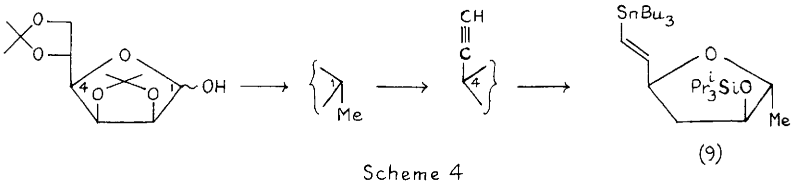
Scheme 2

2,3,4-Tri-O-acetyl-D-ribono-γ-lactone provides a sourse for the racemic nonactic acid derivative (7) via the doubly unsaturated lactone (8) by the sequence outlined in Scheme 3.[5]



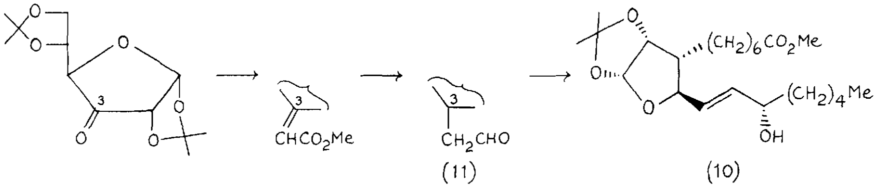
Scheme 3

Compound (9), the C_{11}-C_{17} segment of the antibiotic aplasmomycin, has been prepared from 2,3:5,6-di-O-isopropylidene-D-mannofuranose by a multistep sequence traced in Scheme 4; the alkenylstannane was subsequently coupled with an oxiran derivative to lead on to the antibiotic.[6]

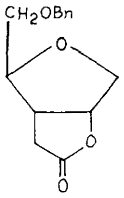


Scheme 4

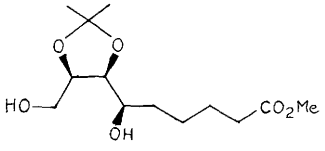
Modified prostaglandins (11-deoxy-11-oxa analogues of prostaglandin E_2, $F_{1\alpha}$ and $F_{2\alpha}$) have been prepared from standard glycos-3-ulose derivatives of D-glucofuranose and D-xylofuranose, e.g., the $PGF_{1\alpha}$ analogue (10) via the branched-chain intermediate (11) (Scheme 5).[7] Other prostaglandin analogues were prepared by a similar approach using related deoxy intermediates, e.g., (12).[8]



Scheme 5



(12)



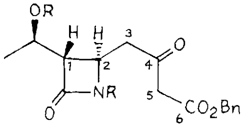
(13)

2 Tetrahydrothiophen Compounds

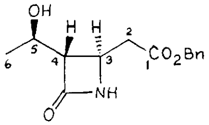
The (+)-biotin precursor (13) has been conveniently prepared from 3,4-O-isopropylidene-D-arabinose by a Wittig reaction followed by hydrogenation,[9] providing a further improvement in the synthesis of this vitamin (see Vol.14.p.217).

3 Pyrazolone Compounds

A 22-step conversion of D-glucosamine to the known (+)-thienamycin precursor (14)(numbered for the glucose skeleton) has been described (overall yield 7.5%); 3-deoxygenation was followed by one-carbon homologation at C-1 using a Wittig reaction ($Ph_3P{=}CHOMe$), the derived amino-acid then being lactamized before final 5-deoxygenation, C-1 alkylation, and 4- and 6-oxidation to give (14).[10]

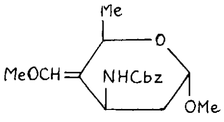


(14) $R = SiMe_2Bu^t$

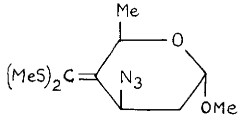


(15)

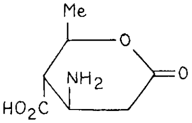
Another report describes the conversion of methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranoside to the β-lactam (15) (glucose numbering), another precursor for thienamycin. In this case a 3-amino-2,3,6-trideoxy-hexos-4-ulose intermediate prepared from D-glucose was converted to the deoxy-branched-chain sugar (16) by a Horner-Wittig reaction, and this on further oxidation and lactamization gave the intermediate (15).[11] A very similar approach from a 3-azido-2,3,6-trideoxy-hexose precursor, leading to the intermediate (17) and hence to the amino-acid (18), has been described by Hanessian's group.[12]



