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Carbohydrate Chemistry

VOLUME 15

Part I

MONO-, DI-, AND TRI-SACCHARIDES AND THEIR DERIVATIVES

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Part I

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

A Review of the Literature Published during 1981

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Preface

This issue in the series of annual Specialist Periodical Reports on Carbohydrate Chemistry heralds the introduction of a new camera-ready format for the report. This radical change from the previous printed issues has been made in an attempt to stem the rapidly escalating costs of the report which have seriously threatened its viability. There is also a very desirable saving in production time, which we appreciate is another important feature governing the value of these surveys, and we hope to make further improvements in this respect with future issues. On the debit side, we hope our readers will bear with any variability in presentation between chapters, and in particular, with hand-drawn formulae which were chosen primarily to save time. Comments and criticisms would be appreciated since our aim is to provide what is most wanted by the users of the report.

The arrangement of chapters follows that adopted in previous reports; journals for 1981 available to us by February 1982 have been abstracted.

We welcome Dr. R.H. Furneaux as a new member of our team of reporters, and we would like to thank Dr. P. Gardam and Mrs. L.A. Turrell at the Royal Society of Chemistry for their encouragement and assistance in producing this report in its new format.

April 1983 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

Part I

MONO-, DI-, AND TRI-SACCHARIDES AND THEIR DERIVATIVES

By
B. E. Davison
R. J. Ferrier
R. H. Furneaux
N. R. Williams

1

Introduction

Although the two parts of this report are now being published separately, the general format and coverage of this section, covering the organic chemistry of mono-, di-, and tri-saccharides, has not been changed. It might be helpful to point out firstly that a hard and fast division has not been drawn between trisaccharides and higher oligosaccharides, particularly in the chapters dealing with glycosides and antibiotics, and secondly that the coverage on glycosides, antibiotics, nucleosides and related compounds containing carbohydrate units is selective for those papers where there is judged to be some specific carbohydrate interest besides any for the aglycone components; in the fringe areas, we hope this principle is acceptable in the interests of keeping the report within reasonable, economic limits.

The trends in research endeavour noted in recent reports have been continued, and the extensive sections on glycoside synthesis, antibiotics and nucleosides reflect the major interest in these areas. The synthesis of tri- and higher oligosaccharides is fast becoming a routine procedure for providing substrates of immunochemical interest. New antibiotic materials continue to be discovered consisting mainly or entirely of carbohydrate components in complex structures, and a ever widening variety of nucleoside analogues have been reported. These areas pose problems in classification, and we hope the distinctions that have been drawn between nucleosides on the one hand and miscellaneous nitrogen compounds on the other have not been too arbitrary for general acceptance. Another growth area has been the application of carbohydrates as chiral templates for the synthesis of a wide range of naturally occurring chiral compounds. Chapters 20 and 21 reflect the fruitful application of both routine and newer developments in spectroscopic techniques for the analysis of carbohydrate compounds and illustrate how much can be learned about relatively complex materials without actually doing any chemistry on them.

Recommendations for the nomenclature of unsaturated[1] and branched-chain[2] sugars, and of conformations of five and six-membered rings[3] have been published during the year.

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2

Free Sugars

The main pathways of reaction of primary free radicals in carbohydrates have been reviewed.[1] A review on the use of sugars in fermentation and for preparation of sweeteners, plastics and chemicals has appeared.[2]

The tastes of chlorinated derivatives of simple monosaccharides have been compared with those of the parent sugars and the disaccharides maltose and trehalose in relation to existing theories of the sweetness sensation.[3]

Isolation and Synthesis

The isolation by gel chromatography of D-threo-pent-2-ulose from the lipopolysaccharide of Pseudomonas diminuta NCTC 8545 represents the first time this sugar has been observed in a microbial polymer.[4]

Two reviews of the formose reaction by the same authors have appeared,[5,6] and in two further papers an overall model for the reaction catalysed by calcium hydroxide is described.[7,8] A key observation that sublimed paraformaldehyde was not transformed into sugars led to the suggestion that carbohydrates may be naturally present in p.p.m. quantities in paraformaldehyde and cause autocatalysis. Glycolaldehyde at 3 p.p.m. is sufficient to initiate autocatalysis. In the absence of traces of sugars the Cannizzaro reaction yielding methanol and formate occurred.

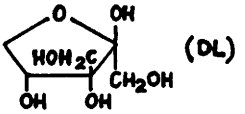
A solution of formose is an effective catalyst for converting formaldehyde to monosaccharides when used in 0.25 - 0.50 wt.% quantities. The induction period was shortened to one-sixth, and the Cannizzaro reaction was reduced by half with concomitant increased yield of monosaccharides from 42 to 60%.[9] Optimization of carbohydrate production in the formose reaction using calcium oxide and formose as co-catalysts gave an overall yield of 76.5%, comprised of hexoses (71%), pentoses (23%) and tetroses (6%).[10] The formose reaction has been studied at cryogenic temperatures: under u.v. irradiation at 20-80K solid formaldehyde underwent polyaddition and polymerization to give polyoxymethylene. A mixture of simple aldoses resulted.[11] A study of the catalytic activity of inorganic bases towards the Cannizzaro reaction of

formaldehyde has shown that barium hydroxide is more effective than calcium hydroxide, and both are considerably more active than magnesium hydroxide. Selectivity for the Cannizzaro reaction increased on addition of copper powder, copper sulphate, ferric sulphate, bismuth chloride, or boric acid, was unaffected by addition of iron or magnesium powder, and decreased by added tin(IV) chloride. Decreasing the temperature from 40 to 10 °C reduced the induction period, reaction time and yield of Cannizzaro products but increased the yield of sugar derivatives.[12] Zinc oxide has been shown to catalyse the formose reaction to give a complex mixture of sugars at pH 5.5 without the Cannizzaro side reaction. Addition of D-glucose or reduction of the formaldehyde-zinc oxide ratio eliminated the otherwise long induction period.[13] G.c. analysis of the formose products under different reaction conditions with calcium salts as catalysts has shown that the complexity of the product distribution was controlled by the ratio of calcium ion-formaldehyde concentrations.[14] A study of the formose reaction in methanol has been conducted.[15] Amines and free amino-acids can provide a necessary complementary interaction between the asymmetric carrier, the metal catalyst, and the synthesized enantiomeric forms of sugars in the formose reaction. Thus heptulose, D-*manno*-oxoheptulose, and D-fructose were obtained in a process utilizing a cellulose carrier and an amino-acid, with calcium and magnesium oxides as catalyst. The product mixture contained 22% neutral and 78% acidic sugars.[16] A study of the catalytic activity of benzoyl carbinol and its 4-methoxy-, 3-chloro-, 4-chloro-, and 2,5-dichloro-derivatives on the condensation of formaldehyde in the presence of triethylamine and lead or calcium hydroxide has confirmed that electron-donating substituents in the organic co-catalyst decreased its catalytic activity and *vice versa*. The rate of condensation did not depend on the concentration of formaldehyde.[17] A selective formose reaction occurs giving 3-*C*-(hydroxymethyl)-pentofuranose (1) when the major part of the calcium ions are removed as sparingly soluble salts at the end of the induction period, followed by addition of basic lead oxide $[Pb_2O(OH)_2]$ and by adjusting to pH 10 with aqueous potassium hydroxide, successively.[18]

The synthesis of the carbohydrates of glycoproteins has been reviewed (in Japanese).[19]

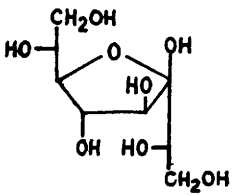
D-*manno*-Heptulose has been prepared by DCC-catalysed isomerization of D-*glycero*-D-*galacto*-heptose and D-*glycero*-D-*talo*-

heptose in yields of 57 and 30% respectively.[20] A separable mixture of 2,3,4,6-tetra-O-benzyl-L-idopyranose and its D-gluco-



(1)

isomer was obtained from L-sorbose by a sequence involving reduction at C-2 and oxidation at C-6 using conventional protecting group methodology.[21] Aldol self-condensation of D-erythrose under weakly alkaline conditions at 105 °C for 2 - 5 h yielded β-D-altro-L-glycero-3-octulofuranose (2) in addition to the known α-D-gluco-L-glycero-3-octulopyranose (3) and D-glycero-tetrulose which were all isolated as their peracetates. Treatment of (2) with an acidic ion-exchange resin yielded 3,6-anhydro-β-D-altro-L-glycero-octulo-pyranose (4).[22]



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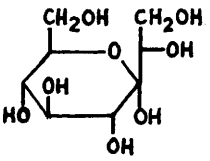

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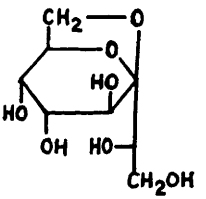


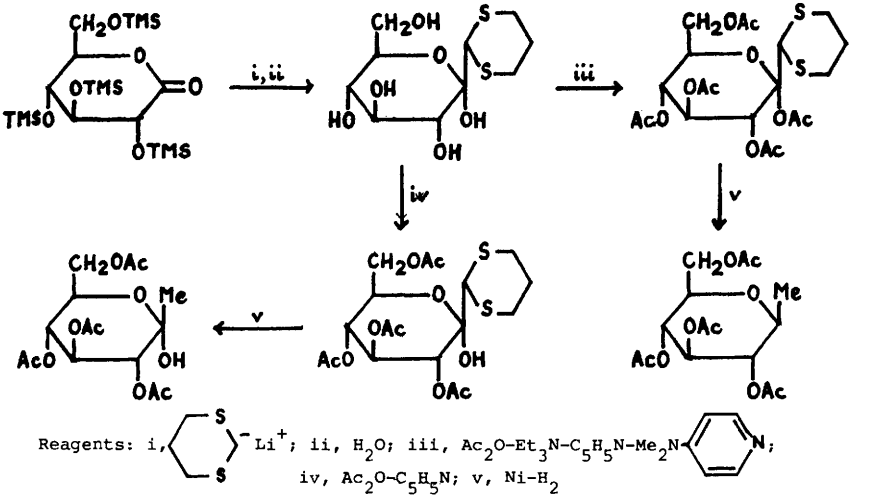
(4)

Reactions of the 1,3-dithiane anion with D-gluconolactone derivatives has enabled syntheses of 1-deoxy-ketoses and C-methyl glycosides as shown in Scheme 1.[23]

A chemicoenzymic approach has been used[24] to prepare enantiomerically pure D- and L-ribose *via* the Diels-Alder adduct (5) as shown in Scheme 2.

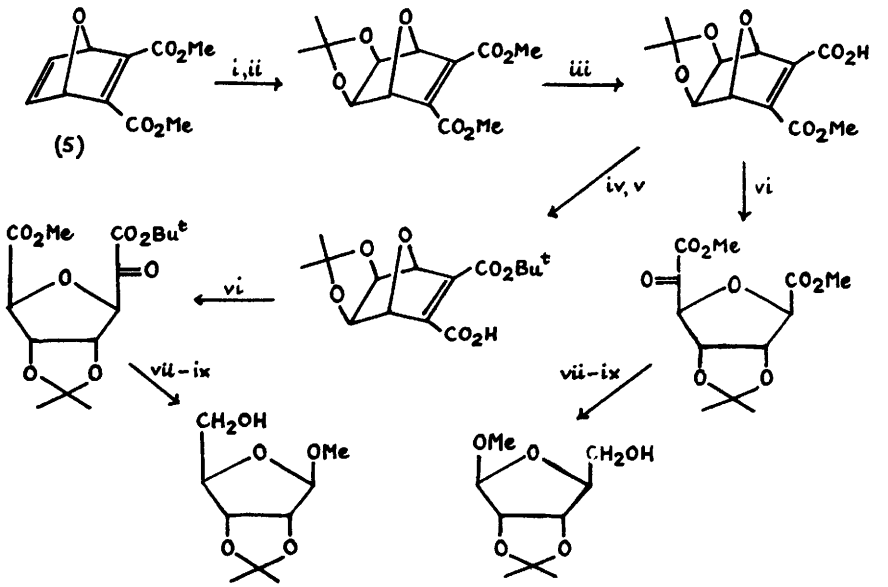
The cadmium complex (6) prepared *in situ* from 2-allyloxybenzimidazole, reacts with 2,3-O-isopropylidene-D- and -L-glyceraldehyde to give the corresponding enantiomeric adducts which were converted into D- and L-ribose by the sequence shown (for the L-enantiomer) in Scheme 3.[25]

A stereoselective synthesis of D-ribulose has been reported (Scheme 4). Addition of metal halides to the initial reaction mixture changed the ratio of (7) and (8) produced. The best results were obtained with zinc bromide at 0 °C when (7) predominated (ratio 95:5) in a total yield of 75%. Complexation as shown in (9)



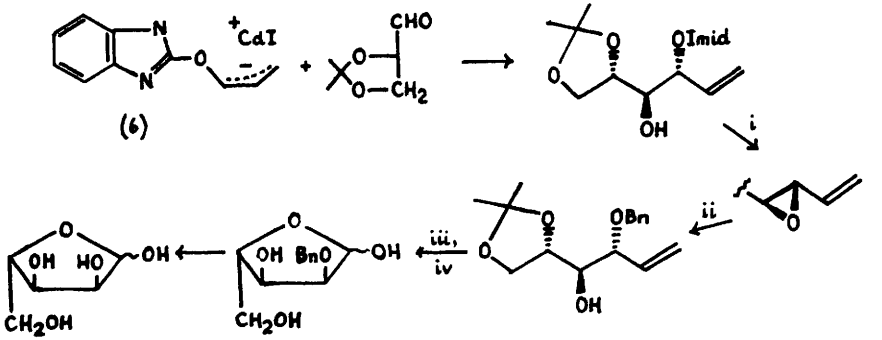
Reagents: i, Li^+; ii, H_2O; iii, Ac_2O-Et_3N-C_5H_5N-Me_2N-; iv, Ac_2O-C_5H_5N; v, Ni-H_2

Scheme 1



Reagents: i, OsO_4-*N*-methylmorpholine-*N*-oxide-Bu^tOH-H_2O-THF; ii, $(Me)_2C(OMe)_2$-*p*-TsOH-Me_2CO; iii, pig liver esterase; iv, $(CH_3)C{=}CH_2$-H^+; v, OH^-; vi, O_3-MeOH, -78 °C; vii, MCPBA; viii, MeOH-HCl; ix, $LiAlH_4$

Scheme 2



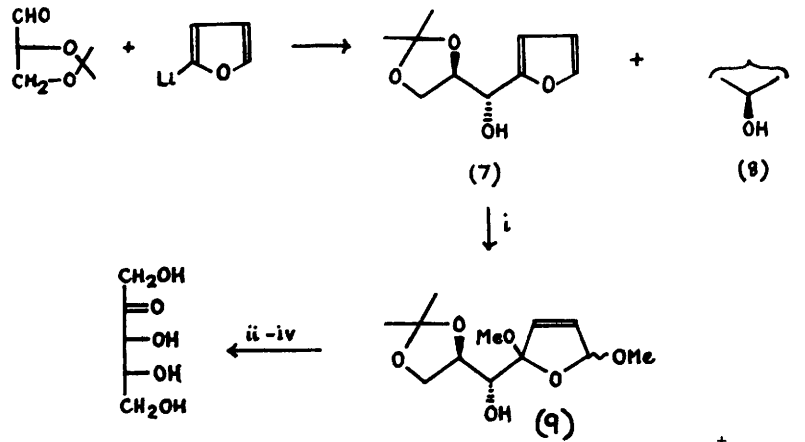
Reagents: i, NaH; ii, BnOH; iii, O_3; iv, Me_2S

Scheme 3

was postulated as the cause of stereoselectivity.[26]

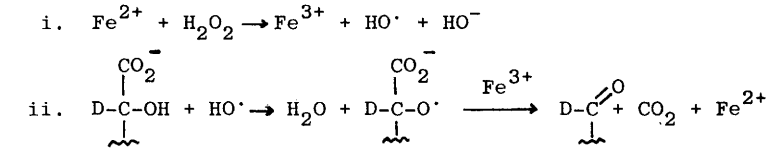
Improved methods for the synthesis of 2-deoxy-D-arabino-hexose and its methyl and benzyl glycosides have been reported.[27]

The mechanism for the Ruff degradation has been revised following the observation that calcium D-[2-H^2]gluconate gave D-[1-H^2]-arabinose, thus eliminating the intermediacy of the gly-2-ulosonic acid (Scheme 5).[28]



Reagents: i, Br_2-MeOH; ii, O_3; iii, $NaBH_4$; iv, H^+

Scheme 4



Scheme 5

An enzymic method for making [5-^{14}C]glucose and [4,5,6-^{14}C]glucose from [2-^{14}C]glycerol and [U-^{14}C]glycerol respectively with D-fructose 6-phosphate uses a mixture of glycerokinase, glycerol 3-phosphate dehydrogenase, triose phosphate isomerase, transaldolase, lactate dehydrogenase and phosphoglucose kinase in the presence of pyruvate to maintain NAD^+ concentration.[29]

4-Nitrophenylhydrazones of maltose, cellobiose and lactose have been degraded to the corresponding 3-*O*-(D-glucosyl or D-galactosyl)-D-arabinose disaccharide by hydrogen peroxide in the presence of molybdate ions.[30]

Physical Measurements

The rates of protonation of the hydroxy groups of twenty-six monosaccharides have been measured in DMSO. The rates for anomeric hydroxy groups, which are, in general, lower than those of the other secondary alcohol groups, are sensitive to the axial or equatorial nature of the neighbouring hydroxy function.[31]

Pulse radiolysis[32] and e.s.r.[33] have been used to study localized electrons in irradiated rhamnose. The mechanism for formation of alkoxy radicals (RCHO·) is briefly discussed. The e.s.r. spectrum of Me_3CNO-trapped radicals produced in standard sugars by γ-radiolysis or aqueous solution u.v. photolysis have been reported.[34] An e.s.r. study of the oxidation of D-glucose and related compounds with the hydroxy radical indicated that it was an indiscriminate reagent generating all six possible carbon radicals; the relative ease of their acid-catalysed fragmentation was studied, and potential fragmentation routes by glycosidic cleavage of first formed radicals identified.[34a] *X*-Ray diffraction of sucrose before and after γ-irradiation has shown that the latter causes damage to the lattice.[35]

An equation relating quantitative dependence between the rate of dehydration of pentoses and hexoses, their physical properties and the characteristics of cationic catalyst used (*e.g.*, $CrCl_3$ or

$AlCl_3$) has been described.[36]

The chemiluminescence spectra of sucrose, xylose, and lactose in aqueous solution have been determined.[37]

Hydrogenation of D-glucose over Raney nickel was found to be first order with respect to hydrogen and zero order with respect to D-glucose when the concentration of the latter was >0.16M. Between 99 and 124 °C the activation energy is 83.06 kJ mol^{-1}. The rate increased with increase in stirring speed.[38] In contrast, it is reported that when hydrogenation of D-fructose and D-glucose is carried out on a nickel-kieselguhr catalyst the reaction is first order in the sugar. With this catalyst the yield of mannitol is <16%.[39] The cathodic reductions of D-glucose[40] and D-xylose[41] at various temperatures have been studied using lead electrodes. The rate of production of sorbitol from D-glucose was accelerated by addition of zinc ions.[40] Rate constants for mutarotation and ring-opening of D-xylose were also determined.[41] Quantitative comparisons between various catalysts in the isomerization of lactose in aqueous alkaline solutions to yield lactulose and epilactose have been made. The isomerization-degradation ratio was maximum for the alkali and alkaline earth hydroxides and it was shown that lactose degrades via intermediate formation of lactulose. The effect of molybdate on epimerization of lactose was also studied.[42]

The most complete description to date of the mutarotation of α- and β-D-galactopyranose has appeared. Three sets of conditions were used and isomer proportions were determined by g.l.c. methods. Rate constants and thermodynamic parameters were determined for the formation of furanoses and the interconversions of pyranoses and acyclic forms were also quantitatively considered.[43] Thermochemistry and thermokinetics of mutarotation of D-glucose have shown that the α to β conversion is accompanied by a loss of energy while the β to α conversion takes place with absorption of energy and increased entropy. These results were taken to suggest increased hydrogen bonding for the β-anomer, which may involve intramolecular or solute-solvent interactions.[44] Bifunctional catalysis of the mutarotation of D-glucose in mixed aqueous solvents has been investigated. Catalysts used included 2- and 4-hydroxy-pyridine, pyrazole, formic acid, and the formate ion in aqueous DMSO or dioxan. Catalytic rate constants were understandable on the basis of reactant solvation and bulk medium structure.[45] Mutarotation of D-glucose in water and in ethylene glycol has been studied and it was shown that hydrochloric acid, acetic acid, 1,1-

and 1,3-dimethylurea all accelerated the rate in both solvents. In water the velocity was at a maximum at 30-40 °C whereas at this temperature the reaction was at a minimum in ethylene glycol.[46] A calculation[47] of the specific rotation of invert syrups gives the observed value if the $[\alpha]_D^{20}$ of D-fructose is taken as -92.4° and that of D-glucose as +52.5 . N.m.r. has been used to study the pH dependence of mutarotation of N-acetyl-D-neuraminic acid. The minimum rate was found to occur at pD 5.4 and at pD < 1.3 or > 11.7 it was too fast to measure.[48]

Specific heat capacity measurements of mono-, di-, and trisaccharides have been taken using an isoperibol twin calorimeter. The results were discussed in relation to hydration number and diffusion constant data.[49,50] The hydrodynamic and electro-osmotic permeability of aqueous D-fructose, D-glucose, and sucrose solutions through a pyrex sinter[51] and through a cholesterol-coated membrane[52] were measured, and the data obtained were shown to be consistent with the sugars increasing the water molecule aggregation. A principle advanced by J.H. Hildebrand relating viscosity with free volume and molar volume in simple liquids has been demonstrated to provide a volumetric interpretation of the viscosities of concentrated and dilute aqueous solutions of sugars.[53] A model of the increasing organization in aqueous solutions of D-fructose, D-glucose, and sucrose with increasing concentration has been proposed on the basis of results obtained by X-ray diffraction. The different behaviour of sucrose was attributed to the formation of intramolecular hydrogen bonds between the two monosaccharide units in concentrated solution.[54] Heats of dilution in water of D-xylose, D-fructose, D-galactose, D-mannose, lactose, and raffinose[55] and those of L-fucose and L-rhamnose[56] have been determined by microcalorimetry and the data used to calculate excess enthalpy terms. The results indicate that solute-solvent interactions predominate over solute-solute interactions. The structure of aqueous monosaccharide solutions has also been studied by measurement of apparent molal volumes. The conclusion in this case however was that the increase with concentration was due to solute-solute interactions.[57] Conductance values for lactose with alkali-metal halides in water and in formamide undergo an abrupt transition on passing from unsaturated to supersaturated solution. This transitional behaviour was discussed in terms of solute-solvent interactions.[58]

Conformations of free sugars are discussed in Chapter 20.

Oxidation

One-electron oxidation of monosaccharides has been reviewed (in Russian).[59]

A one-electron mechanism for the oxidation of D-arabinose by copper(II) sulphate or iron(III) sulphate in ethanol or propanol, whose key step is the formation of an oxy-cation at C-1 which then reacts with solvent, has been proposed.[60] Rate constants as their logarithms have been listed for the oxidation of several aldoses by iron(III), mercury(III), and silver(I), and shown to be linear functions of free energies.[61] The oxidation of D-xylose, L-arabinose,and D-ribose by vanadium(V) in hydrochloric acid media was shown to be first order in both substrate and oxidant. The rate increases with increasing concentration of hydrogen ion and chloride ion. A chloro-complex of vanadium was assumed to be the active species.[62] The kinetics of oxidation of D-glucose by thallium(III) perchlorate have been determined, and the rate shown to be first order in both thallium(III) and the sugar. Addition of chloride ion or acetate ion inhibited the reaction.[63] Formic acid and arabonic acid were the products of oxidation of D-mannose by copper(II) in the presence of hydroxylamine. Rate data suggested that enolization was the rate-determining step, and that the enediol anion was the intermediate.[64] The kinetics of oxidation of D-glucose by potassium bromate have been measured; a mechanism was suggested based on the fact that the rate is first order in sugar and potassium bromate and second order in hydrogen ion concentration.[65] Radicals are the proposed intermediates in the oxidation of L-sorbose by vanadium(V) ions. The authors conclude that the ketose is attacked by $[V(OH)_3]^{2+}$ in the rate-determining step with support for the proposed mechanism coming from linear Hammett-Zucker and Bunnett plots.[66] Other authors have studied the kinetics of oxidation of L-sorbose by vanadium(V); the oxidation of D-fructose by the same oxidant and of the two ketoses by chromium(VI) were also investigated. From enthalpies and entropies of activation and the observations that a change of medium from water to deuterium oxide affected the rate for chromium(VI) but not for vanadium(V), it was suggested that the former proceeds without formation of an intermediate complex but the latter forms a 1:1 intermediate.[67]

A review of alkaline oxidation and degradation of sugars includes data for alkaline copper and related reagents acting upon glycolaldehyde, glyceraldehyde and dihydroxyacetone.[68]

The reaction between sorbitol and cerium(IV) sulphate in aqueous sulphuric acid proceeds as a normal second order oxidation, the rate decreasing with increasing acid concentration.[69]

Hexacyanoferrate(III) in ammoniacal media is a catalytic oxidant for cellobiose and melibiose. The rate is first order in di-saccharide and half order in ammonia; intermediate enediolate anions were suggested.[70]

Other Reactions

The selective conversion of D-fructose to 5-hydroxymethyl-furan-2-carboxaldehyde using an ion-exchange resin in biphasic liquid medium has been reported. The product is extracted as it forms and before it becomes converted into laevulinic acid and formic acid.[71] The same reaction has been carried out in high yield (~90%) using strong acid ion-exchange resin in DMSO.[72] D-Erythrose gives a range of dihydroxybenzene and 2-hydroxymethylfuran derivatives in weak aqueous acid.[73]

Products from D-fructose radicals produced by γ-radiolysis in aerated solution included D-*arabino*-hexosulose, D-*threo*-2,5-hexodiulose, D-*threo*-2,3-hexodiulose, and D-*lyxo*-hexos-5-ulose.[74]

The homogeneous catalytic hydrogenation and transfer hydrogenation of D-glucose using Wilkinson ruthenium catalyst has been investigated. Dioxan, propan-2-ol, butan-2-ol, and 2-methoxyethanol were used as proton donors. Under hydrogen atmosphere the main product was D-sorbitol whereas under nitrogen another unspecified side reaction occurred. The effect of added bases was also studied.[75]

Thermal degradations of sucrose have been reviewed.[76]

Reactions of D-fructose, D-psicose, D-tagatose, L-sorbose, and their various 5- and/or 6-*O*-alkylated derivatives, with β-alanine have been studied, and the rate of reaction of the sugar during the ketosylamine rearrangement was shown to be related to the portion of free keto group in the sugar.[77]

The degradation of D-ribose, D-ribose 5-phosphate, and various ribonucleosides and ribonucleotides by ozone in aqueous solution was investigated as a first step in elucidating its role in virus inactivation. The ribose moiety was degraded more slowly than the base portion in nucleosides and nucleotides, except in the case of adenosine in which the adenine is most stable to ozone. Ribose 5-phosphate resisted attack of ozone. It was suggested that the

guanine might be the initial site of attack in RNA.[78] Several aldoses and ketoses have been examined for inhibition of human acrosin to find the structural determinants.[79]

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3
Glycosides

1 O-Glycosides

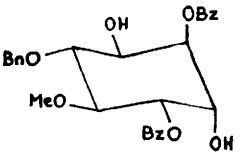
1.1 Synthesis of Monosaccharide Glycosides.- Fischer glycosidation of 2-amino-2-deoxy-D-glucose 6-phosphate in methanol gave access to the anomeric pyranosides and their 6-(methyl phosphate) esters which were separated by ion-exchange chromatography,[1] and reversed phase h.p.l.c. was used to resolve the four methyl glycosides similarly derived from D-glucose, D-fructose, D-ribose and D-xylose.[2]

A novel synthesis of α-glucopyranosides is based on reduction of 1-O-acyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranoses with sodium borohydride in diglyme in the presence of boron trifluoride. Isolated yields were about 60% when simple acyl groups like acetyl and butanoyl were used, but the main product formed from 1-esters which had α-alkoxy substituents within the acyl groups was 1,5-anhydro-tetra-O-benzyl-D-glucitol.[3]

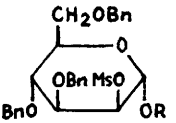
Glycosidations involving the use of 1,2-orthoesters and amide acetals have been briefly reviewed.[4]

Selective α-galactosylation of the equatorial hydroxy group of the pinitol derivative (1) was effected using the imidate procedure, the axial group being relatively unreactive, and in this way 1D-2-O-(α-D-galactopyranosyl)-4-O-methyl-chiro-inositol was produced.[5]

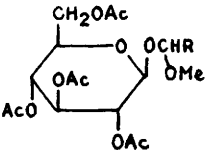
1-O-Sulphonates have been employed in a new approach to the synthesis of β-linked D-mannopyranosides and L-rhamnopyranosides, the esters (2) and (3), for example, giving access to simple mannosides



(1)



(2) R = Ts
(3) R = $CF_3CH_2SO_2$

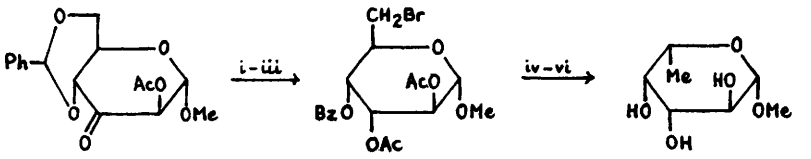


(4) R = H, Pr, Ph, Bn, CH_2Cl, etc.

and disaccharides.[6] In a modified procedure, sugars carrying O-benzyl substituents at all oxygen atoms except O-1 were treated with trifluoromethanesulphonic anhydride and then with hydroxylated amino-acids as their N-benzyloxycarbonyl benzyl esters to give α- and β-anomers of products from which α- and β-O-glycosyl-L-serine, -L-threonine and L-hydroxyproline were obtained.[7] Alternatively, 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose has been condensed with a range of alcohols (including monohydroxy-sugars) by treatment with trimethylsilyl bromide in dichloromethane (in the presence of $CoBr_2$, Bu_4NBr, and molecular sieve). High yields and α:β ratios of about 3-5 were recorded.[8] 2,3,4,6-Tetra-O-acetyl-1-O-trimethylsilyl-β-D-glucose, condensed with mixed acetals of simple aldehydes in the presence of catalytic trimethylsilyl triflate, gave good yields of the acetals (4),[9] and the same catalyst was shown to catalyse efficiently both the reaction of glycosyl 1,2-trans-diacetates or 1,2-oxazolines with alcohols, and also the rearrangement of 1,2-orthoesters.[10]

Reaction of sugar peracetates with 2,2,2-trichloroethanol in the presence of boron trifluoride gives the corresponding glycosides - mainly those with the 1,2-trans-configuration.[11] The reaction has also been carried out with a 2-deoxy-2-(N-phthalimido)-glycosyl acetate, the tributyltin derivative of the alcohol and tin(IV) chloride.[12] 2,2,2-Trichloroethyl β-D-galactopyranosides (and tert-butyl analogues) can be anomerized efficiently by use of boron trifluoride and the glycosidic bonds cleaved under mild conditions.[13]

Reaction of N-bromosuccinimide in methanol with tri-O-acetyl-D-glucal followed by reductive debromination gives access to methyl 2-deoxy-α- and β-D-arabino-hexopyranoside,[14] and methyl β-L-fucopyranoside was prepared by the methods indicated in Scheme 1, the



Reagents: i, $NaBH_4$; ii, Ac_2O; iii, NBS-CCl_4; iv, AgF; v, MeO^-; vi, H_2-Pd

Scheme 1

C-3 deuterated analogue being available by appropriate use of sodium borodeuteride.[15]

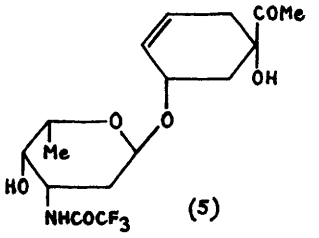
Glycosides derived from 2-(trimethylsilyl)ethanol have been pre-

pared from free sugars, unsaturated derivatives, and glycosyl halides by standard methods; these glycosides are converted readily to the free sugars by mild reaction with lithium tetrafluoroborate:

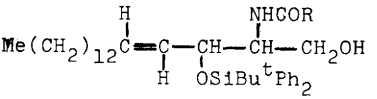
$$ROCH_2CH_2Si(Me)_3 + LiBF_4 \rightarrow ROH + CH_2{=}CH_2 + FSiMe_3.$$[16]

Allyl α-D-galactopyranoside, on epoxidation and controlled hydrolysis of the epoxide rings, affords the diastereomeric 2,3-dihydroxypropyl glycosides (isofloridosides).[17]

Tetra-O-benzyl-β-D-glucopyranosyl fluoride has been shown to react with simple and complex alcohols - including sugar derivatives - to give good yields of glycosides having α:β ratios in the range 4-8:1.[18] β-D-Mannopyranosides can be made by converting 2,3:4,6-di-O-cyclohexylidene-α-D-mannose to the corresponding α-chloro-compound using methanesulphonyl chloride and triethylamine followed by reaction with alcohols; useful syntheses of various disaccharides were achieved.[19] Koenigs-Knorr procedures have been used to prepare β-D-glucopyranosyl derivatives of L-serine[20] and 2-acetamido-2-deoxy-D-glucopyranosyl analogues[21] required for making glycopeptides, and, for pharmaceutical purposes, 4-O-(β-D-galactopyranosyl)paracetamol,[22] the cyclohexenyl glycoside (5) which is related to a component part of daunomycin,[23] hexo-[24] and pento-pyranosyl and -furanosyl[25] derivatives of gentamines, and 16-β-D-glucuronosylestriol, the concentration of which correlates in pregnancy with foetal maturity.[26]



(5)



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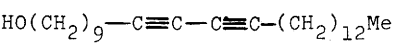
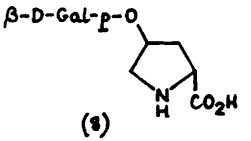


(7)

Koenigs-Knorr β-galactosylation of the alkenes (6) gave natural cerebrosides with the erythro- and threo-configuration,[27] and similar β-glucosylation of the diyne (7) afforded a product which forms lyposomes which, before and after polymerization, react with concanavalin A.[28]

The trans-4-hydroxyproline β-D-galactopyranoside (8) has been obtained from an arabinogalactan peptide of wheat endosperm, and also prepared by Koenigs-Knorr synthesis.[29] A series of glycosides related to the nitroxide (9) were similarly prepared as spin



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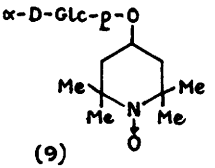

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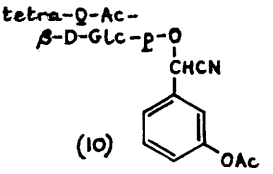
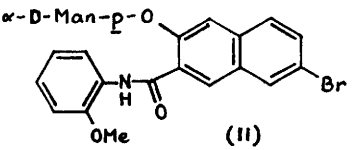


(10)

labelled compounds.[30]

A set of cyanogenic glycosides has been studied by ^{13}C n.m.r. spectroscopy.[31] The pentacetate (10) of holocalin has been prepared by the Koenigs-Knorr method.[32]

Aryl β-glucosides and -galactosides have been synthesized using glycosyl halides by the phase-transfer technique; yields were in the region 30-70% and products of hydrolysis and elimination were formed in side reactions.[33] 4-Formylphenyl glycosides, prepared by the Koenigs-Knorr method, have been used to obtain compounds containing the 4,4,5,5-tetramethylimidazolidine-1-oxide ring as further spin-labelled derivatives.[34] The same group of workers produced 3-hydroxy-2-nitrophenyl β-D-galactosides and 6-deoxy analogues which chelated lanthanide metal ions, giving complexes which were found to bind to β-D-galactosidase and to the *lac* repressor of E. coli, making them useful as n.m.r. probes of active sites.[35] Further Koenigs-Knorr syntheses reported include the naphthyl glycoside (11), a chromogenic substrate for mannosidase,[36] *O*- and *C*-β-D-glucosides of tetrahydrocannabinol,[37] and various *O*-glycosylated xanthones.[38]

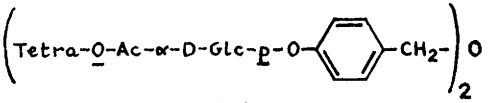


(11)

A novel way of making aryl glycosides or their 1-thio analogues uses carbodi-imide coupling of phenols and thiophenols with 2,3,4,6-tetrabenzyl-α-D-glucopyranose in the presence of copper(I) ions. Good yields are obtained mainly of β-products.[39] Otherwise, the same sugar derivative can be condensed with phenols in the presence of *p*-nitrobenzenesulphonyl chloride, silver methanesulphonate, and triethylamine; in this case α-products predominate.[40] Various reports have appeared on the use of sugar peracetates in the

synthesis of aryl glycosides. Tin(IV) chloride as catalyst leads to α-galactosides, -maltosides and 1-thio-analogues in some cases, but a more general way of preparing such compounds uses acetylated β-glycosyl chlorides and sodium phenates in HMPT.[41] Use of anhydrous copper(II) sulphate prevents anomerization in reactions involving glycosyl acetates;[42] the stereoselectivities of such reactions has been followed by ^{13}C n.m.r. spectroscopy.[43] o-Nitrophenyl α-D-galactopyranoside has been made from the sugar peracetate using a zinc chloride catalyst.[44]

Syntheses from pre-formed glycosides include p-aminophenyl α-D-mannopyranoside and α-L-fucopyranoside from the nitro-analogues,[45] and the symmetrical diglycoside (12), which was produced by condensing the corresponding α-bromobenzyl and α-hydroxybenzyl glycosides.[46]



(12)

1.2 Synthesis of Disaccharides and Their Derivatives.- A useful synthesis of non-reducing disaccharides involves condensing free sugars, benzylated at all centres except the anomeric, using trifluoromethanesulphonic anhydride. α-Linked products are favoured.[47] A 2-amino-2-deoxy analogue of α,α-trehalose has been prepared from 2,3,4,6-tetra-O-(p-chlorobenzyl)-α-D glucose with 3,4,6-tri-O-acetyl-2-(2,4-dinitrophenyl)amino-2-deoxy-α-D-glucosyl bromide; α-D-mannopyranosyl 2-amino-2-deoxy-α-D-glucopyranoside was similarly obtained.[48] The trehalose uronic acids (methyl 4-O-methyl-D-glucopyranosyluronate) (methyl 4-O-methyl-D-glucopyranuronate) have also been reported.[48a]

Reducing disaccharides are noted according to the nature of the non-reducing moieties. Methyl α- and β-maltosides have been prepared by direct Fischer glycosidation.[49] A procedure for converting maltose into the corresponding 4-O-altropyranosyl-D-glucose *via* anhydro intermediates is described in Chapter 4.