(16)



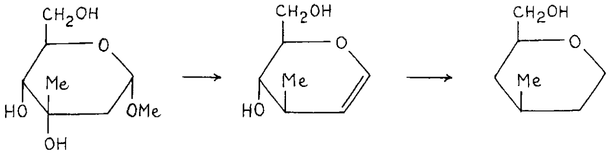
(17)



(18)

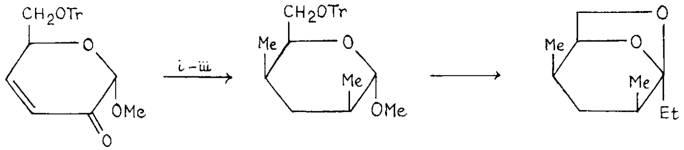
4 Tetrahydropyran Compounds

A 19-step synthesis of (-)-*cis*-rose oxide from D-glucose involves the conversion of the branched-chain sugar (19) to the rose-oxide precursor (20) via the glycal (21) using established methods.[13]



(19) (21) (20)

Three papers report syntheses of (-)-α-multistriatin (22). Fraser-Reid's group used glycenosulose (23) to prepare the deoxy-branched-chain sugar (24), which was then converted by standard reactions to (22)(Scheme 6).[14] Another reported sequence also uses compound (24) in a similar approach from D-glucose, but the ethyl side-chain is here introduced via the dithiane intermediate (25).[15]

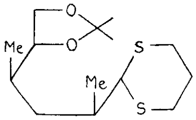


(23) (24) (22)

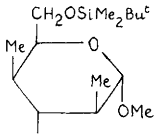
Reagents: i, CuBr-Me_2S-MeLi; ii, $Ph_3P{=}CH_2$; iii, H_2-Pd

Scheme 6

Lukac's group use D-galactose to prepare the branched-chain sugar (26), introducing the branch methyl groups using lithium dimethyl cuprate on oxiran intermediates, followed by 3-deoxygenation via the xanthate ester.[16]

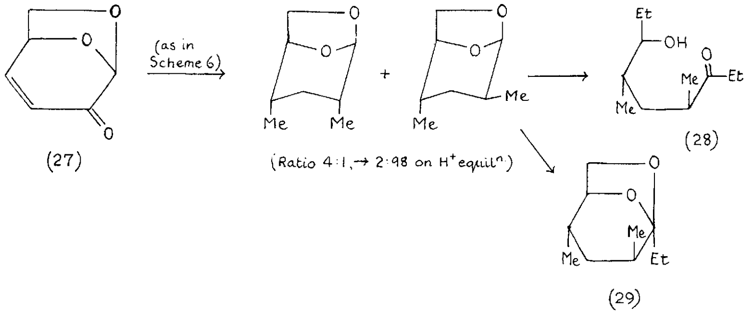


(25)



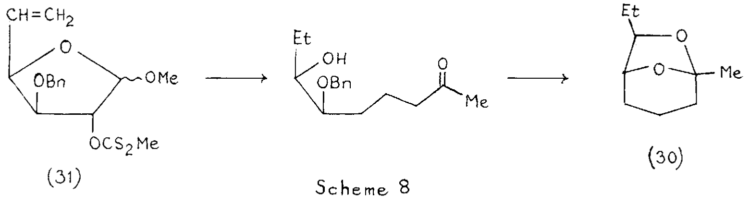
(26)

Laevoglucosenone (27) provides a convenient starting material for a chiral synthesis of the insect sex pheromone serricornin (28) and for (-)-δ-multistriatin (29)(Scheme 7), the kinetically formed C-2 axial epimer of the 2,4-di-C-methyl-anhydro sugar intermediate isomerizing to the required C-2 equatorial isomer in acid.[17]



Scheme 7

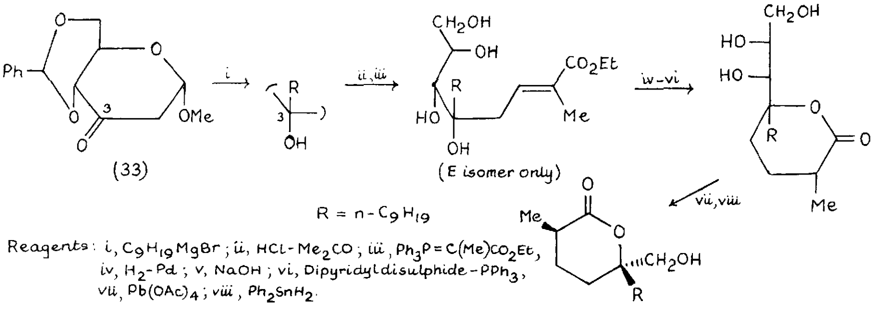
Fraser-Reid's group have published another synthesis of (+)-exo-brevicomin (30) in which glucose is converted to the glyceno-furanose (31), which was elaborated to the pheromone utilizing a Wittig reagent ($Ph_3P=CHCOMe$) with the free sugar (Scheme 8).[18]