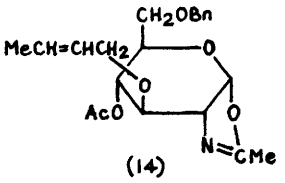
The anomeric peracetates of 3-O-β-D-glucopyranosyl-D-arabinofuranose and -pyranose have been isolated after reacetylation of the products of sodium methoxide-catalysed degradation of octa-O-acetylcellobiononitrile.[50] The glucosylgalactoside derivative (13)

α-D-Glc-p(1 → 2)β-D-Gal-p-O-lysyl-glycine
(13)

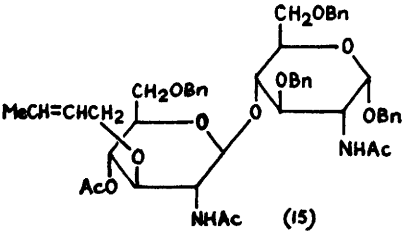
has been synthesized by conventional methods for biological studies, the α-glucosylation being effected by the amidate procedure.[51]

6-O-Acetyl-2-azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosyl bromide is a useful reagent for preparing α-linked 2-amino-2-deoxy-D-glucose derivatives, and has been used to make several disacchardies.[52] Several other papers have reported glucosamine-containing disaccharides. Methyl 6-O-(2-amino-2-deoxy-β-D-glucopyranosyl)-D-glucopyranoside and the isomeric glycoside having the amino group in the reducing moiety were both active against leukemia virus in mice in the form of their 2-(β-chloroethyl-N-nitrosoureido) derivatives.[53] 4-O-(2-Amino-2-deoxy-α-D-glucopyranosyl)-L-(6-^{3}H) idose and eight derivatives varying in having sulphate esters or N-acetyl groups or 1,6-anhydro rings on the idose residue, have been isolated from carboxyl-reduced heparin (NaB^3H_4) after acid hydrolysis.[54] Similar reduction of 3-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-galactose 6'-sulphate, obtained enzymically from keratan sulphate, yielded the corresponding [1-^{3}H]galactitol derivative which is suitable as a substrate for monitoring (1 → 3)-N-acetyl-β-D-glucosaminidase activity.[55] The above (1 → 3) linked disaccharide (unsulphated) and corresponding disaccharides involving 4-β-links to D-galactose and 2-acetamido-2-deoxy-D-glucose and a 6-link to D-galactose have been synthesized using the oxazoline procedure.[56] Similar methods were used to obtain derivatives of 6-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-mannose[57] and related work using a β-glycosyl chloride afforded (1 → 3), (1 → 4) and (1 → 6) linked (2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-mannose derivatives.[58]

Several reports of disaccharides comprising two 2-amino-2-deoxy-D-glucose units have appeared. The differently substituted glycosylating agent (14) has been developed for use in making

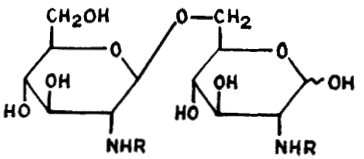


(14)



(15)

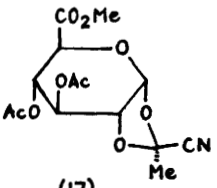
oligosaccharides containing 2-acetamido-2-deoxy-D-glucose as a branching point, and from it the chitobioside (15) was prepared.[59] Di-N-acetylchitobiose, oxidized to the aldonic acid, afforded long-chain alkyl amides which were used in binding studies with lectins.[60] The oxazoline method was used to prepare the 6-linked disaccharide (16) which is part of the lipid A component of



(16) R= -COCH(OH)$(CH_2)_{10}$Me

bacterial lipopolysaccharides[61] and, in related studies, similar methods were used to produce a 3,4,6'-tri-O-2,2'-di-N-palmitoyl derivative of the same compound.[62]

D-Glucuronic acid-contining disaccharides continue to attract attention. The 1,2-O-cyanoethylidene derivative (17) afforded good means of making the 6-linked compound (18) when condensed with the



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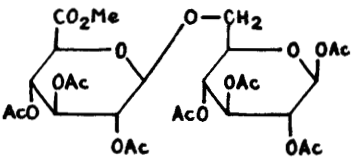
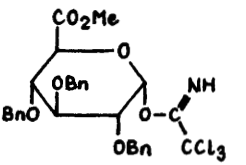


(18)



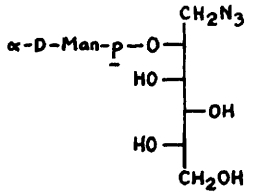
(19)

corresponding 6-trityl ether.[63] In related work the benzyl ether, methyl glycoside analogue of compound (18) and other aldobiuronic acid derivatives were made using the trichloroamidate (19) as glycosylating agent.[64]

2,5-Anhydro-O-(β-D-glucopyranosyluronic acid)-D-mannitol and the corresponding α-L-idopyranosyluronic acid derivative and their sulphate esters have been isolated in labelled form after nitrous acid deamination of heparin followed by reduction with NaB^3H_4.[65] Methanolysis and subsequent saponification of 2-O-(4-O-methyl-α-D-glucopyranosyluronic acid)-D-xylose gave the corresponding anomeric xylofuranosides and -pyranosides which were characterized by ^{13}C n.m.r. spectroscopy. Similar treatment of the corresponding 4-O-(α-D-galactopyranosyluronic acid)-D-xylose gave, as expected,

only the two pyranosides. Methylation (Hakamori method) of 4-O-methyl uronic acid derivatives caused partial elimination of this substituent.[66] In related studies 2-O-(4-O-methyl-α-D-glucopyranosyluronic acid)-D-xylose was synthesized using a glycosyl halide method.[67]

Two reports have appeared on the preparation of the disaccharide part of bleomycin, 2-O-(α-D-mannopyranosyl)-L-gulose. One used 2,4,6-tri-O-acetyl-3-O-(N-acetylcarbamoyl)-α-D-mannopyranosyl bromide and benzyl 3,4,6-tri-O-benzyl-β-L-gulopyranoside (also 1,6-anhydro-3,4-di-O-benzyl-β-L-gulopyranose), and gave the 3-O-carbamoyl disaccharide.[68] The other linked the mannose unit to O-5 of a 6-azido-6-deoxy-D-glucofuranose derivative and obtained the 2-O-substituted L-gulitol (20) which on photolysis gave the required disaccharide.[69]



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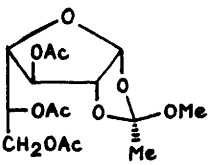


(21)

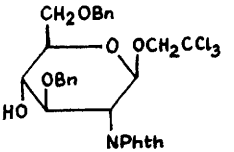
Orthoester (21) is useful as a β-D-galactofuranosylating agent and has been used to produce (1 → 2), (1 → 3) and (1 → 6) linked derivatives of methyl α-D-mannopyranoside which served as model compounds in a ^{13}C n.m.r. study of a D-galacto-D-mannan isolated from cell walls of *Trypanosoma cruzi* protozoa.[70] In the D-galactopyranosyl series a set of α-D-galactopyranosyl chloride derivatives, *e.g.*, 2,4-di-O-benzoyl-3,6-di-O-benzyl-α-D-galactosyl chloride, were developed for preparing oligosaccharides containing β-galactopyranosyl units bearing sugar substituents at O-4 or O-2 and O-4.[71] The *p*-nitrophenyl glycoside of 6-O-(β-D-galactopyranosyl)-β-D-galactopyranose was obtained by mercury(II) cyanide-catalysed Koenigs-Knorr glycosylation of *p*-nitrophenyl 2-O-benzoyl-4,6-O-isopropylidene-β-D-galactopyranoside. During the reaction the isopropylidene acetal migrated from the 4,6- to the 3,4-diol.[72]

In the series of compounds having D-galactose bonded to an amino-sugar, compound (22) was prepared for immunological studies,[73] and

β-D-Gal-p(1 → 3)α-D-ManNAc-O$(CH_2)_2$NHCO$(CH_2)_4CO_2$Me

(22)

Lemieux and colleagues have synthesized the analogous α-glycoside having methyl 9-hydroxyoctanoate as aglycone.[74] β-D-Galactosylation of compound (23) gave access to lactosamine derivatives,[12,75]



(23)

and other derivatives of this amino-sugar have been prepared from lactose itself.[76] 2-Acetamido-N-(β-L-asparty1)-2-deoxy-4-O-(β-D-galactopyranosyl)-β-D-glucopyranosylamine, a chemical and biochemical intermediate in the synthesis of glycopeptides, has been synthesized by a Koenigs-Knorr procedure.[76a] A related compound, phenyl 2-acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-galactopyranoside, a substrate for sialyltransferase, gives a sialylated trisaccharide of uncharacterized linkage on enzymatic sialylation.[77]

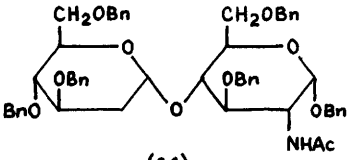
Incubation of phenyl β-D-xylopyranoside with the β-D-xylanase of *C. albidus* gives xylobiose, xylotriose and xylotetraose, offering means of preparing ^{14}C labelled (1 → 4) linked β-D-xylose oligosaccharides.[78] The same set of compounds have been obtained using 1,2,3-tri-O-acetyl-4-O-benzyl-β-D-xylopyranose by way of the corresponding glycosyl bromide and the derived 1,2,3-triacetate.[79,80] ^{1}H And ^{13}C n.m.r. methods have been used to study the six hexa-O-acetyl-reducing xylobioses.[81]

p-Nitrophenyl 2-O-α-L-fucopyranosyl-β-D-galactopyranoside has been prepared utilizing the disaccharide glycosyl bromide.[82] Alternatively, alkyl and aryl glycosides of 2-acetamido-2-deoxy-3-O-(α-L-fucopyranosyl)-β-D-glucopyranose have been made by halide-ion catalysed fucosylation of the corresponding 2-acetamido-2-deoxy-4,6-O-(p-methoxybenzylidene)-D-glucopyranosides.[83] Disaccharides produced in similar manner, comprising α-L-fucopyranose linked separately to O-6 and O-4 of 2-acetamido-2-deoxy-D-glucose have also been reported, activation of the hydroxy groups being achieved by use of diphenylcyclopropenyl ethers.[84]

Tri-O-benzyl-α-L-rhamnopyranosyl bromide affords β-glycosides when used with silver silicate, and has been used to produce several β-linked disaccharides.[85] 3-O-α-L-Rhamnopyranosyl-D-galactose and the β-anomer, which are components of antigenic polysaccharides of *Salmonella*, have been prepared and converted into the corresponding

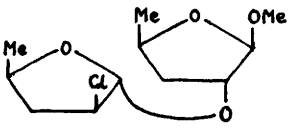
deuterium-labelled alditols.[86]

In the area of deoxydisaccharides, the 2-deoxy compound (24) has been prepared by treatment of tri-O-benzyl-D-glucal with PhSeCl and



(24)

benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside, followed by reduction of the C-2-selenium bond with triphenyltin hydride.[87] Treatment of methyl 3,5-dideoxy-β-D-erythro-pentofuranoside with triphenylphosphine and carbon tetrachloride resulted in the formation of a set of oligosaccharides of which (25) and (26) are the lowest members.[88]



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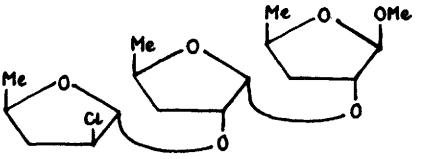
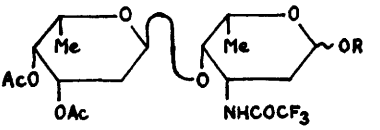


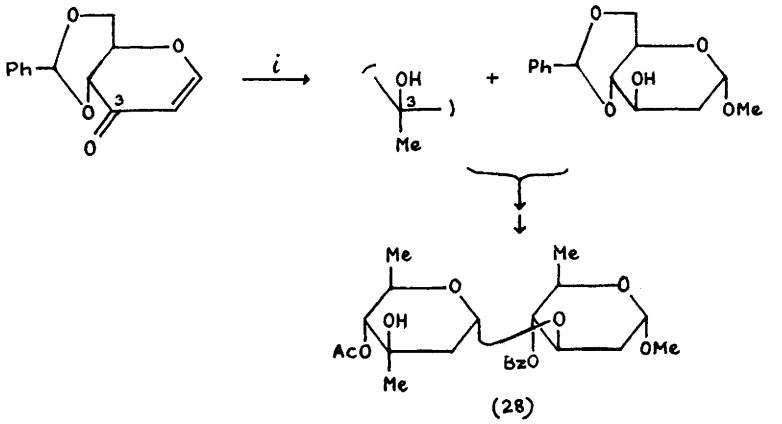
(26)

Two groups have reported synthesis of tetradeoxydisaccharide derivatives (27) as components of anthracycline antibiotics.[89,90] The latter prepared the non-reducing moiety from a methyl 3-azido-



(27)

6-bromo-2,3,6-trideoxyhexopyranoside and inversion at C-5 was effected *via* the 5-alkene. In this case the disaccharide product was coupled to daunomycinone. The avermectins are a group of broad spectrum antiparasitic agents comprising α-L-oleandrosyl-α-L-oleandrosyl derivatives of pentacyclic lactones.[91] The terminal disaccharide of olivamycin A has been synthesized as derivative (28) as indicated in Scheme 2, and the C-3' epimer, which is a derivative of the terminal disaccharide of mithramycin, has also been prepared.[92]

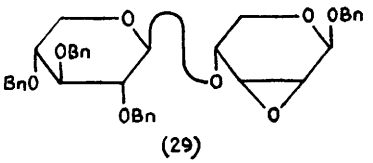


Reagents: i, MeLi

Scheme 2

Standard glycosylating procedures were used to prepare 3-O-(3,6-dideoxy-α-D-xylo-hexopyranosyl)-α-D-mannopyranosides of 9-hydroxynonanoic acid and of p-trifluoroacetamidophenol.[93]

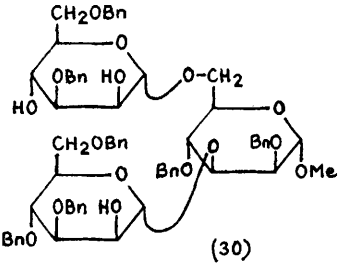
1.3 Synthesis of Tri- and Higher-saccharides.- References 78-80 contain reports of (1 → 4)-β-linked D-xylose oligosaccharides. 2,4-Di-O-(β-D-xylopyranosyl)-D-xylose was synthesized by way of the epoxide (29) which, treated with the anion derived from benzyl alcohol, gave (surprisingly) the corresponding 3-O-benzyl-D-xylose



product which was then condensed with tri-O-acetyl-α-D-xylopyranosyl bromide.[94] In the series of glucotrioses α- and β-cellotriose were synthesized as their peracetates by Koenigs-Knorr procedures, and 6,6',6"-triacetamido, -chloro, -deoxy, and -iodo derivatives of methyl β-cellotrioside were reported following selective tritosylation.[95] Kojitriose, α-D-glucopyranosyl-(1 → 2)-α-D-glucopyranosyl-(1 → 2)-D-glucose, and the α-(1 → 2)-β-(1 → 2) linked isomer were prepared by Koenigs-Knorr procedures known to give mixed anomers,[96] and 3,6-di-O-(β-D-glucopyranosyl)-D-glucose, a component of the anti-tumour glucans lentinan and schizophyllan, was syn-

thesized from benzyl 3-O-acetyl-2,4-di-O-benzyl-α-D-glucopyranoside.[97]

Methyl 2,6-di-O-(α-D-mannopyranosyl)-α-D-mannopyranoside, the trisaccharide repeating unit of the cell wall mannan of two dermatophytes, was synthesized by the Koenigs-Knorr method[98] as was the 3,6-disubstituted compound (30) which was used in the synthesis of a hexasaccharide.[99] In the D-galactose series the β-(1 → 6)-β-(1 → 6) trisaccharide has been made by use of 6-O-chloroacetyl



(30)

esters as temporary protecting groups,[100] and the β-(1 → 2)-β-(1 → 2) linked compound was synthesized as its methyl β-glycoside by use of 2-O-benzoyl-3,4,6-tri-O-benzyl-1-O-toluene-p-sulphonyl-α-D-galactose in an iterative procedure. The sensitivity of the glycosidic linkage in the product to basic conditions, however, prevented continued application of the procedure to the synthesis of higher oligosaccharides.[101]

In the area of heterotrisaccharides, methyl (methyl 4-O-methyl-α- and β-D-glucopyranosyluronate)-(1 → 2)-β-D-xylopyranosyl-(1 → 4)-β-D-xylopyranoside have been synthesized.[48a] Major attention, however, has been given to trimers containing aminosugar residues because of their biological importance. The blood group determinant β-D-galactopyranosyl-(1 → 4)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1 → 6)-D-mannose has been prepared by use of a disaccharide oxazoline derivative[102] and an N-phthalimido derivative,[103] and the isomeric β-(1 → 4)-β-(1 → 2) compound has also been synthesized[104] as has the β-(1 → 4)-β-(1 → 3) isomer, the postulated trisaccharide of human erythrocyte membrane sialoglycoprotein.[105] The related compound α-D-galactopyranosyl-(1 → 3)-β-D-galactopyranosyl-(1 → 4)-2-acetamido-2-deoxy-D-glucose has been reported, the α-bond being produced by use of the amidate procedure,[106] and a derivative of (2-amino-2-deoxy-β-D-glucopyranosyl)-(1 → 3)-α-D-galactopyranosyl-(1 → 4)-L-rhamnose, the repeating unit of the lipopolysaccharide of E. coli 075, has also

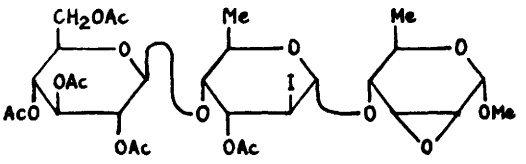
been synthesized following the investigation of the effectiveness of various α-D-galactopyranosyl halides as glycosylating agents.[107]

The branched aminotrisaccharide 3-O-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-4-O-(β-D-mannopyranosyl)-D-galactose and other tri- and tetra-saccharides containing the β-D-mannopyranosyl unit have been synthesized using the glycosyl bromide together with silver silicate precipitated on alumina to promote the formation of β-linkages.[108]

(2-Acetamido-2-deoxy-α-D-glucopyranosyl)-(1 → 4)-β-D-galactopyranosyl-(1 → 4)-(2-acetamido-2-deoxy-D-glucose) and other α-linked compounds have been made using 6-O-acetyl-2-azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosyl bromide,[52] and the methyl 9-hydroxy-nonanoate glycoside of (2-acetamido-2-deoxy-α-D-galactopyranosyl)-(1 → 3)-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-(1 → 3)-α-L-rhamnose has been made as an antigenic determinant.[109] The branched trisaccharides methyl 2,4- and 3,6-bis-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-α-D-mannopyranoside were prepared as components of glycopeptides using 3,4,6-tri-O-acetyl-2-deoxy-2-phthalamido-β-D-glucopyranosyl chloride.[58]

L-Rhamnose trisaccharides have figured prominently. Several reports have appeared on the synthesis of β-D-mannopyranosyl-(1 → 4)-α-L-rhamnopyranosyl-(1 → 3)-D-galactose, the repeating unit of the O-antigenic polysaccharide of S. newington, and of isomers varying in the configurations of the anomeric bonds,[86,110-112] and the flavonol trisaccharides α-L-rhamnopyranosyl (1 → 2)- and (1 → 3)-α-L-rhamnopyranosyl-(1 → 6)-D-galactose have been made by use of the acetylated rhamnose disaccharide bromides.[113] Also in connection with flavonoid chemistry 3,4-di-O-(α-L-rhamnopyranosyl)-D-galactose was synthesized using benzyl 2,6-di-O-benzyl-β-D-galactopyranoside and coupled to the flavone kaempferol.[114] L-Fucose-containing trisaccharides to have been reported are 2'-O-α-[115] and 3'-O-α- and 3'-O-β-L-fucopyranosyl lactose,[116] and 6-O-(α-L-fucopyranosyl)-di-N-acetylchitobiose.[117] Methyl 2,3-di-O-(β-D-glucopyranosyl)-α-L-fucopyranoside and the corresponding digalactopyranosylfucopyranoside have also been prepared.[118]

Synthesis of the trisaccharide derivative (31) was achieved by use of the disaccharide glycal derivative (32) which, in turn, was prepared from the corresponding methyl 2,3-anhydro-alloside derivative.[119]



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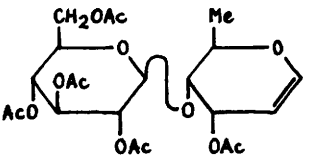


(32)

The use of the 4,4-(ethylenedithio)pentanoyl group in tetrasaccharide synthesis is referred to in Chapter 6. Tetrasaccharides (33),[120] (34),[120,121] and (35),[122] which are antigenic

α-D-GalNAc(1 → 3)β-D-Gal(1 → 4)-D-GlcNAc
↑2
|1
α-L-Fuc (33)

α-D-Gal(1 → 3)β-D-Gal(1 → 4)-D-GlcNAc
↑2
|1
α-L-Fuc (34)

α-L-Fuc(1 → 2)β-D-Gal(1 → 3)-D-GlcNAc
↑4
|1
α-L-Fuc (35)

determinants of human blood group substances, have all been synthesized, and related work has produced other tetramers of interest in biology. The linear tetrasaccharide (36), required for studies

α-D-Man(1 → 3)β-D-Man(1 → 4)β-D-GlcNAc(1 → 4)α-D-GlcNAc-1-PO_3H_2 (36)

associated with the biosynthesis of glycoproteins, has been prepared as its peracetate from the Man-Man-GlcNAc trimer isolated from mannosidosis urine, which was condensed with a 2-acetamido-2-deoxy-D-glucose derivative using an oxazoline procedure.[123] Diglycosylation of a lactose derivative, again using the oxazoline procedure, afforded the core structural component (37) of complex oligosaccharides of human milk,[124] and the 1,3-linked dimer of N-acetyl-lactosamine(38) has also been produced by this method using the 2+2 strategy.[125]

β-D-GlcNAc(1 → 3)β-D-Gal(1 → 4)β-D-Glc
↑6
|1
β-D-GlcNAc (37)

β-D-Gal(1 → 4)β-D-GlcNAc(1 → 3)β-D-Gal(1 → 4)D-GlcNAc (38)

Several tetrasaccharides which constitute the repeating units of microbial polysaccharides have been produced synthetically. Methyl 2,4,6-tri-O-(α-D-mannopyranosyl)-α-D-mannoside is related to the cell wall mannan of two dermatophytes,[98] and the methyl 9-hydroxynonanoate glycoside of α-L-Rha(1 → 2)α-L-Rha(1 → 3)α-L-Rha(1 → 2)α-L-Rha was prepared to mimic a streptococcal antigenic determinant.[109] The other L-rhamnose-containing tetramers (39) and (40) to have been synthesized are the repeating units of the

α-D-GlcUA(1 → 6)α-D-Glc(1 → 2)α-L-Rha-OMe
↑3
|1
α-L-Rha (39)

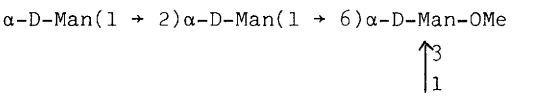
β-D-Man(1 → 4)α-D-Gal(1 → 4)L-Rha
↑3
|1
β-D-GlcNAc (40)

capsular polysaccharide of Streptococcus pneumoniae Type II[126] and the lipopolysaccharide of E. coli 075.[127]

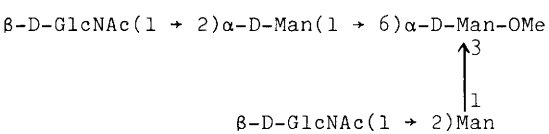
Degradative deamination of N-desulphated beef lung heparin followed by borohydride (^3H) reduction yielded a family of tetrasaccharides based on (α-L-IdoUA) → (α-D-GlcN) → (α-L-IdoUA) → (2,5-anhydro-D-mannitol).[128]

In the pentaose series Ogawa and co-workers have produced the following range of compounds based on D-mannose in connection with work on glycoproteins: (41),[129] (42),[129] (43),[130] (44),[131] (45)[131] and (46).[132] The lactosamine pentamers (47)[133] and (48)[104] have been reported and the pentasaccharide repeating unit (49) of the lipopolysaccharide of Shigella dysenteriae has also been prepared.[134,135]

Ogawa and his colleagues have extended their work to give the D-mannose hexasaccharides (50),[99] (51)[130] and (52),[132] and two reports have appeared on "lacto-N-neohexaose" (53), a human milk



(41)



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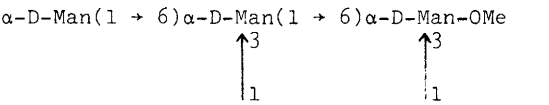

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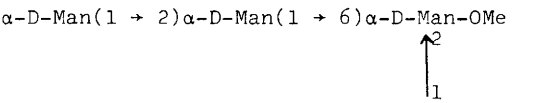

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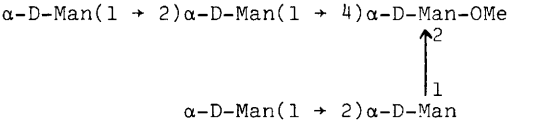

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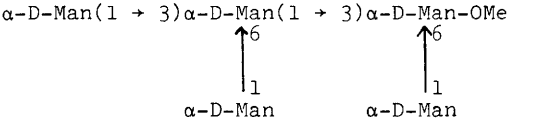

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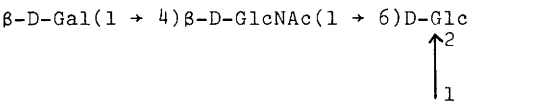

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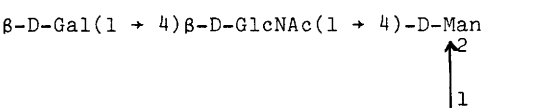

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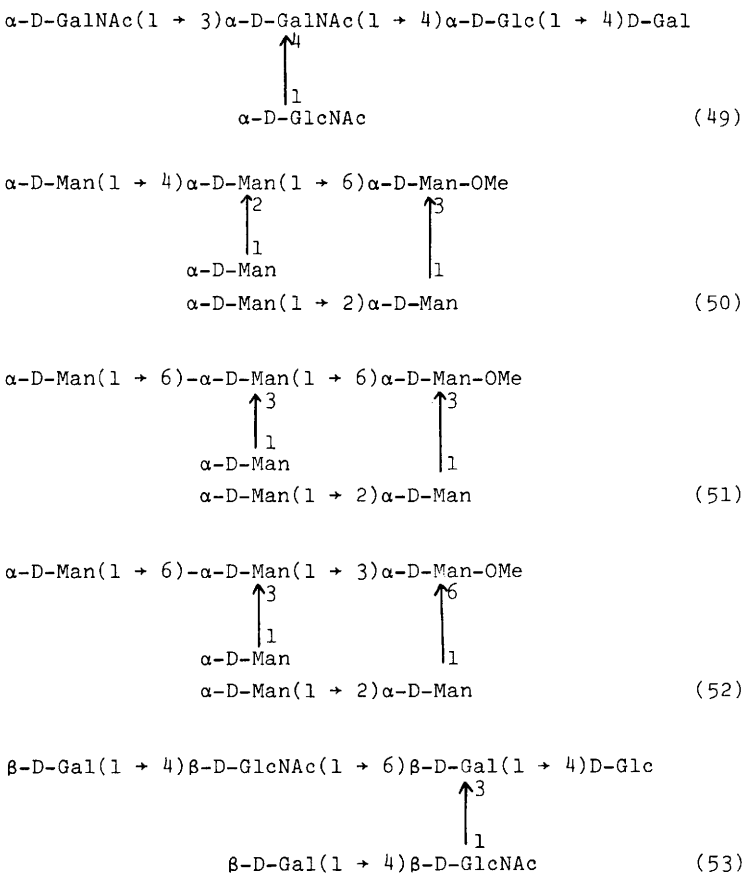


oligosaccharide based on lactose and lactosamine. Synthesis was effected by condensing N-acetyl-lactosamine with a suitably protected lactose derivative using the oxazoline procedure.[136,137]

1.4 O-Glycosides Isolated from Natural Products.- As usual, this section is highly selective; many examples of simple and complex glycosides have been reported.

Arabinopyranosides isolated from Lycopodium inundatum have been assigned the L-configuration by comparison of their ^{13}C n.m.r. spectra with those of 3-O-α-D- and 3-O-α-L-arabinopyranosides of methyl oleanolate.[138]

D-Allose has been found as a constituent of several glycosides. A set of iridoid diglycosides containing D-glucose and either

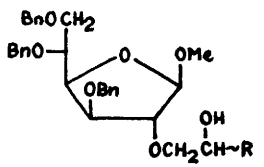
6-deoxy-D-glucose, 4-deoxy-L-*erythro*-pentose or D-allose has been reported from *Mentzelia* species,[139] 4-*O*-formyl-D-allose was isolated from a glycosidic component of *Helicia erratica*,[140] and 2-*O*-(6-*O*-acetyl-β-D-allopyranosyl)-D-glucose as a flavanoid component of *Veronia filiformis*.[141]

(2*R*)2-(β-D-Glucopyranosyloxy)-3-hydroxy-3-methylbutanonitrile, a new cyanogenic glycoside, is a constituent of *Acacia sieberiana*,[142] and 2-*O*-(α-D-galactopyranosyl)-4-*O*-methyl-*chiro*-inositol and two related galactosylinositols have been isolated from soya bean.[143]

The unusual 6-deoxyaltropyranose occurs as a terpenoid glycoside in *Carthamus turkistanikus* but the absolute configuration was not determined,[144] and D-apiose, carrying a β-D-glucopyranosyl substituent on the branched hydroxymethyl group, is a component of *Sarothamnus scoparius*.[145] Apiose has also been found as part of a trisaccharide component of the glycoside myricoside which is a worm antifeedant.[198]

1.5 Hydrolysis and Other Reactions and Features.- The rate of invertase-catalysed hydrolysis of sucrose has been examined as a function of concentration. It increases with concentration and then decreases, the decrease being irregular. The results were discussed in terms of the "folding" of the molecule which is deemed to occur at higher concentrations.[146]

A kinetic study of the hydrolysis of cellobiose, gentiobiose, maltose and maltotriose by dilute sulphuric acid and polystyrenesulphonic acid has been reported.[147] The acid-catalysed rearrangement in methanol of 2-*O*-(2-hydroxyethyl) and 2-*O*-(2-hydroxypropyl) derivatives of methyl 3,5,6-tri-*O*-benzyl-β-D-glucofuranoside (54) initially gives the 1,4-dioxans (55) and then the bicyclic products (56).[148]



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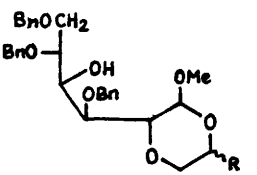

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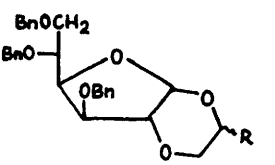
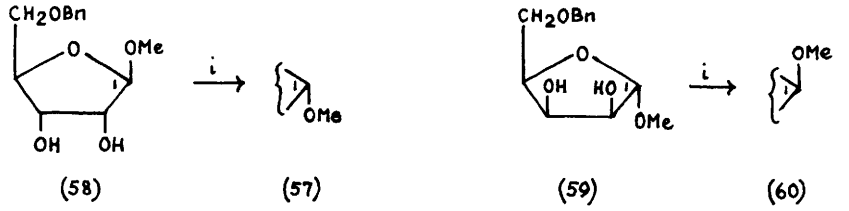


(56)

R = H or Me

An ingenious method of determining linkages in oligosaccharides involves permethylation, methanolysis and p-bromobenzoylation. The u.v. absorbing products (non-reducing terminii are thereby excluded) are separated by t.l.c. and their circular dichroism spectra measured. The number of ester groups can be determined by mass spectrometry. Differences in $\Delta\varepsilon$ values of the extrema at 238 and 253 nm are then used to give the orientational relationship of the ester groups. For triesters the observed differences represent the sum of the values for the three constituent pairs of diesters. Likewise, the tetrabenzoate values are the sum of the six interacting pairs of dibenzoates.[149]

A long paper by Japanese workers has detailed studies of the anomerization of methyl glycofuranosides by Grignard reagents. tert-Butylmagnesium bromide gave 95% of the α-anomer (57) from the β-riboside (58), and 88% of the β-lyxoside (60) from the α-anomer (59) (Scheme 3). Oxygen-magnesium complexes were invoked.

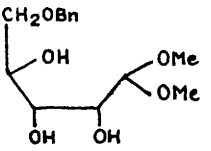


(58) (57) (59) (60)

Reagent: Bu^tMgBr

Scheme 3

Methylmagnesium iodide tended to give acyclic products, e.g., (61), as well as the anomerized glycofuranosides.[150]



(61)

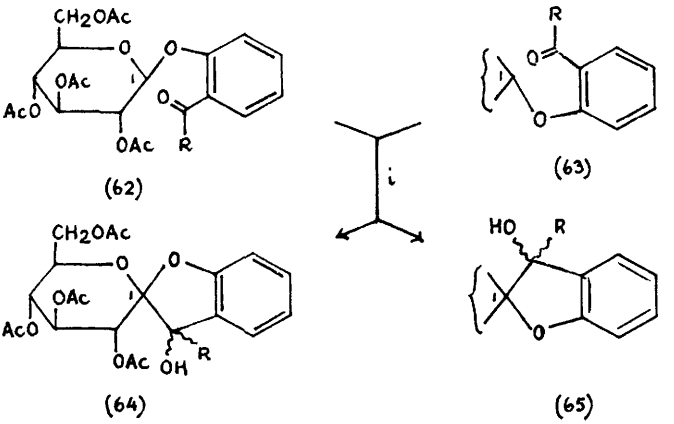
The major pathway for alkaline degradation of phenyl β-D-glucopyranosides was confirmed to involve displacement of the aglycone by the hydroxy group at C-2. The p-nitrophenyl glycoside, however, degrades by two competing mechanisms - the above, and a displacement involving nucleophilic attack on the aromatic ring.[151] In a study of the alkaline degradation of mono-O-methylsucroses it

was shown that derivatives substituted at O-1 and O-3 of the fructose moiety were much more stable than others. This supports the view (Vol. 14, Chapter 3, Scheme 5) that the surprisingly rapid degradation of sucrose results from a rate-determining S_N1cB attack by an oxyanion at C-1 (or C-3) of the fructose unit at C-1 of the glucose moiety which causes an isomerization with production of an alkali sensitive, carbonyl-containing disaccharide.[152]

In a related piece of work p-chlorophenyl α-D-xylofuranoside was shown to be stabilized appreciably by methylation at O-5 which suggests that the anion at this position is involved in the alkaline hydrolysis of the unsubstituted glycoside.[153]

2-O-(4-O-Methyl-α-D-glucopyranosyluronic acid)-D-xylose undergoes elimination to give the 4,5-unsaturated product on treatment with the anion derived from DMSO, and the product is then hydrolysed with acid 70 times more readily than the precursor. Relative rates of acid-catalysed hydrolysis of several disaccharides of this series were reported in this study of fundamental aspects of the chemistry of wood xylans.[154]

Photolysis of the anomeric acylated aryl glycosides (62) and (63) gave mixtures of the spiro-tricyclic products (64) and (65) (Scheme 4). In the case of the products (64, R = H)(65, R = H) derived from formyl substituted starting materials, Collin's oxidation afforded the corresponding ketones, the first of which could be converted into the second under boron trifluoride catalysis.[155]

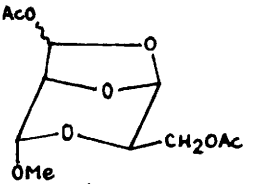


Reagent: hν

Scheme 4

Thermolysis of sucrose in the presence of alcohols gives mainly glucose and corresponding fructofuranosides, and conditions were optimized for producing the latter. Phenols also react in this way but the products degrade further to give 2,6-anhydro-D-fructose.[156] Both cellobiose and its phosphates on heating lose water to give initially 1,6-anhydro-β-D-glucose and then further degradation products. Thermodynamic parameters were determined.[157]

Glycopyranosides with 1,2-cis-diols react with periodate 4-16 times faster than those with only trans-diols. Reaction intermediates formed from the first cleavage exist partly in the form of unreactive cyclic hemiacetals, those derived from α-anomers being more stable than those from β-anomers in the hexose series, but not in the pentose series.[158] The major product derived from initial periodate oxidation of methyl α-D-galactopyranoside, followed by acetylation, is the bicyclic compound (66) which arises from the dialdehyde produced by cleavage of C-3–C-4. The β-glycoside affords the analogous epimer.[159] Periodate oxidation of methyl β-



(66)

lactoside occurs initially, as expected, within the galactosyl residue, and the resulting dialdehyde forms an inter-residue hemiacetal bond with the hydroxy group at C-3 of the glucose moiety.[160]

In a study of structure-taste relationships of methyl glycopyranosides and related compounds, it was found that sweet tasting compounds had oxygen spacings in the range 3.5-5.5 Å whereas non-sweet compounds had spacings outside these limits. Two synclinal vicinal hydroxy groups in cycloalkanes do not engender sweetness, whereas anticlinal and antiperiplanar groups do.[161] The same group then reported on the taste of α- and β-D-glucopyranosides of a series of α,ω-alkanediols. 2-Hydroxyethyl α- and β-glycosides were sweet, the 3-hydroxypropyl β-derivative was tasteless and members with extended alkylene chains were bitter but their di-O-β-D-glucosides were tasteless. 1,4-Anhydroerythrityl β-D-glucoside was bitter.[162]

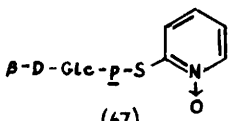
A quantum mechanical and statistical treatment of the fragment (67) of glycosides is reported in Chapter 20.

The interaction of sucrose with tetraalkylammonium iodides in DMF has been studied conductimetrically,[163] and sucrose-metal hydroxide complexes for Li, Na and K have been examined by ^{1}H n.m.r. methods.[164]

2 S-Glycosides

Ogawa and colleagues have used tin compounds in the synthesis of thioglycosides. Various glycosylating agents, e.g., halides or acetates, treated with tributyltin alkylsulphides, afford such compounds in some cases. In others, as when 3,4,6-tri-O-acetyl-2-deoxy-2-phthalamido-β-D-glucosyl chloride was treated with the methylsulphide, elimination occurred as the main reaction.[10,165]

The glycoside (67) and the corresponding uronic acid derivative have been prepared by Koenigs-Knorr procedures as analogues of metabolites of sodium and zinc salts of 2-pyridinethiol-N-oxide (antifungal and antibacterial compounds),[166] and the β-D-glucuronic acid glycoside of 2,4-dinitrothiophenol was obtained from a fully substituted 1-thiol derivative by treatment with dinitrochloro-



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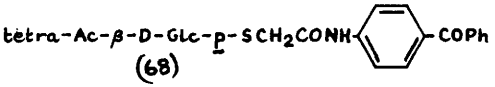

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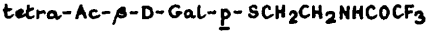
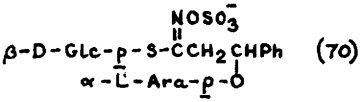


(69)

benzene in the presence of sodium methoxide.[167] Compound (68) was one of a set of carbohydrate derivatives prepared for their fluorescing properties,[168] and the galactoside (69) was used to obtain glycolipids comprising cholesterol bonded to 1-thio-D-galactose by means of the hydrophilic linkages $-CH_2CH_2NH[CO(CH_2OCH_2)_2CH_2NH]_2CO_2-$, where n = 1 or 2.[169]

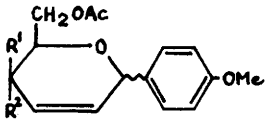
The new glucosinolate (70), isolated from two Sesamoides, is the first reported example containing arabinose and having a β-D-glucosyl bond.[170]



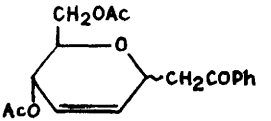
(70)

3 C-Glycosides

Several reports have appeared on the production of C-glycosides from unsaturated sugar derivatives. Tri-O-acetyl-D-glucal and -D-galactal, on reaction with anisole in the presence of tin(IV) chloride gave the 2,3-unsaturated compounds (71) and (72),[171] and the analogous products (73), in which the α-form dominated, were produced by boron trifluoride-catalysed reaction between tri-O-acetyl-D-glucal and 1-trimethylsilyloxystyrene. On treatment with base the α-product was largely converted into the β-anomer.[172] A



(71) R^1 = H, R^2 = OAc
(72) R^1 = OAc, R^2 = H



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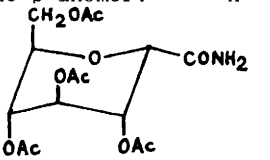
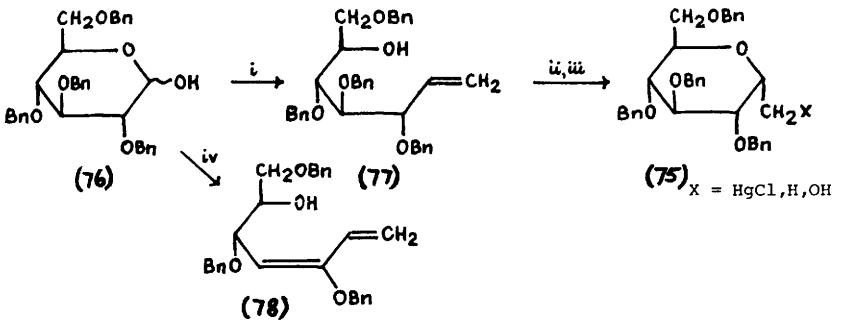