Scheme 8

Full details of the synthesis of (-)-frontalin from glucose have been published (see Vol. 10, p.204).[19]

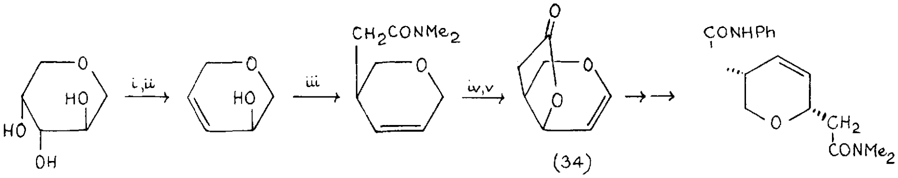
The marine antibiotic (-)-malyngolide (32) has been enantiospecifically synthesized from D-glucose via the 2-deoxy-3-ulose intermediate (33) by the sequence outlined in Scheme 9.[20]



Reagents: i, $C_9H_{19}MgBr$; ii, HCl-Me_2CO; iii, $Ph_3P=C(Me)CO_2Et$, iv, H_2-Pd; v, NaOH; vi, Dipyridyldisulphide-PPh_3, vii, $Pb(OAc)_4$; viii, Ph_2SnH_2.

Scheme 9

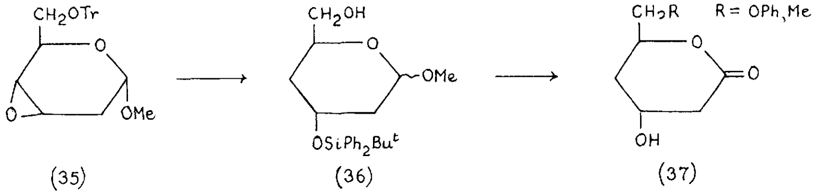
The use of D-ribose for preparing key intermediates in the synthesis of pseudomonic acids is referred to in Chapter 13 (ref.11). Syntheses of the bicyclic unsaturated lactone (34) and its enantiomer have been developed from D- and L-arabinose respectively. Both sequences utilized a stereospecific Claisen rearrangement to convert a pentenose intermediate to the branched-chain amide which underwent iodo-lactonization and unsaturation to the required lactones, as illustrated in Scheme 10.[21]



Reagents: i, $HC(OEt)_3$-HOAc; ii, Δ; iii, $MeC(OMe)_2NMe_2$; iv, I_2-H_2O-THF; v, DBU

Scheme 10

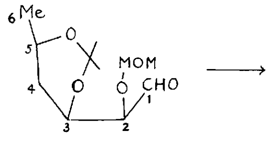
The 3,4-epoxide (35), obtained from triacetyl-D-glucal, has been used to prepare the dideoxyhexose derivative (36) leading to the analogues (37) of mevinic acids (enzyme inhibitors)(Scheme 11).[22]



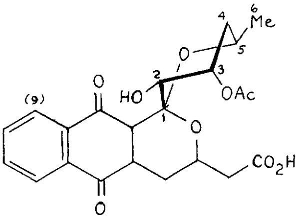
Scheme 11

A 2,4,6-trideoxy-6-iodo-hexose derivative prepared from D-glucose also with potential as a chiral intermediate for synthesizing inhibitors of this enzyme is mentioned in Chapters 7 and 11. The synthesis of spirobis-1,4-dioxans from 2-chloroethyl fructopyranoside is mentioned in Chapter 3 (ref.6), and the formation of tricyclic pyrone derivatives from unsaturated sugars is referred to in Chapter 12 (ref.31).