(74)

further report on unsaturated derivatives describes the production of compounds with the groups $C(OH)Me_2$ and $CONH_2$ at C-1 and different configurations at C-2 when tetra-O-acetyl-2-hydroxy-D-glucal and -D-galactal were irradiated in acetone in the presence of formamide. The amide (74) and the α-D-manno- and -galacto-isomers all existed in chloroform solution with the amide group equatorial, i.e. with appreciable axial interactions within the pyranoid rings. In more polar solvents the alternative $^5C_2$ chairs were adopted, and the β-anomers adopted this chair form in all solvents. The reverse anomeric effect largely accounts for these observations.[173]

The α-D-glucopyranosyl C-glycosides (75) have been obtained from

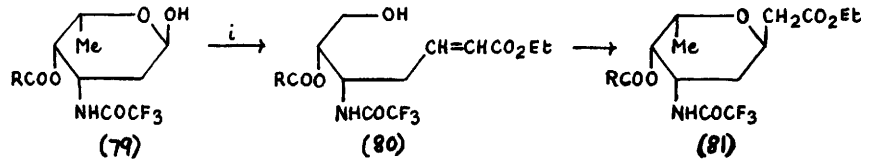


(76) (77) (78) (75) X = HgCl, H, OH

Reagents: i, $Ph_3P^+CH_3Br^-$, BuLi, PhMe; ii, $Hg(OAc)_2$, THF; iii, KCl; iv, $Ph_3P^+CH_3Br^-$, NaH, DMSO

Scheme 5

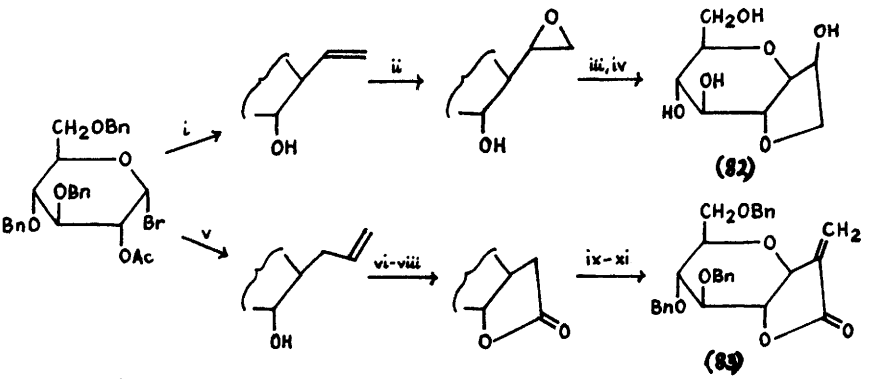
2,3,4,6-tetra-O-benzyl-D-glucose (76) by treatment with a methylene Wittig reagent followed by cyclization of the alkene intermediate (77) by alkoxymercuration (Scheme 5). When the Wittig reaction was conducted under different conditions the diene (78) was obtainable in high yield.[174] In similar fashion the free sugar (79) gave the alkene (80) which, because of the presence of the ethoxycarbonyl group, readily ring closed to afford the C-glycoside (81) (54%) together with smaller proportions of the β-anomer (Scheme 6). From the main product the derived aldehyde, acid and alcohol were produced.[175]



Reagents: i, $Ph_3P{=}CHCO_2Et$ R = $O_2NC_6H_4$

Scheme 6

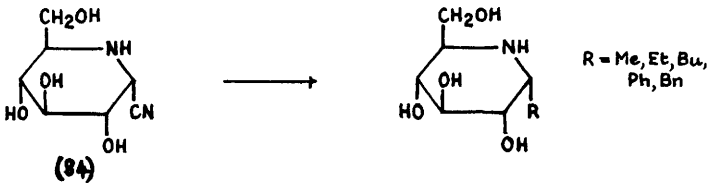
The bicyclic C-glycosidic compounds (82) and (83), containing the bicyclic ring systems found in the ezomycins and octosyl acids, have been prepared as outlined in Scheme 7.[176]



Reagents: i, $CH_2{=}CHMgBr$; ii, m-$ClC_6H_4CO_3H$; iii, camphorsulphonic acid; iv, $Pd/C\text{-}H_2$; v, $CH_2{=}CHCH_2MgBr$; vi, $KMnO_4$,$NaIO_4$; vii, CH_2N_2; viii, TsOH; ix, $Me_2\overset{+}{N}{=}CH_2I^-$; x, MeI; xi, $NaHCO_3$

Scheme 7

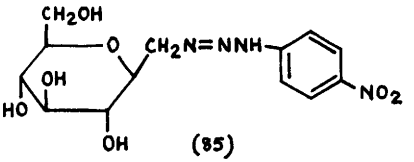
Treatment of the trimethylsilylated nojirimycin derivative (84) with Grignard reagents followed by deprotection affords corresponding α-C-glycosides with 5% or less of β-anomers (Scheme 8),[177] and other glycosyl cyanides have been used to prepare compounds such as



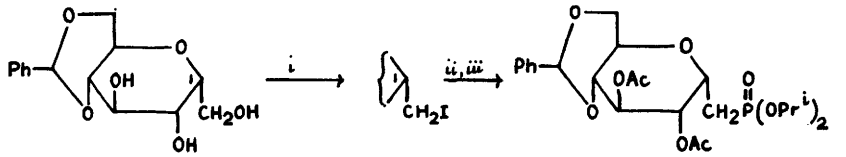
Reagents: i, TMSCl; ii, RMgX; iii, H^+

Scheme 8

(85) as active site directed inhibitors for enzymes.[178]



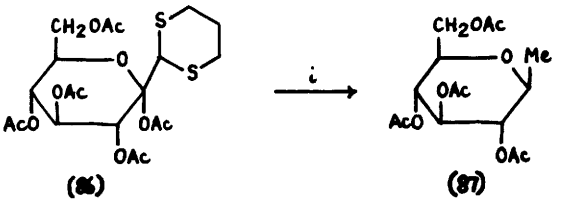
The synthesis of phosphonates corresponding to α-D-gluco-pyranosyl and α-D-galactopyranosyl phosphates has been carried out as indicated in Scheme 9, the starting materials being produced by the photochemical addition of formamide to acetylated 2-hydroxyglycals.[179]



Reagents: i, NIS-Ph_3P; ii, Ac_2O-py; iii, $P(OPr^i)_3$

Scheme 9

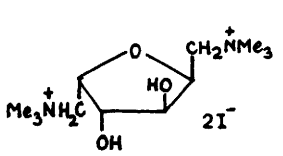
Hydrogenation of the lactone-derived dithiane (86) affords the methyl β-C-glucoside (87) (Scheme 10). The corresponding 1-hydroxy compound did not undergo deoxygenation on such treatment.[180]



Reagent: i, H_2-Ni

Scheme 10

Considerable work has been carried out with furanoid C-glycosides. Compound (88), which is a biologically inactive analogue of epi-allo-muscarine, has been prepared from the dimesylate (89).[181] Application of the Nef reaction to compounds



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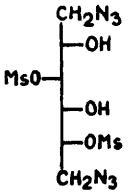
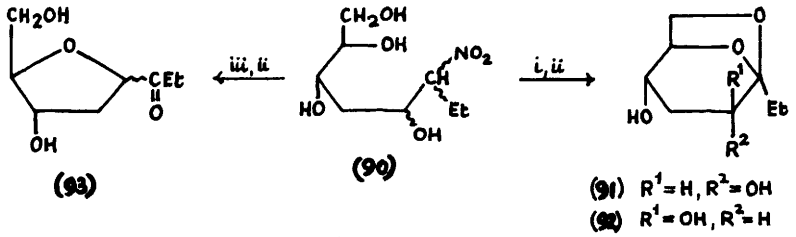


(89)

(90), produced from 2-deoxy-D-erythro-pentose and 1-nitropropene, gave the anhydro compounds (91) and (92) in low yields. With sodium methoxide base, however, (90) underwent β-elimination and intramolecular Michael addition, leading to the C-furanoside (93) (Scheme 11).[182]



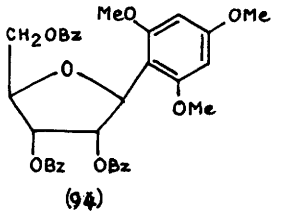
(93) (90) (91) $R^1 = H, R^2 = OH$ (92) $R^1 = OH, R^2 = H$

Reagents: i, $O\bar{H}$; ii, $\overset{+}{H}$; iii, NaOMe

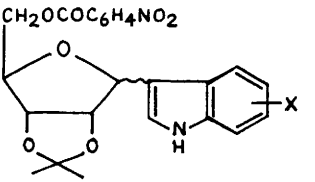
Scheme 11

Condensation between D-ribose and 5-deoxy-D-xylose and nitromethane in basic conditions and in the presence of 18-crown-6-ether gave C-glycofuranosylnitromethanes, and use of methyl nitroacetate gave analogues with the methoxycarbonylnitromethyl substituent at C-1.[183]

Direct glycosylations were used in some cases. 1-O-Acetyl 2,3,5-tri-O-benzoyl-β-D-ribofuranose condensed with tri-O-methylchloroglucinol in the presence of trimethylsilyl trifluoromethanesulphonate gave (94) in 60% yield,[184] and 3-C-glycosylindoles have been produced by condensation of the indoles with glycosyl halides with non-participating groups at C-2. Best yields were obtained in the series (95).[185]

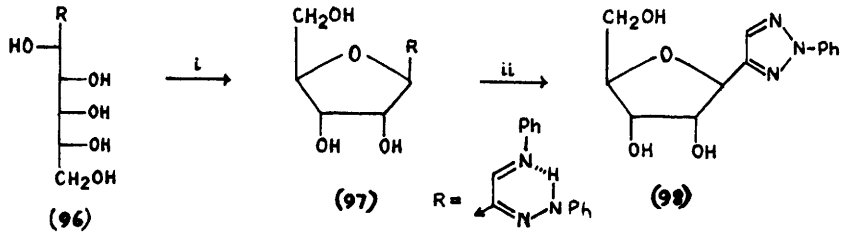


(94)



(95) X= 5-NO_2, 5-Br, 6-NO_2, or H

Dehydrative cyclization of D-altro-2-heptulose phenylosazone (96) yields compound (97), with smaller proportions of the α-anomer; the main product was converted into the C-nucleoside analogue (98) (Scheme 12).[186] Analogous tetrose compounds were

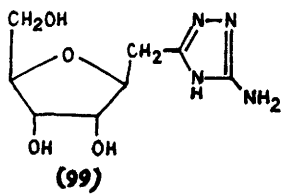


(96) (97) (98)

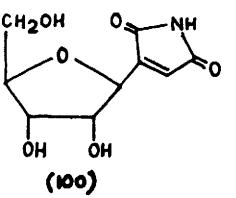
Reagents: i, H_2SO_4-MeOH; ii, $CuSO_4$

Scheme 12

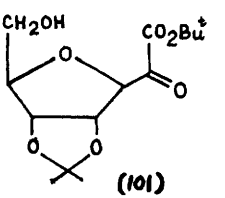
then described from hexose phenylosazones.[187] A full report (see Vol.9, p.23) of the synthesis of the racemic homo-C-nucleoside (99) has appeared,[188] and showdomycin (100) has been made from (101) which was prepared from non-carbohydrates and obtained optically



(99)



(100)

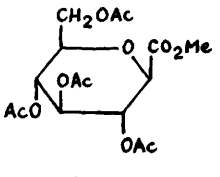


(101)

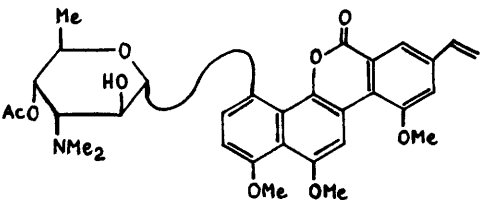
pure by enzymic methods.[189] Other C-glycosides are referred to in ref. 190 and Chapter 19 (C-Nucleosides).

A review of naturally occurring C-glycosides of flavanoids[191] has appeared, and several new reports of such compounds containing C-glucosyl and C-arabinosyl moieties have appeared.[192-196] The β-configuration of the C-glycosidic bond of carminic acid, the main

component of cochineal food dye, has been established as β by ozonolytic degradation to give a product isolated as the known anhydro-heptonic acid (102).[197] C-Bonded β-D-glucuronic acid



(102)



(103)

derivatives of tetrahydrocannabinol have been obtained together with O-linked isomers by a Koenigs-Knorr procedure.[37]

The unusual C-glycoside (103) is a component of ravidomycin (absolute configuration not determined).[197]

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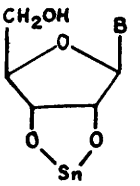
4

Ethers and Anhydro-sugars

1 Ethers

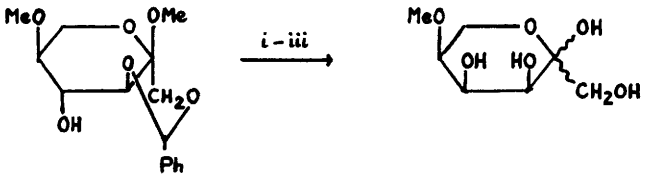
Methyl Ethers.- Dimsyl potassium, prepared from potassium hydride and DMSO, rather than dimsyl sodium, has been recommended for use in the Hakamori permethylation procedure, since it is more readily prepared (at ambient temperature), and the derived methylation products are cleaner.[1] The mechanism of monomethylation of diols by use of methanolic diazomethane in the presence of catalytic tin (II) chloride was shown to involve initial formation and precipitation of tin (II) methoxide, which then reacted with the diols to produce 2-stanna-1,3-dioxolan complexes [e.g. (1)]. The oxygen atoms of these complexes were then activated towards diazomethane, but since tin-bound oxygen atoms not contained within such a bidentate complex were not activated, the reaction ceased after monomethylation. Thus from complex (1), a mixture of the 2′- and 3′-O-methyl ethers resulted.[2]



(1)

5- and 6-O-Methyl and -benzyl ethers of L-sorbose, L-psicose, D-fructose, and D-tagatose have been prepared. Thus methylation and reductive demesylation of methyl 1,3-O-benzylidene-4-O-mesyl-α-L-sorbopyranoside led to compound (2), from which 5-O-methyl-L-sorbose was obtained by deprotection. Alternatively, epimerization at C-4 in compound (2) by the oxidation-stereoselective reduction shown in Scheme 1 led to 5-O-methyl-L-psicose (3). The 5-O-alkylated D-fructoses and the C-4 epimeric D-tagatose derivatives were obtained in an analogous fashion. 6-O-Methyl and benzyl-L-psicose were obtained by alkylation of 1,2: 3,4-di-O-isopropylidene-β-D-psicofuranose.[3]

In the methylation (MeI-NaOH-CH_3CN) of methyl 2,6-dideoxy-α-D-lyxo-hexopyranoside, the 3-O-methyl ether was formed twice as fast



(2) (3)

Reagents: i, RuO_4 ; ii, $NaBH_4$; iii, H_3O^+

Scheme 1

as the 4-O-methyl ether, but the 3,4-di-O-methyl ether was produced ten times faster from the 3- than from the 4-O-methyl ether. The differential reactivity of the hydroxy - groups in the α-D-xylo-analogues was less marked.[4] 3-O-[^{11}C]Methyl-D-glucose has been synthesized by a conventional route employing labelled methyl iodide for use in tissue distribution studies.[5] Mono-methyl ethers of methyl α-D-glucopyranoside and 1,2-O-isopropylidene-α-D-gluco-furanose were obtained using a methyl iodide-based reagent (MeI-MeONa-MeOH-DMSO).[6] Mono- and di-methyl ethers of methyl 2-acetamido-2-deoxy-α- and β-D-galactopyranoside were synthesized by conventional procedures for ^{13}C-n.m.r. and c.i.-m.s. studies,[7,8] while those of L-arabinose were obtained using partially benzylated precursors.[9] Other references to ^{13}C n.m.r. and mass spectrometry of methyl and benzyl ethers appear in Chapters 20 and 21, respectively.

Other Alkyl and Aryl Ethers.- Allyl ethers as protecting groups have been reviewed, and an application in the synthesis of a di-galactosyl diglyceride was detailed.[10] The cationic iridium complex, [Ir(1,5-cyclo-octadiene)$(PMePh_2)_2$]$^+PF_6^-$, catalysed the isomerization of allyl ethers into trans-1-propenyl ethers in high yield, whereas the use of tris(triphenylphosphine) rhodium chloride gave some byproducts formed by hydrogenation.[11] The regiospecific allylation, benzylation, and methoxymethylation of a variety of stannylidenated benzyl β-D-galactopyranoside derivatives was shown to proceed much better in benzene solution and in the presence of quaternary ammonium halides.[12]

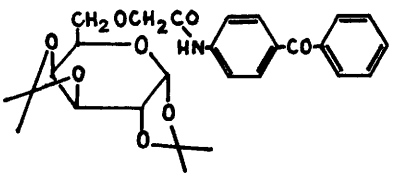
A new benzylation procedure using benzyl trichloroacetimidate ($BnOC(=NH)CCl_3$) and catalytic trifluoromethanesulphonic acid is compatible with both acid- and base-labile protecting groups.[13] Selective benzylation (BnCl-MeONa-MeOH-DMSO) of 1,2-O-iso-

propylidene-α-D-glucofuranose provided the 3-O-benzyl ether (75-80%).[6]

The 3-O-benzyl ether of 2-O-allyl-1,6-anhydro-β-D-galactopyranose was obtained by reductive ring opening of the 3,4-O-benzylidene derivative with $AlCl_3$ - LAH, while the 4-O-benzyl ether was obtained by regioselective benzylation of the 3,4-O-dibutylstannylidene derivative.[14] Reduction of 4,6-O-benzylidene-hexopyranosides with $NaBH_3CN$-HCl yielded 4-hydroxy-6-O-benzyl derivatives, benzoyl, benzyl and N-acetyl protecting groups being unaffected.[15] Other hydrogenolyses of benzylidene acetals leading to benzyl ether derivatives are referred to in Chapter 5.

Benzyl ethers were cleaved effectively under catalytic transfer hydrogenation conditions, with palladium hydroxide on charcoal as catalyst and cyclohexene as hydrogen donor. The benzyl groups of methyl 4,6-O-benzylidene-2,3-di-O-benzyl-α-D-glucopyranoside were selectively removed prior to acetal cleavage under these conditions.[16] Acetolysis (1% H_2SO_4 - Ac_2O) cleaved benzyl ethers from the 6,3,2, and 4 positions in methyl α-D-glucopyranoside derivatives selectively and in the given order.[17] Further references to benzyl and o-nitrobenzyl ethers are found in Chapter 19.

Syntheses of 2-O- and 3-O- [(R)- and (S)-1-carboxyethyl]-D-glucose have been reported. Alkylation of ethyl 3,5,6-tri-O-benzyl-α,β-D-glucofuranoside, and of 1,2: 5,6-di-O-isopropylidene-α-D-glucofuranose, with (±)-2-chloropropanoic acid yielded diastereomeric glucolactylic derivatives, which could be separated into their pure (R)- and (S)- isomers by chromatography. Alternatively, the use of (R)-2-chloropropanoic acid yielded pure (S)-isomers.[18,19] Fluorescent sugar derivatives, such as the 6-O-alkylated-D-galactose derivative (4), have been synthesized.[20]



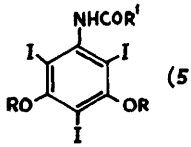
(4)

Dimolar tritylation of cellobiose produced the expected 6,6′-di-O-trityl derivative and the unusual 2,6′-di-O-tritylcellobiose, trityl 6′- and 6-O-trityl-β-cellobiosides in the ratio 60:2:2:1,[21] while the influence of 6- and 6′-O-trityl ether groups on selective

acetylation of, and on the position of the ^{1}H n.m.r. signals of the resulting acetate groups in, cellobiose derivatives has been reported.[22]

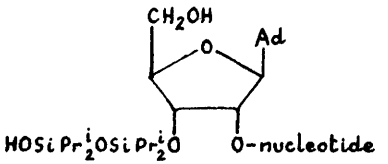
In the mono-tritylation of ribonucleoside 3′-phosphates, over-tritylation was found to increase with the pK_a of the base used as catalyst. Thus the use of 6-nitroquinoline (pK_a 2.7) rather than pyridine (pK_a 5.35) totally suppressed N-tritylation, reduced 2′-O-tritylation, and led to 5′-O-trityl derivatives in good yield.[23] Alkoxytrityl ethers are referred to in Chapter 22.

Monophenylation of diols was effected by use of triphenylbismuth diacetate.[24] 2,4-Dinitrofluorobenzene and 1,4-diazabicyclo-[2.2.2] octane in DMF were used to introduce the 2,4-dinitrophenyl ether group into different positions of glucose and galactose, including the anomeric position. The β-anomers which were formed exclusively by this procedure could be converted into their α-anomers with potassium carbonate in DMF.[25] Bis(glucos-, allos-, and fructos-3-yl) ether derivatives such as (5) were prepared by standard methods and have potential as non-ionic contrast reagents for radiography.[26]



(5) R = Glucos-3-yl
R' = Me, CH_2OH, CH(OH)Me, CH_2OMe

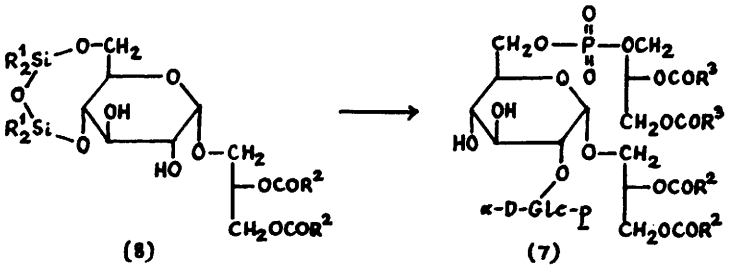
Silyl Ethers.- The TIPS (tetraisopropyldisiloxane-1,3-diyl) protecting group has found further use. Selective hydrolysis of a 3′,5′-O-TIPS protected nucleotide derivative gave the 3-silylated product (6) with a free 5′-hydroxy-group, which was utilized in the synthesis of an oligonucleotide.[27]



(6)

In the synthesis of the phosphatidyl α-diglucosyl diglyceride (7) (Scheme 2), the 4,6-O-protected derivative (8) was subjected to 2-O-glucosylation and acid-catalysed rearrangement to give the 3,4-protected isomer, allowing O-6-phosphorylation.[28] The di-tert-

butylsilylene group has been used for the protection of non-carbohydrate diols.[29] Other references to silyl ethers are found in Chapters 18 and 19.



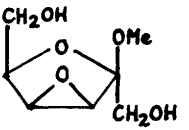
(8) (7)

R^1 = $CH(Me)_2$; R^2 = $(CH_2)_{14}CH_3$; R^3 = $(CH_2)_{16}CH_3$

Scheme 2

2 Intramolecular Ethers (Anhydro-sugars)

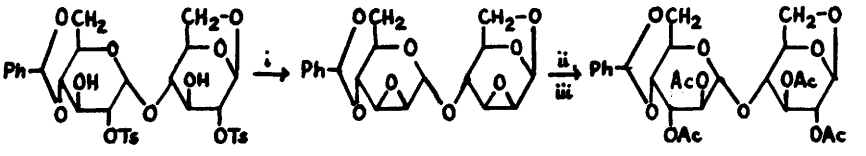
Oxirans. - Further direct syntheses of epoxides from 1,2-diols by the use of diethyl azodicarboxylate-triphenylphosphine (DEAD-TPP) have been reported. Methyl 4,6-O-benzylidene-α-D-altropyranoside gave the 2,3-anhydro-D-mannoside (90% isolated) under mild conditions, while the α-D-glucoside analogue gave the 2,3-anhydro-D-alloside (80% isolated) only under forcing conditions.[30] Methyl β-D-fructofuranoside gave the 3,4-anhydro-D-tagatofuranoside (9) in 84% yield, the α-anomer behaving analogously.[31] Triphenylphosphoranediyl derivatives obtained with this reagent are referred to in Chapter 19.



(9)

Base treatment of the ditosyl maltose derivative (10) initially resulted in the formation of an epoxide on the 1,6-anhydro-hexose ring, but extended reaction led to the diepoxide (11) which on alkaline hydrolysis and acetylation gave the O-α-D-altropyranosyl-(1 ⟶ 4)-O-D-glucopyranose derivative (12) (Scheme 3), from which the parent disaccharide was obtained.[32]

The 2,5: 3,4-dianhydrides (13) and (14) were obtained from the known 2,5-anhydro-D-xylose derivative (15) as shown in Scheme 4, and were used to synthesize branched-chain C-nucleosides[33] (see Chapter 19). Polymerization of 1,2-anhydro-3,4,6-tri-O-benzyl-α-D-

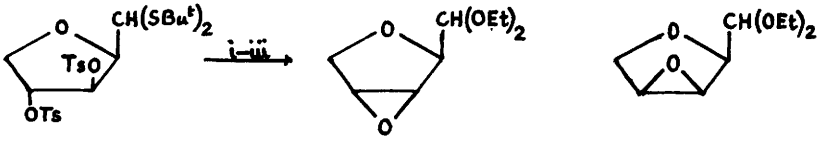


(10) (11) (12)

Reagents: i, NaOMe-MeOH; ii, OH^-; iii, Ac_2O-Py

Scheme 3

glucopyranose with phosphorus pentafluoride at -60 °C gave a β-(1→2)-D-glucopyranan predominantly, other Lewis acids resulting in less stereoselectivity and lower molecular weight products.[34] Other oxirans are referred to in Chapters 8 and 17.



(15) (13) (14)

Reagents: i, Br_2-Et_2O-H_2O; ii, HCl-EtOH, iii, MeONa

Scheme 4

Other Anhydrides. - 1,3-Anhydro-2,4,6-tri-O-benzyl-β-D-manno-pyranose (16) was synthesized as shown in Scheme 5 from the derivative (17) obtained by conventional protecting group methodology. The tri-O-p-bromobenzylated analogue was also prepared.[35]

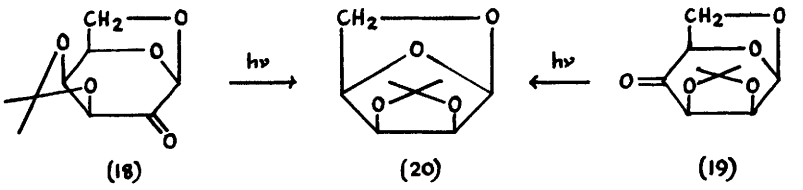
(17) (16)

Reagents: i, HCl-Et_2O ; ii, NaH

Scheme 5

Photochemical decarbonylation of 1,6-anhydrohexos-2- and -4-ulose derivatives (18) and (19) gave the 1,5-anhydro-β-D-lyxofuranose (20) (Scheme 6), although the yields were not high. 1,5-Anhydro-β-D-ribofuranose, 2,6-anhydro-β-D-psicofuranose and 2,6-anhydro-1-deoxy-β-D-psicofuranose acetal derivatives were obtained in an analogous fashion.[36]

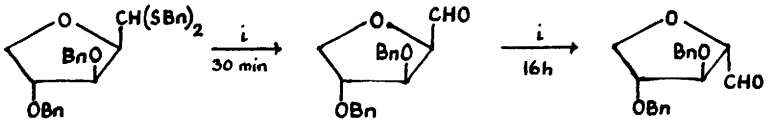
The equilibria established in acid between the 16 possible D-glycero-aldoheptoses and their anhydrides have been reported. The



Scheme 6

total anhydride content varied from less than 1% to greater than 99% depending upon the sugar configuration, and 1,6-anhydropyranose (sometimes the sole component), 1,6-anhydrofuranose (up to 12%) and 1,7-anhydropyranose (up to 39%) forms were encountered.[37] Analogous anhydride formation is mentioned in Chapter 2.

2,5-Anhydro-aldehydo-pentose dithioacetal derivatives were converted to the free aldehydo-forms on acid or mercury (II) salt-assisted hydrolysis, although epimerization at C-2 was encountered, as shown in Scheme 7.[38]



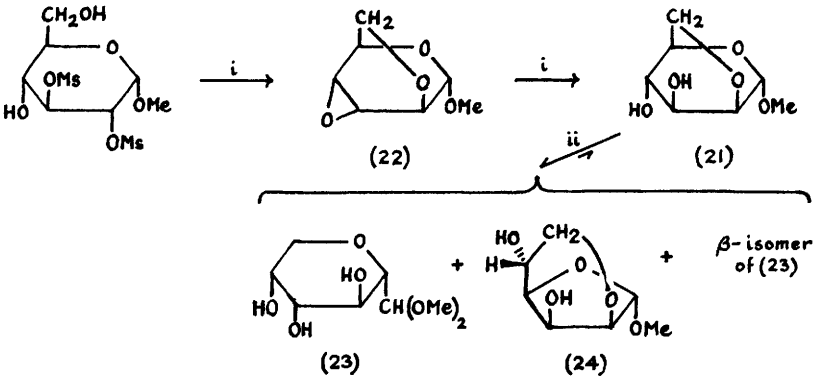
Reagent : i, $HgO-HgCl_2-H_2O$

Scheme 7

Methyl 2,6-anhydro-α-D-mannopyranoside (21) was obtained by epoxide ring opening of the 2,6:3,4-dianhydride (22) as shown in Scheme 8.[39] Methanolysis of (21) yielded mainly 2,6-anhydro-D-mannose dimethylacetal (23), along with minor amounts of the furanoside (24) and the β-anomer of the initial compound (21). Conversion of the dimethylacetal (24) to its D-altro-isomer was achieved by 4,5-O-isopropylidenation, C-3 epimerization involving oxidation-stereoselective reduction, and deprotection.[40]

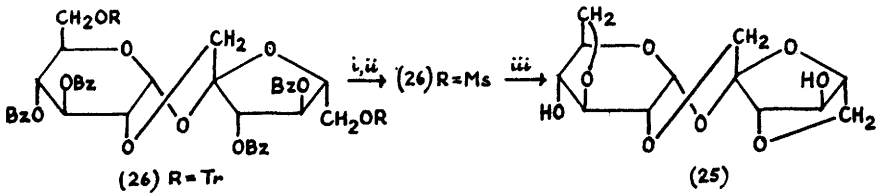
Another example has been recorded of 3,6-anhydro-2-deoxy-D-glucose occurring in free form in a fern.[41]

1′,2: 3,6; 3′,6′-Trianhydrosucrose (25) was synthesized by two routes,[42] one of which (Scheme 9) started with the previously characterized 1′,2-anhydrosucrose derivative (26). This trianhydride (25) was shown not to be identical to the product previously thought to have this structure (Lemieux and Barrette, 1959).



Reagents: i, OH^- ; ii, HCl-MeOH

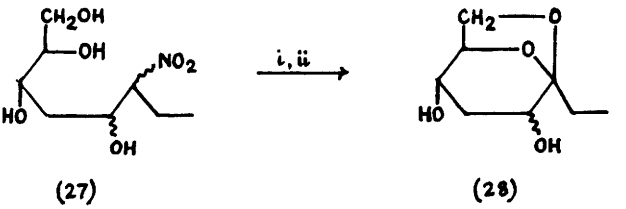
Scheme 8



Reagents: i, HBr - HOAc ; ii, Mesylation, iii, MeONa-MeOH

Scheme 9

Conditions were found to effect the Nef reaction (Scheme 10) on the nitrosugar mixture (27) derived by condensation of 2-deoxy-D-erythro-pentose with nitropropane, but the epimeric 3,8-anhydro-octulopyranoses (28) were obtained in only 12% yield.[43]



Reagents: i, OH^-; ii, conc. HCl

Scheme 10

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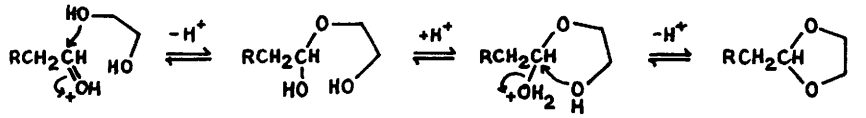
5

Acetals

Methods for the preparation of acetals from alcohols or oxirans and carbonyl compounds have been reviewed.[1] The mechanism of dioxolan formation has been reconsidered. Evidence was presented that the most likely reaction pathway is as shown in Scheme 1.[2]



Scheme 1

Isopropylidene Acetals

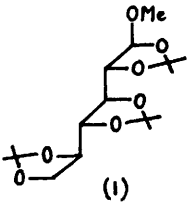
Acetonation of carbohydrates under kinetic control using 2-alkoxypropenes has been surveyed.[3]

A simple, high-yielding, room-temperature preparation of carbohydrate isopropylidene derivatives consisted of using 2,2-dimethoxypropane as both reagent and solvent with toluene-p-sulphonic acid as catalyst. The time required for completion of the reaction (10 min to 96 h) depended upon the solubility of the carbohydrate. Thus the 2,3-O-isopropylidene acetal of methyl α-L-rhamnoside was obtained in 10 min, 98% yield, while that of the β-anomer required 96 h and gave 69% yield.[4] The use of iron(III) chloride as catalyst for the preparation of isopropylidene derivatives with acetone has been reported.[5]

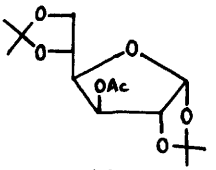
Isopropylidenation of L-sorbose has been reviewed,[6] and a mathematical model based on a four-step mechanism proposed.[7] A similar treatment of the three-step process for isopropylidenation of L-sorbose when ion-exchange catalysis is used has been presented.[8] The kinetics of the same reaction catalysed by sulphuric acid at 14 °C show that the rate is maximal between 2 and 3 h and complete in 3-4.5 h. Although 96% of the sorbose went into solution after 1 h (concentration:3g dm^{-3}) the diacetone sorbose constituted only 2.5% weight at that time.[9]

Attempted formation of higher substituted acetals of sucrose using 2,2-dimethoxypropane and toluene-p-sulphonic acid resulted in cleavage of the glycosidic bond giving, after acetylation, the known acetals, (1) to (3), and the new acetals, (4) and (5), the latter of which was converted to a number of derivatives.[10] The

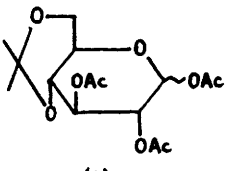
mixtures obtained on acetonation of maltose with 2,2-dimethoxypro-



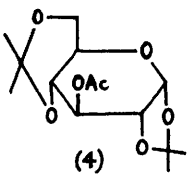
(1)



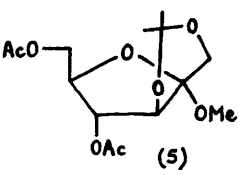
(2)



(3)

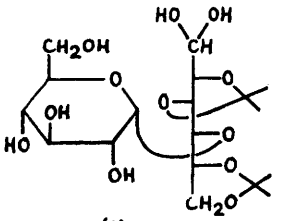


(4)

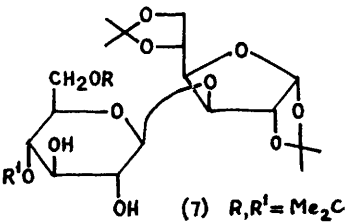


(5)

pane varied with solvent, temperature, and toluene-p-sulphonic acid concentration. Using DMF as solvent, fair yields of the 1,2-, 4′, 6′-, and 1,2:4′,6′-di-O-isopropylidene-maltoses, the inter- residue linked 2′,3:4′,6′-di- and 1,6:2′,3:4′,6′-tri-O-isopropylidenemaltoses, and the acyclic 4-O-α-D-glucopyranosyl-2,3:5,6-di-O-isopropylidene-D-glucose aldehydrol (6) and its 4′,6′-O-isopropylidene dimethyl acetal analogue could be obtained. The use of 1,4-dioxan as solvent favoured formation of the acyclic dimethyl acetal and 4′, 6′-O-isopropylidene dimethyl acetal analogues of (6).[11] The same



(6)

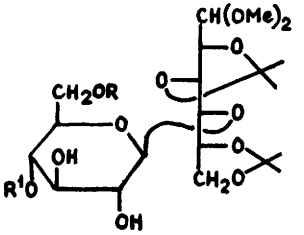


(7) $R,R^1 = Me_2C$

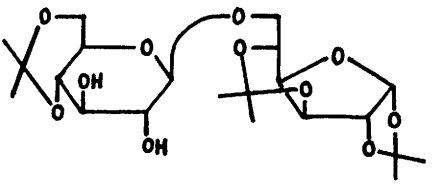
(8) $R = R^1 = H$

authors have carried out similar studies on laminaribiose, cellobiose and gentiobiose. When a trace of toluene-p-sulphonic acid in DMF was used laminaribiose gave the triacetal (7) whereas under the same conditions with excess sulphonic acid the diacetal (8) was obtained. Cellobiose, similarly treated, gave many products, but when 1,4-dioxan was used in place of DMF the main products were acyclic β-glucosides (9) and (10). The principal products from gentiobiose using toluene-p-sulphonic acid and 1,4- dioxan

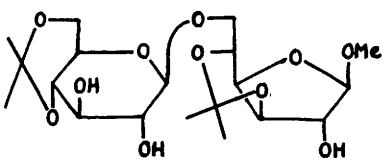
were the cyclic acetals (11) and (12), separated as their acetates, and the acyclic glucoside (13) obtained in 9% yield.[12] Treatment of galactitol with 2,2-dimethoxypropane in DMSO without catalysis gave the hitherto unknown 1,2:3,4:5,6-tri-O-isopropylidene-galactitol in 19% yield.[13]



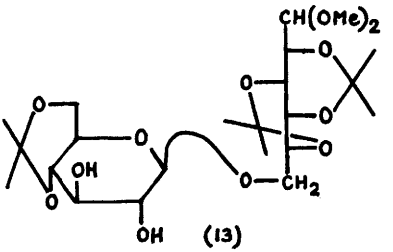
(9) R=R'=H
(10) R,R' = Me_2C



(11)



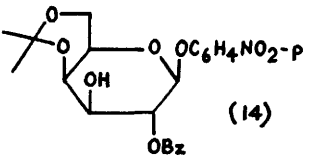
(12)



(13)

A mild and efficient specific hydrolysis of the 5,6- acetal in 2,3:5,6-di-O-isopropylidene-D-mannose and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose uses copper(II) chloride in alcohols.[14]

Migration of isopropylidene groups from 4,6- to 3,4- positions has been noted in mercury(II) cyanide glycosylations of the p-nitrophenyl galactoside (14) (See also Chapter 3).[15]



(14)

The chemical ionization mass spectra of dimethyl acetals and diethyldithioacetals is referred to in Chapter 21.

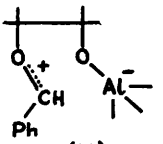
Benzylidene Acetals

The experimental procedures for benzylidenation of sugar diols with

α,α-dihalotoluenes have been described.[16]

A new protecting group, 2-methoxybenzylidene acetal, stable in neutral and basic solution but about eleven times more labile than benzylidene acetals in methanolic hydrogen chloride, is easily prepared from α,α,2-trimethoxytoluene. Thus the syntheses of the 4,6-O-(2-methoxybenzylidene) derivatives of methyl α-D-glucopyranoside and β-D-galactopyranoside were achieved in 96 and 93% yields respectively.[17]

Aluminium chloride has been used to equilibrate exo and endo phenyl groups in benzylidene acetals. Regeneration of the ring from the suggested intermediate (15) gives the isomers in thermodynamically controlled ratio.[18]



(15)

Hydrogenolysis of benzylidene acetals with lithium aluminium hydride-aluminium chloride to yield hydroxy-benzylated derivatives proceeds with some regioselectivity depending on whether the phenyl group is in an exo or endo configuration.[19, 20] Products from these reactions are covered in Chapter 4. Hydrogenolysis can also be carried out using sodium cyanoborohydride and hydrogen chloride.[21]

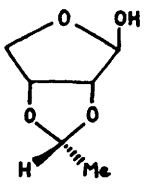
The use of the photosensitive o-nitrobenzylidene acetal as a temporary protecting group in glycosylation reactions is described in Chapter 3.