Coupling of the 4,6-dideoxy-aldehydo-hexose derivative (38), obtained from 6-deoxy-L-gulonolactone in 10 steps, with a bromonaphthalene derivative leads to (+)-9-deoxygriseusin B (39)(hexose numbering). CD spectral comparison of (39) with natural griseusin B suggests that the latter has the opposite rather than the same configuration.^{23}



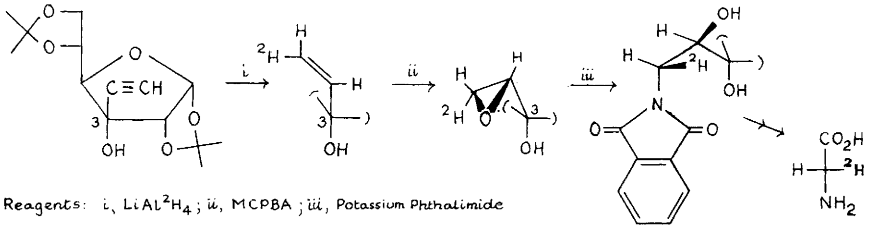
(38)



(39)

5 Acyclic Compounds

2-O-Octadecanoyl and 2-O-eicosanoyl derivatives of (R)-glyceric acid have been synthesized from the corresponding 2,5-di-O-alkyl-1,3(R):4,6(R)-di-O-benzylidene-D-mannitol derivatives using a conventional periodate cleavage sequence.^{24} Similar cleavage of 5-O-benzyl-D- and L-rhamnitol furnished (R)- and (S)-2-benzyloxypropanal required for the synthesis of adenosine deaminase inhibitors.^{25} D-Glucose has been used as a chiral template for the synthesis of chiral glycine as outlined in Scheme 12; the enantiomer was similarly prepared using $C_2{}^2H_2$ and $LiAlH_4$, and the approach can also be

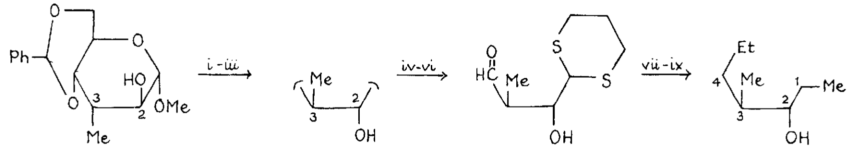


Reagents: i, $LiAl^2H_4$; ii, MCPBA; iii, Potassium Phthalimide

Scheme 12

adapted to yield chiral acetic acid.[26]

(2S,4S)-4-Methylheptan-3-ol (41)(glucose numbering), a pheromone component of the smaller European elm bark beetle, has been prepared conventionally from D-glucose via the 3-deoxy-3-C-methyl-altroside (42) as outlined in Scheme 13, utilizing an oxidation-reduction sequence to effect double epimerization at C-2 and C-3, and Wittig reactions to lengthen the chain appropriately.[27]

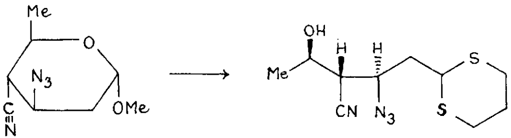


(42) (41)

Reagents: i, $(CF_3CO)_2O$-DMSO ; ii, Et_3N-DMSO ; iii, $LiAlH_4$; iv, H_3O^+ ; v, $HS(CH_2)_3SH$-HCl ; vi, $Pb(OAc)_4$; vii, $Ph_3P{=}CHMe$; viii . BnBr-BaO-$Ba(OH)_2$; ix, MeI-Me_2CO ; x, $Ph_3P{=}CH_2$; xi, H_2-Pd

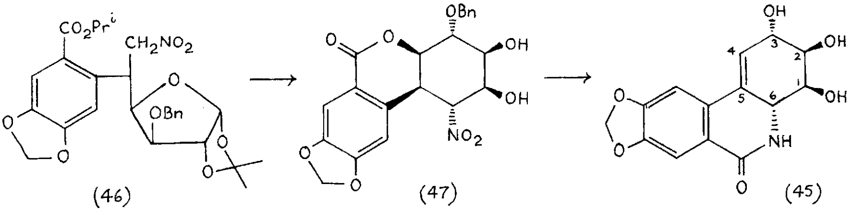
Scheme 13

A key chiral template (43) for a synthesis of thienamycin has been prepared from the azido-cyano sugar (44) obtained from 2,6,-dideoxy-D-arabino-hexose (see Chapter 13,ref.31).[28] Full details of the synthesis of the chromomycinone sidechain from D-arabinose have now appeared (see Vol.14,p.219).[29]



(44) (43)