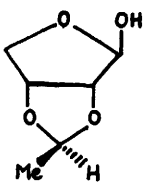
Other Acetals

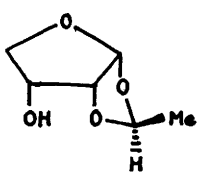
Migration of the acetal of 2,4-O-ethylidene-D-erythrose occurs during acid-catalysed hydrolysis to yield the endo- and exo-2,3- and exo-1,2-O-ethylidene-α-D-erythrofuranoses,(16), (17), and (18) respectively.[22] The diastereoisomeric 2,3-O-[2-phenyl-2-methyl-1,3-dioxolans] of methyl α-L-rhamnopyranoside (19) have been synthesized and their stereochemistries determined by X-ray analysis. Comparison of the X-ray data with that from n.m.r. suggests that the same conformation is adopted in solution as in the solid state.[23]

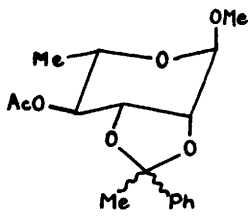
The barium salts of the endo- and exo- 3,4-O-(1-carboxyethylidene)-β-D-galactopyranosides (20) were synthesized as model compounds for n.m.r studies of galactans containing pyruvate acetal residues. The desired acetal was introduced by reaction of acetoxy-

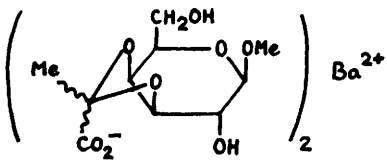
acetone with an appropriate 3,4-diol, followed by deacetylation to the 3,4-O-hydroxyisopropylidene derivative, and catalytic oxidation to the acid.[24] X-Ray crystal structures of 2-cyanoethylidene acetals have been determined.[25]


(16)

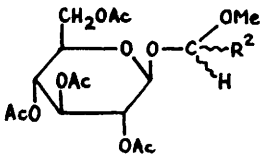

(17)

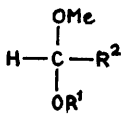

(18)


(19)


(20)

Acetals derived from p-methoxyacetophenone have been prepared from 1,2-cis-, 1,3-cis-, and 1,3-trans-diols of cyclic carbohydrates. These protecting groups are more readily removed under acidic conditions or by hydrogenolysis than are the more usual acetals.[26] A series of 1,1′-α- and 1,1′-β- diacetals of the types shown in (21) have been synthesized in 70-90% yields by reaction of the mixed acetals (22) with the 1-O-trimethylsilyl glycoside in the presence of trimethylsilyl trifluoromethyl sulphonate.[27, 28] In a search for new cancerostatic agents, a series of new acetals of L-ascorbic acid


(21) R^2 = H, CH_2Ph, Ph, CH_2Cl, etc.
R^1 = Me, Ph


(22)

with α-keto-aldehydes, e.g., methylglyoxal and their vinylogues, and some α,β-unsaturated aldehydes, have been prepared.[29]

The use of polymer acetals for supports for other reactions is included in Chapter 6.

Chiral Reductions with Acetals

Three papers on the continuing investigation into asymmetric reduction of ketones using sodium borohydride in the presence of 1,2:5,6-di-O- isopropylidene-α-D-glucofuranose have appeared from the same group in Japan. Optical yields of 28-68% were obtained when zinc chloride was used as acid catalyst,[30] and 4-83% with chiral carboxylic acids.[31, 32] Other diacetals were tried but generally gave lower optical yields.[32]

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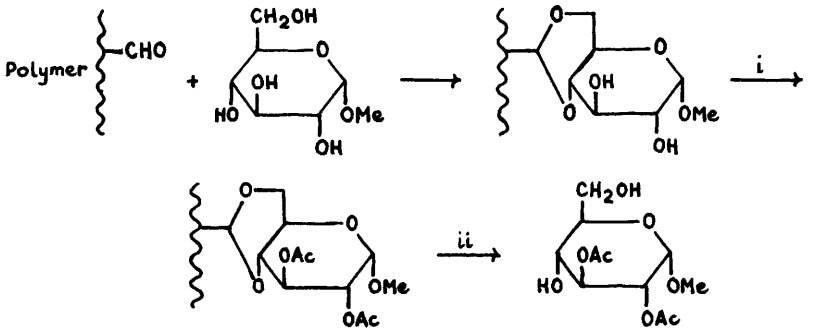
6
Esters

A review of the diethyl azodicarboxylate-triphenylphosphine reagent includes many examples of esterification of carbohydrates and other sugar reactions.[1]

The synthesis and application of organic polymers as supports and protecting groups has been reviewed. Some applications to carbohydrates and esterification reactions are discussed, e.g., as in Scheme 1.[2]



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

Scheme 1

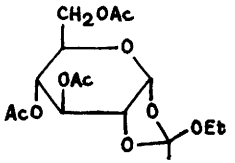
Carboxylic Esters

A terminal 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl unit has been found to occur naturally in the disaccharide saponin epitrillenoside C-PA, isolated from Trillium kamtschaticum tubers.[3]

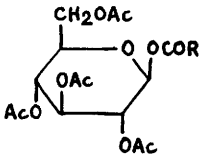
Two methods of making glycosyl esters have been described.[4] Ortho-esters such as (1) treated with carboxylic acids yield the β-glycosyl esters (2), while the corresponding β-manno-ortho-esters yield the α-glycosyl ester. An alternative procedure is treatment of a sugar bearing a free anomeric hydroxy group, e.g., (3), with the carboxylic acid in the presence of trifluoroacetic anhydride; α:β ratios are variable and some glycosyl trifluoroacetates are produced.

A low yield of 1,2,4-tri-O-acetyl-α-D-arabinopyranose was isolated following partial acetylation of β-D-arabinose, while

similar treatment of methyl β-D-arabinopyranoside gave a 2:1 mixture of the 3,4- and 2,4-di-O-acetates in 25% yield. The reactions were also carried out on the L-enantiomers.[5] The α:β ratio



(1)



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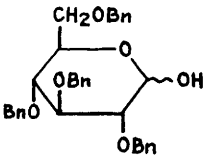


(3)

of pyranoses and furanoses in peracetylations of D- and L-arabinose has been investigated by ^{13}C-n.m.r. With sodium acetate as catalyst the α-pyranose acetates predominate, whereas with zinc chloride, sulphuric acid, or perchloric acid the principal products are the β-pyranoses and the β-furanoses. When pyridine was used as solvent, the yield of furanoses increased with temperature.[6] The primary hydroxy groups of sugars are acetylated by ethyl acetate in the presence of alumina (Woelm neutral, W-200-N) while secondary hydroxy groups remain unesterified. Yields between 64 and 99% were obtained.[7,8] Selective acetylation of primary hydroxy groups has been accomplished in 22 - 73% yield using ethyl acetate-silica.[9]

The observation that, in selective acylations of (1→4)-linked disaccharides, the 3-OH is the least reactive secondary hydroxy group was confirmed in the case of 6,6'-di-O-trityl-cellobiose and its methyl β-glycoside, following fractionation of the complex mixtures obtained on treatment with acetyl chloride in pyridine-toluene at 1-4 °C. The order of hydroxyl reactivity was established as 3'-OH > 2-OH > 2'-OH > 4'-OH ≫ 3-OH in the case of the β-glycoside. Considerable data relating to g.l.c.-m.s. of the trimethylsilylated partially methylated derivatives of glucitol, glucose and methyl glucoside was presented in the course of this work.[10] Related papers from the same group examined the effects of the 6- and 6'-O-trityl groups on the relative reactivity towards acetylation of the secondary hydroxy groups of cellobiose and its methyl glycoside,[11] and presented the ^{1}H-n.m.r. spectra of 6-O-trityl-, 6'-O-trityl, and 6,6'-di-O-trityl-β-cellobiose peracetates, using specifically trideutero-acetylated analogues prepared from the variety of partially acetylated derivatives obtained in the work reported in References 10 and 11.[12]

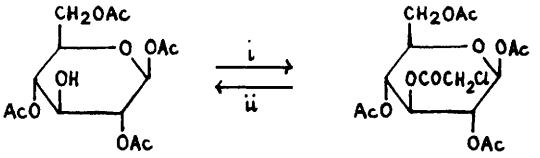
A mild method for preparing glycosyl trifluoroacetates is to

treat the trimethylsilyl glycoside with trifluoroacetic anhydride for three hours (see Scheme 2 for an example using a D-mannose derivative). Analogously prepared were the trifluoroacetate derivatives of D-glucofuranose and D-galactopyranose.[13]

Reagents: i, $(Me_3Si)_2NH$-H_2SO_4(tr.), 2h at reflux; ii, $(F_3CCO)_2O$, 3h

Scheme 2

The preparation and selective removal under mild conditions of chloroacetyl groups from D-glucose derivatives is shown in Scheme 3.[14] Strong base ion-exchange resins can be used to deacetylate or debenzoylate sugars using methanol as solvent. The procedure



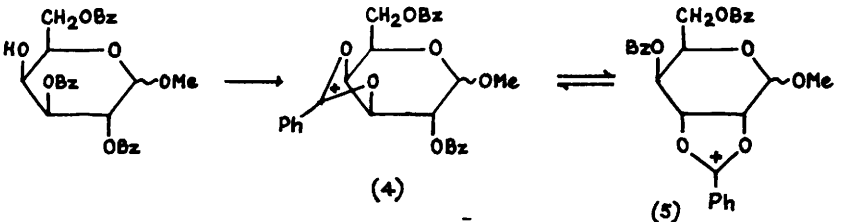
Reagents: i, $ClCH_2COCl$-Py; ii, $CS(NH_2)_2$-MeOH

Scheme 3

has some advantages over the Zemplen method in that cleaner products are obtained.[15] Regioselective O-deacylation of fully acetylated glycosides and 1,2-O-isopropylidene aldofuranose derivatives may be accomplished with hydrazine. From the study of a large range of compounds, it was shown that, in general, the 2-O-acyl groups are most labile, while those on the primary positions are most resistant to cleavage. The reaction was used to prepare compounds containing one free hydroxy group only.[16]

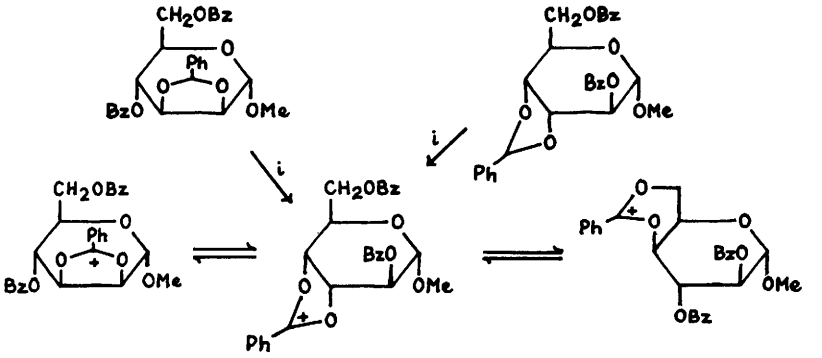
Two further papers on the migration of dioxolanylium ions have appeared. The equilibrium between the galacto- and gulo-ions, (4) and (5) shown in Scheme 4 was measured in acetonitrile by studying the products formed on opening the ionic rings with bromide ion. It was shown that the anomeric configuration influences the equilibrium.[17] A similar study on the manno-, altro-, and ido-system shown in Scheme 5 was carried out. The position of equilibrium could be varied by introduction of substituents into the benzene

rings.[18]



Reagent: i, BF_4^-

Scheme 4



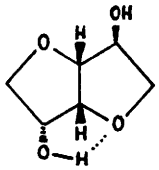
Reagent: i, BF_4^-

Scheme 5

Selective benzoylations have been carried out using the stannylation procedure and the regioselectivity shown to depend on time of reaction, temperature, and molar equivalents used. At room temperature the main product for methyl α-D-glucopyranoside was the 2,3,6-tri-O-benzoyl derivative, for methyl α-D-mannopyranoside the 3,6-dibenzoate, for α,α-trehalose the 2,3,6,2',3',6'-hexabenzoate, for sucrose the 2,3,6,1',6'-penta-benzoate, and for lactose the 2,6,3',6'-tetrabenzoate. When the reaction with methyl α-D-glucopyranoside was carried out at -10 °C the major product was the 6-benzoate, while between -10 and -5 °C over a longer period a 100% yield of 2,6-dibenzoate was obtained.[19]

Hydroxy groups which can form intramolecular hydrogen bonds, e.g., the 5-hydroxy group of 1,4:3,6-dianhydro-D-glucitol (6) are

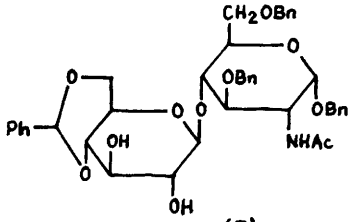
less readily esterified with acid chlorides under phase transfer conditions. Thus unimolar benzoylation of (6) gave the 2-, 5-, and 2,5-di-O-benzoyl derivatives in 46,17, and 12% yield respectively. The selectivity under these conditions is the reverse of that generally observed for acylation in pyridine solution.[20]



(6)

Selective benzoylation of tert-butyl or 2,2,2-trichloroethyl α-D-galactopyranoside gave 2,3,6-tribenzoates which were useful intermediates in oligosaccharide synthesis.[21]

Regioselective benzoylation of the disaccharide (7) with N-benzoylimidazole in dichloromethane gave the 3'-O-benzoyl derivative in 91% isolated yield.[22]



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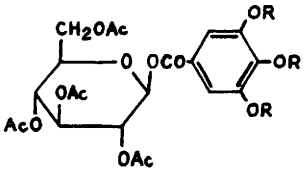


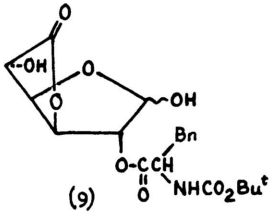
(8) R= H, Me, Bn

Synthesis of 3,4,5-trihydroxybenzoate derivatives (8) of 2,3,4,6-tetra-O-acetyl-D-glucose has been accomplished by conventional means. The methyl ether derivatives are useful neoplasm inhibitors.[23]

Laevulinic acid esters,[24] and 4,4-(ethylenedithio)pentanoyl esters as masked laevulinoyl esters,[25] have been used as protecting groups in oligosaccharide synthesis. The laevulinoyl group is removed rapidly under mild conditions by hydrazine; the reaction is selective and has been carried out in the presence of acetyl groups.[24] 4,4-(Ethylenedithio)pentanoyl chloride selectively acylates primary hydroxy groups, e.g., in methyl 3,4-O-isopropylidene-α-D-galactopyranoside. The dithioacetal function is stable under conditions for glycosidation, but may easily be converted to the laevulinoyl ester. A synthesis of a branched tetrasaccharide

containing glucose and galactose is described, utilizing this protection method.[25]

Selective acylation of maltose with 8-, 12-, 14-, 16-, and 18-carbon fatty acid chlorides in pyridine gave mainly mono-esters purified by chromatography. The mono-stearoyl and -palmitoyl mixtures were effective antitumour agents.[26] The relative reactivity of hydroxy groups in D-glucofuranurono-6,3-lactone and its anomeric methyl glycosides towards selective pivaloylation follows the order 5-OH > 2-OH > 1-OH.[27] The same paper identifies a minor product, which had previously been obtained from the reaction of 1-O-[N-(tert-butoxycarbonyl)-L-phenylalanyl]-α-D-glucuronic acid with diazomethane, as 2-O-[N-(tert-butoxycarbonyl)-L-phenylalanyl]-D-glucofuranurono-6,3-lactone (9), having resulted from diazomethane catalysed 1,2-acyl migration prior to lactonization and ring contraction.[27]



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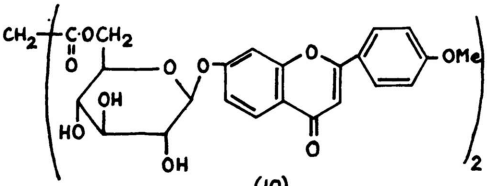
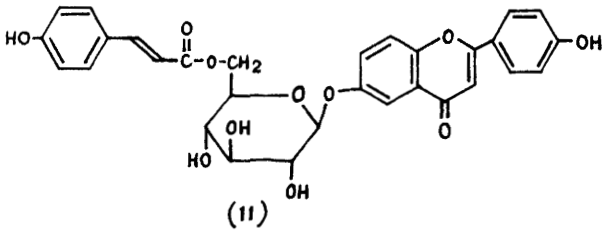


(10)

Cord factor analogues have been synthesized by reaction of 2,3,4,2',3',4'-hexa-O-benzyl-6,6'-di-O-mesyl-trehalose with potassium salts of 4-[p-(hexadecyloxy)phenyl]butanoic acid, corynomycolic acid, or mycolic acid (from *Mycobacterium bovis*) followed by removal of the benzyl groups by hydrogenolysis.[28]

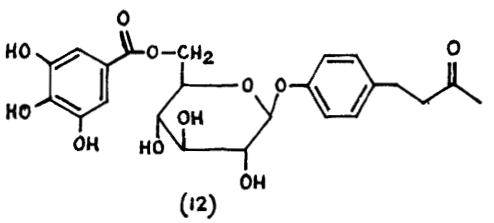
Methyl 6-O-malonyl-β-D-glucopyranoside has been isolated from the roots of *Rumex obtusifolius* and its structure confirmed by synthesis using malonic acid-dicyclohexylcarbodi-imide on methyl β-D-glucopyranoside in dry dioxan.[29] Agastachin (10), containing two glycosylflavone units bridged by a malonic acid diester, was isolated from *Agastache rugosa* (Labiatae).[30] The novel 6-O-coumaroyl flavonoid (11) has been isolated from Patchouli (*Pagostemon cablin*).[31] 1,2,6-Tri-O-galloyl-β-D-glucopyranose and lindleyin (12) have been isolated from commercial rhubarb. Lindleyin is of medical interest since it has analgesic and anti-inflammatory activity.[32] p-Hydroxycinnamyl glycosides of mixed di- and trisaccharides of glucose and rhamnose with lone caffeyl and coumaryl ester groups, e.g., (13), have been isolated from

Boschniakia rossica.[33]



(11)

Fatty acid monoesters of D-glucose have been shown to be consistently less effective antitumour agents than those of D-maltose, indicating the need for the correct hydrophilic-lipophilic balance.[34]



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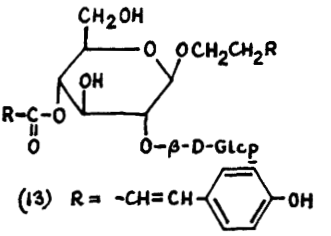
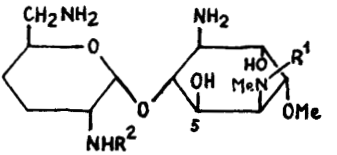


(13) R = -CH=CH-OH

Esters of sugars with antibiotic activity are referred to in Chapter 18.