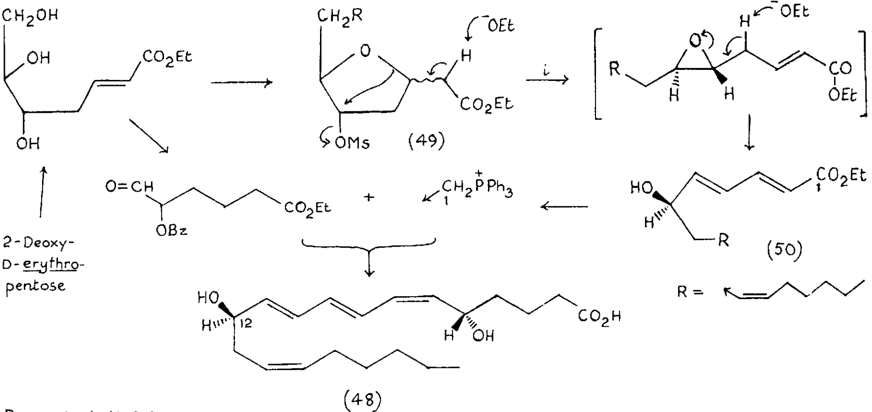
A synthesis of (+)-lycoricidine (45)(glucose numbering) from D-glucose involved addition of an aryl carbanion to an unsaturated nitro-sugar to give the adduct (46) which gave the muco-cyclitol derivative (47) on hydrolysis (Scheme 14).[30]



(46) (47) (45)

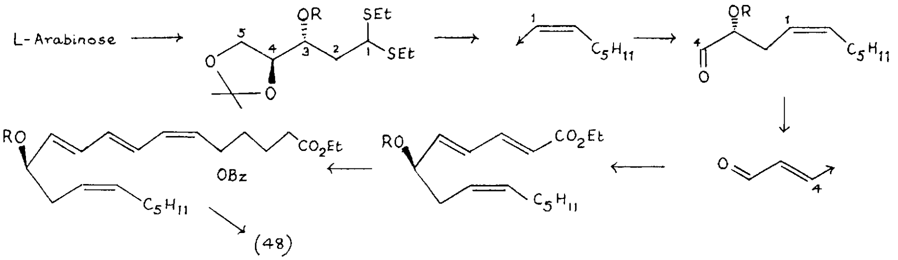
Scheme 14

A stereospecific synthesis of leukotriene B_4 (LTB_4)(48) from 2-deoxy-D-erythro-pentose has been described, outlined in Scheme 15. A key step in the synthesis utilized the discovery that furanose C-glycosides having a good leaving group at C-3 act as diene precursors, illustrated in the conversion of (49) to (50).[31] (See also Vol.15,p.254). The authors have also shown that the synthesis of LTB_4 and 12-epi-LTB_4, using L- and D-arabinose respectively as the source of chirality at C-12 in (48), allows greater synthetic flexibility and versatility than the use of 2-deoxy-D-erythro-pentose (Scheme 16).[32]



Reagent : i, NaOEt

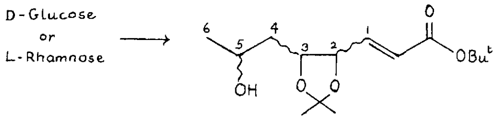
Scheme 15



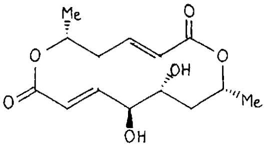
Scheme 16

6 Macrocyclic Compounds and Their Components

Epimeric poly-hydroxy-trans-unsaturated esters (51)(hexose numbering), required for the synthesis of the 14-macrolide colletodiol (52) and its stereoisomers, have been prepared from D-glucose and L-rhamnose respectively via 4,6-dideoxy-hexose intermediates.[33]

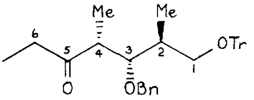


(51)

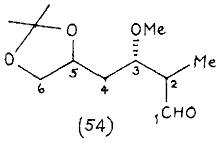


(52)

Chiral syntheses have been described for two segments representing C_{19}-C_{24} (53) and C_{25}-C_{29} (54) of rifamycin S, using multi-step sequences from D-glucose.[34] Another paper reports the enantiospecific synthesis of the C_{17}-C_{29} fragment (55) of rifamycin W,

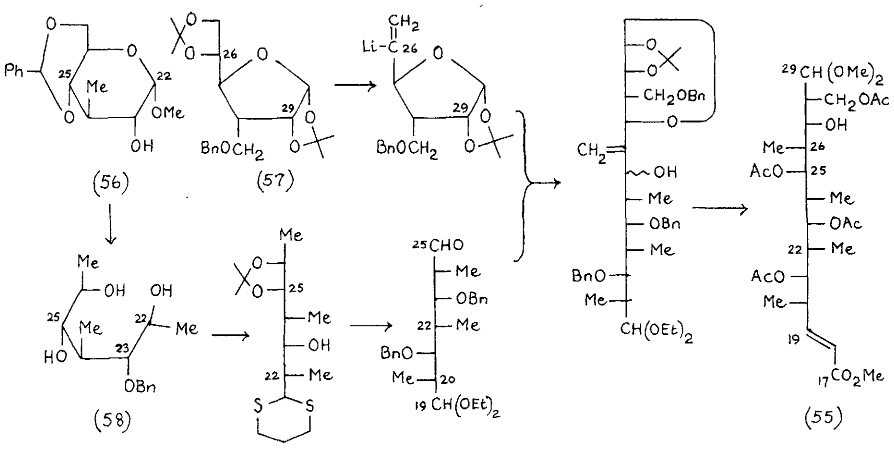


(53)



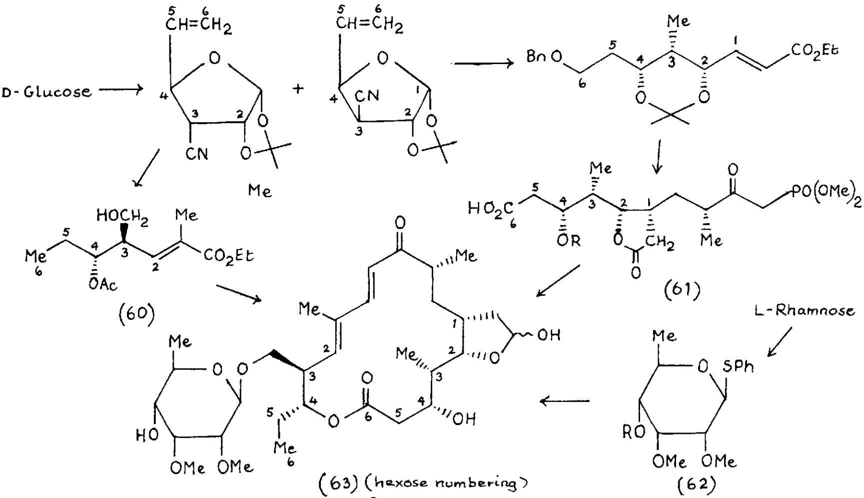
(54)

using the 3-deoxy-3-C-methyl-glucoside (56) and the 3-deoxy-3-C-hydroxymethyl branched-chain alloside (57) as starting materials, as outlined in Scheme 17. Reactions of interest include a highly stereospecific addition of methylmagnesium iodide to the free aldose leading to the alditol (58), and a highly regiospecific cleavage by lithium dithiane of a secondary-secondary oxiran (C_{22}-C_{23}) prepared from (58), leading to (59).[35]



Scheme 17

Three segments (60)-(62) of the macrolide antibiotic O-mycinosyltylonolide (63) have been synthesized from D-glucose and L-rhamnose as outlined in Scheme 18,[36] and these were then condensed to give the complete antibiotic.[37]



Scheme 18

Details of the synthesis of the 16-macrolide antibiotic A 26771B obtained from P. turbatum have been published (see Vol.14,p.221), together with the synthesis of stereoisomers (C-5 and C-15, R and S); the 5-(S)-antibiotic was derived from 5-deoxy-D-xylo-hexose, whereas the 5-(R)-antibiotic was similarly prepared from 2-deoxy-D-arabino-hexose, after preliminary inversion to 5-deoxy-D-lyxo-hexose. It is of interest that all four stereoisomers showed antibiotic activity, the 5-(R),15-(R) form being even more active than the natural 5-(S),15-(R) isomer, thereby providing an incentive for the preparation of unnatural stereoisomers of other macrolide antibiotics.[38]

The synthesis of crown-ethers incorporating glucose and dianhydro-mannitol units is referred to in Chapter 4.

7 Miscellaneous Compounds

The synthesis of cyclopentanone and cycloheptanone derivatives from D-mannose is covered in Chapter 17 (ref.38).

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