Under basic conditions 4-N-acylfortimicins such as (14) give 2'-N-acylfortimicins e.g., (15), by acyl migration shown to occur via the 5-hydroxy group.[35]



(14) $R^1 = COCH_2NH_2$, $R^2 = H$

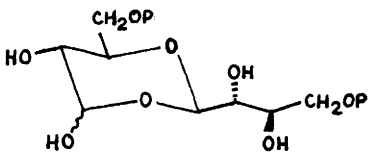
(15) $R^1 = H$, $R^2 = COCH_2NH_2$

Phosphate and Related Esters

2-Pyridylmethyl has been described as a new phosphate protecting group in oligonucleotide synthesis. The reagent is easily prepared by reaction of 2-pyridylmethanol with phosphoric acid in the presence of phosphorus pentaoxide and the protecting group is easily removed by cuprous chloride or toluene-p-sulphonic acid.[36] Thallium(I) oxy-salts have been used to synthesize phosphate, phos-

phite, sulphite, and xanthic esters at anomeric, secondary, and primary hydroxy groups. Higher yields were often obtained than when using conventional methods.[37]

In a study by ^{1}H- and ^{13}C-n.m.r. of concentrated (1M) aqueous solutions of D-erythrose 4-phosphate, it was shown that an equilibrium mixture is present consisting of the monomeric aldehyde and hydrated aldehyde forms, which interconvert rapidly, together with three dimers. In dilute solutions (~ 0.04M) the hydrated monomer predominates with no detectable dimers. Use of $[4,4'-^{2}H_2]$ and $[3,4,4'-^{2}H_3]$ derivatives and comparison with glycolaldehyde, glyceraldehyde, and DL-glyceraldehyde 3-phosphate allowed the dimer structures to be elucidated, which were thus shown to be the anomeric pairs of the asymmetrically substituted 1,3-dioxan (16) and a 1,3-dioxolan (17).[38]



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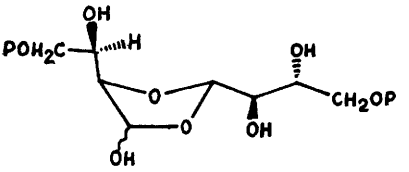


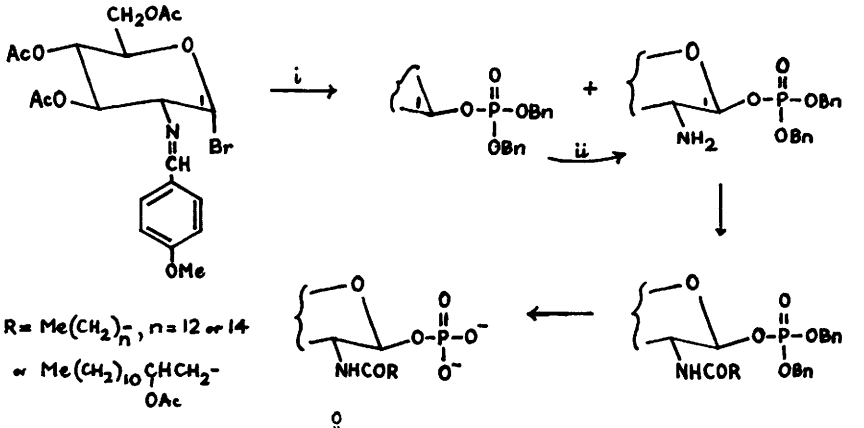
(17)

By combining the free energy obtained for hydrolysis of adenosine to give adenine and ribose with that for reaction of ribose 1-phosphate with adenine to give adenosine and inorganic phosphate, the Gibbs free energy of hydrolysis of α-D-ribose 1-phosphate was estimated to be -11.8 kJ mol^{-1} at an ionic strength of 0.1M and 25 °C.[39]

A new, and apparently general, procedure for the synthesis of 2-(acylamino)-2-deoxy-α-D-glucopyranosyl phosphates, outlined in Scheme 6, has been described.[40]

2,3,4,6-Tetra-O-decanoyl- and -hexadecanoyl-β-D-glucopyranosyl phosphate have been synthesized by phosphorylation of the corresponding α-bromides using dibenzyl silver phosphate followed by catalytic hydrogenolysis.[41]

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl phosphate has been prepared by reaction of exo-3,4,6-tri-O-acetyl-1,2-O-(tert-butylorthoacetyl)-α-D-glycopyranose with H_3PO_4-P_2O_5. Deacetylation with aqueous lithium hydroxide gave the β-D-glucopyranosyl phosphate, but use of aqueous ammonia led to the diglucosyl phosphate.[42] A new synthesis of the extremely alkali-labile P^1-moraprenyl, P^2-α-D-galactopyranosyl pyrophosphate (18), its D-glucosyl analogue,

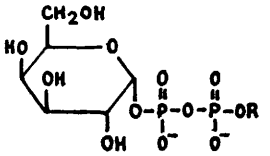


Reagents: i, $Bu_3SnOP(OBn)_2$-Et_4NBr, 40 °C; ii, SiO_2 gel;

iii, RCOCl-2,6-lutidine-CH_2Cl_2; iv, H_2-Pd/C-MeOH

Scheme 6

and two oligosaccharide analogues from the appropriate glycosyl phosphates using the reagent (19) has been described.[43] The synthesis of D-galactose 6-phosphate by direct phosphorylation of D-galactose with polyphosphoric acid, which is used commercially and was previously considered to give pure material, has been shown to result in a product containing about 20% D-galactose 3- and 5-phosphates. Purified 6-phosphate, separated by anion-exchange chromatography, was shown to exist in aqueous solution as 32% α-pyranose, 64% β-pyranose, and no more than 4% furanose forms.[44]



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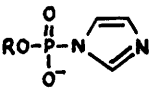

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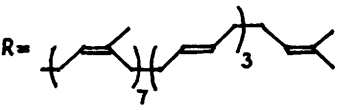
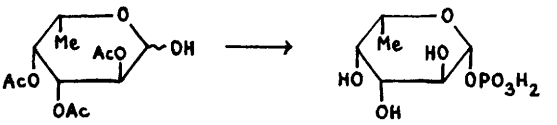


An improved synthesis of β-L-fucopyranosyl phosphate has been reported (Scheme 7). The product was converted into guanosine diphosphate fucose, which is the substrate involved in L-fucose incorporation into blood group substances.[45]

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-manno-, -gluco-, and -galacto-pyranosyl phosphates were prepared by treatment of the corresponding oxazoline derivatives with dibenzyl phosphate

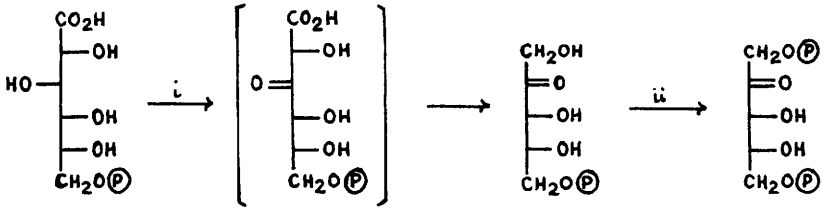
followed by hydrogenolysis of the benzyl groups. The products were converted into the uridine diphosphate N-acetylhexosamines.[46]

Enzymic syntheses of D-erythro-pentulose 5-phosphate and 1,5-diphosphate of practical importance have been accomplished (Scheme 8).[47]



Reagents: i, o-phenylene phosphochloridate-collidine; ii, $Pb(OAc)_4$; iii, OH^-

Scheme 7



Reagents: i, oxidase; ii, Kinase

Scheme 8

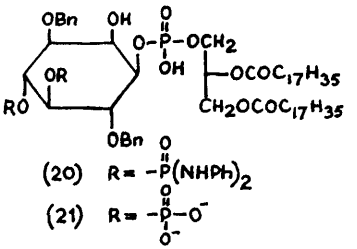
The synthesis of fructose 2,6-diphosphate from its 1,6-isomer by intramolecular cyclization followed by hydrolysis using the method of H.G. Portis and C.L. Fischer (Biochem. J., 1963, 89, 452) has been reported.[48] Both diphosphates were studied by ^{31}P- and ^{13}C-n.m.r. and the 2,6-diphosphate was shown to consist entirely of the β-anomer.[49,50] Aldolase-catalysed condensation of dihydroxyacetone monophosphate with D-glyceraldehyde gave D-fructose 1-phosphate, which on hydrolysis yielded crystalline D-fructose. When (±)-glyceraldehyde was used, a mixture of D-fructose 1-phosphate and L-sorbose 1-phosphate resulted. Hydrolysis and addition of calcium chloride gave the crystalline D-fructose-calcium chloride complex, and crystalline sorbose was obtained from the mother liquor by chromatography.[51]

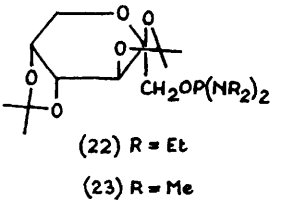
Complexes between ATP, AMP, ribose 5-phosphate, glucose 1-phosphate, or glucose 6-phosphate and metal cations are thought to be responsible for the catalysis observed in reactions of acetic acid, glycine, β-alanine, alanine, lysine, glutamic acid, or histidine with hydroxylamine to give the corresponding hydroxamic acids in

the presence of Ni^{2+}, Co^{2+}, Ca^{2+}, Mn^{2+}, Mg^{2+}, Zn^{2+}, or Be^{2+}. The reaction proceeded without release of inorganic phosphate.[52]

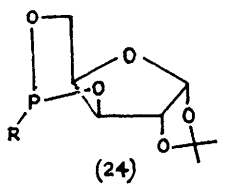
Two equivalents of diphenylphosphoryl chloride in pyridine react with 2,5-anhydromannitol to produce 32% mono-, 40% 1,6-di-, and 28% 1,4,6-tri-phosphate. The corresponding figures for 2,5-anhydro-glucitol were 30%, 56%, and 14%.[53] The glyceryl cyclitol derivative (20) has been prepared and converted to the triphosphate derivative (21) by treatment with isoamyl nitrite.[54]

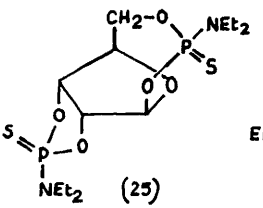
The preparation of the fructose phosphodiamide derivatives (22) and (23) by treatment of 2,3:4,5-di-O-isopropylidene-fructopyranose with the appropriate hexa-alkyl phosphotriamide has been reported. Alcoholysis, oxidation, and sulphurization of (22) gave the corresponding dibenzyl phosphite, diamidophosphate, and the di-amidothiophosphate, respectively.[55]

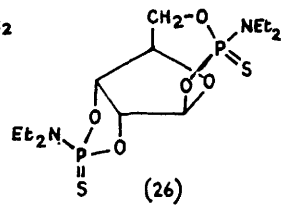




Phosphorylation of 1,2-O-isopropylidene-α-D-xylofuranose with PR_3 or $EtOPCl_2$ gave the cyclophosphites (24) (R = Cl, Me_2N, Et_2N, EtO) in 40 - 65% yield.[56]

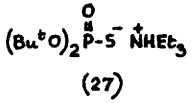




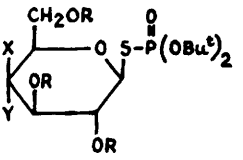


N.m.r. studies (^1H, ^{31}P, and ^{13}C) of the β-D-ribofuranose 1,5; 2,3-bis(N,N-diethylphosphoramidothionates) prepared by amidothiophosphorylation of D-ribose with $P(NEt_2)_3$ and sulphur, suggested the two diastereoisomeric forms (25) and (26).[57] Reaction of 2,3,4,6-tri-O-acetyl(or benzyl)-α-D-gluco- or -galacto-pyranosyl bromide with the thiophosphate (27) gave exclusively the S-β-thiophosphates (28) and (29), respectively. When the reaction was

carried out in the presence of tetra-n-butyl ammonium bromide (to anomerize the glycosyl halide) a mixture of the α- and β-thiophosphates was formed. With the same reagent (27) the peracetyl β-glycosyl chlorides gave the expected α-thiophosphates (30) and (31), together with the 2,3,4,6-tetra-O-acetyl-D-glucose and -D-galactose, formed via the 1,2-acetoxonium derivative.[58]

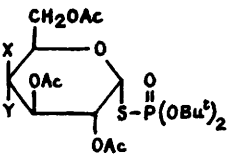


(27)



(28) X=H, Y=OR, R=Ac or Bn

(29) X=OR, Y=H, R=Ac or Bn



(30) X=H, Y=OAc

(31) X=OAc, Y=H

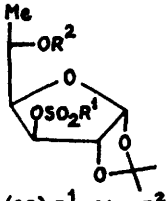
Sulphonates

The use of imidazolylsulphonate as a good leaving group for displacement reactions has been reported. High yields (60 - 90%) were reported for displacements using tetra-n-butylammonium fluoride, chloride, iodide, and benzoate, and with sodium azide at primary and secondary positions including C-2 in methyl 3-O-benzyl-4,6-O-benzylidene-2-O-imidazolylsulphonyl-α-D-glucopyranoside.[59]

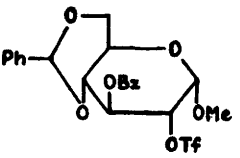
Mesylation of sucrose using three mol. equiv. mesyl chloride in pyridine followed by acetylation and chromatographic separation gave (as the peracetates) 14% 1',6,6'-tri-O-mesyl, 12% 1',2,6,6'-tetra-O-mesyl, and 6% 1',2,4,6,6'-penta-O-mesyl sucrose. When four mol. equiv. mesyl chloride were used the yields of the same compounds were 8%, 27%, and 10%,respectively. The tri- and tetra-mesylates were converted to azides and hence amines conventionally.[60] C-Substitution in mesylates by alkyl halides has been shown to occur as a side-reaction of O-alkylations.[61,62] Thus the monomesylate (32) gave the ethylsulphonate (33) with methyl iodide, and the 2-phenylethylsulphonate (34) with benzyl chloride in dimethylformamide in the presence of potassium hydroxide.

Treatment of tri- and tetra-O-mesylates of methyl α-D-glucopyranoside with base initially gives mono-anhydro esters which react further to give other anhydro and dianhydro derivatives. Alkenes can also be formed.[63]

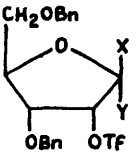
Substitutions at C-2 in the 2-O-triflate (35) have been accomplished with benzoate, azide, thiomethyl, thiophenyl, and methoxy



(32) R^1 = Me, R^2 = H
(33) R^1 = Et, R^2 = Me
(34) R^1 = CH_2Bn, R^2 = Bn



(35)

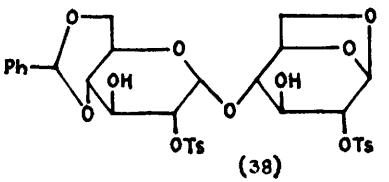


(36) X = H, Y = OMe
(37) X = OMe, Y = H

anions in DMF to yield the manno-products.[64] A similar study on the two anomeric triflates (36) and (37) gave the 2-fluoro-, chloro-, bromo-, iodo-, and azido-2-deoxy-D-arabinofuranosides. The displacements proceeded well with the α-anomer (36) and less so with the β-anomer (37).[65]

Nucleophilic reactions of tosyl groups in enolic sugar derivatives have been reviewed.[66]

Selective tosylation of 1,6-anhydro-4',6'-O-benzylidene-β-D-maltose with 4.2 molar equivalents of tosyl chloride in pyridine at 0 °C gave 68% 2,2'-di-O-tosyl derivative (38) along with four other tosylated products.[67] Co-ordination control using stannyl complexes referred to in the section on carboxylic esters has also been used to effect selective sulphonation of methyl α-D-glucopyranoside. Thus tosylation in the presence of bis(tributylstannyl)oxide for three days at 20 °C gave 40% 2-O-tosyl, 16% 2,6-di-O-tosyl, and 36% 6-O-tosyl derivatives. When the reaction was allowed to proceed seven days, 81% 2,6-di-O-tosyl derivative was obtained. Similar results were found for mesylation.[19] Sugar tosylates can be prepared under halide-free conditions by toluene-p-sulphinylation with toluene-p-sulphinimidazolide, followed by oxidation with m-chloroperbenzoic acid.[68]

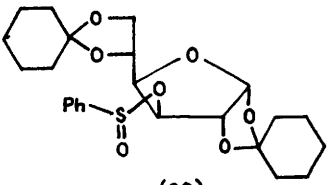


(38)

Other Esters

The syntheses of D-galactose 3- and 4-sulphates and D-glucose 4-sulphate *via* specifically protected compounds have been achieved. ^{13}C-N.m.r. studies of these and several other hexose monosulphates have shown that the position of the sulphate group can be determined because the bonded carbon atoms are deshielded by 6-10 p.p.m., while the adjacent carbon atoms are shielded by 1-2.5 p.p.m. Deuterium-induced differential isotope shift analysis also assisted with assignments of signals.[69] A new method for preparing carbohydrate sulphates uses hydrogenolysis (H_2-PtO_2) of benzenesulphonates. Other conversions may be carried out in the presence of the sulphonate as a protected sulphate with the hydrogenolysis as a final stage. In this way glucose 3-sulphate is available from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.[70]

Diastereomeric sulphinate esters of 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose, *e.g.*, phenylsulphinate (39), with approximately 50% enantiomeric excess of one isomer have been synthesized, and used in the synthesis of optically active sulphoxides through reaction with Grignard reagents.[71]

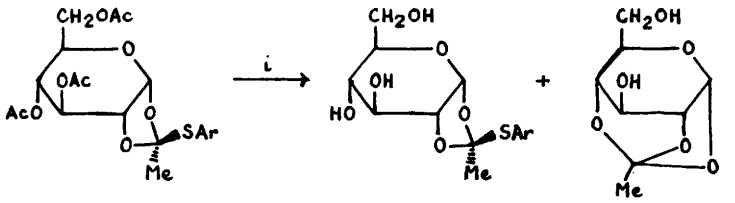


(39)

Cyclic thionocarbonates have been prepared from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside by means of thiophosgene and pyridine-dioxan for the former and thiophosgene and 2,4,6-trimethylpyridine-dioxan for the latter.[72]

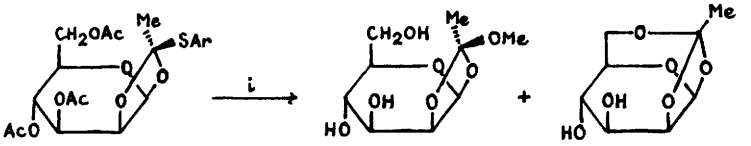
The syntheses of orthoesters have been reviewed.[73] Further studies on *spiro*-orthoesters prepared by reaction of aldonolactones with oxirans or *vic*-di(trimethylsilyl)ethers have been published.[74,75] Zemplen deacylation of benzoylated and acetylated sugar 1,2-thio-orthoesters bearing an *S*-aromatic residue gave, as a side reaction, substitution of the arylthio group (Schemes 9 and 10). The side reaction could be reduced by using methanolic sodium methoxide in pyridine.[76]

Amidosulphation of monosaccharides has been accomplished by



Reagent: i, NaOMe-MeOH

Scheme 9



Reagent: i, NaOMe-MeOH

Scheme 10

taking the sugar in DMSO with 10% excess sodium methoxide in methanol and adding dimethylamidosulphonyl chloride. The reaction is reported to be regioselective according to the relative acidities of the hydroxy groups.[77]

Regioselective phenylcarbamoylation of hydroxy groups in ribonucleosides has been achieved with dibutylstannane-phenylisocyanate. The work-up is simplified compared to the more usual bis(tributylstannyl)oxide-phenyl isocyanate procedure.[78]

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7

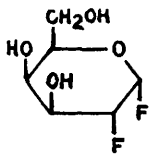
Halogeno-sugars

In a review of the diethyl azodicarboxylate-triphenylphosphine reagent, many examples of halogenations of carbohydrates are given.[1] Triflate displacements have been used to prepare 2-deoxy-2-halogeno-D-arabinofuranose derivatives,[2] whilst the use of the imidazolylsulphonate leaving group is claimed to give higher yields.[3] Preferential halogenations of primary alcohols can be achieved using triphenylphosphine-carbon tetrahalide; near quantitative yields were obtained, e.g., inosine gave 95% 5'-chloro-5'-deoxyinosine and methyl α-D-glucopyranoside gave 97% methyl 6-chloro-6-deoxy-α-D-glucopyranoside.[4] Various 6- and 6'-mono-, and 6,6'-dihalogeno-substituted derivatives of methyl β-laminaribioside have been synthesized by tosyl displacement reactions.[5]

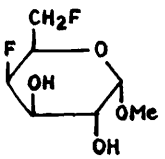
The preparation of 2'-deoxy-2'-halogenoguanosines is referred to in Chapter 19, and halogen derivatives of 5-enofuranoses are described in Chapter 12.

A review of fluorination methods in organic chemistry includes some carbohydrate examples.[6] Glycosyl fluorides in 60 - 90% yields were obtained on treatment of the corresponding bromide with 2,4,6-trimethylpyridine hydrofluoride.[7] Various fluorinated cyano- and amino-sugars have been synthesized by the routes shown in Scheme 1.[8]

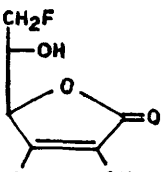
A synthesis[9] of [^{18}F]-2-deoxy-2-fluoro-D-glucose by fluorination of 3,4,6-tri-O-acetyl-D-glucal using $^{18}F_2$, and a semiautomated method using this reaction for production of the labelled fluorosugar have been described.[10] The methyl glycosides of 2-deoxy-2-fluoro- and 4-deoxy-4-fluoro-β-D-galactose have been prepared by methanolysis of the glycosyl fluoride (1) on the one hand, and by fluoride displacement of the mesylate group of methyl 6-O-benzoyl-2,3-di-O-benzyl-4-O-methansulphonyl-β-D-glucopyranoside



(1)

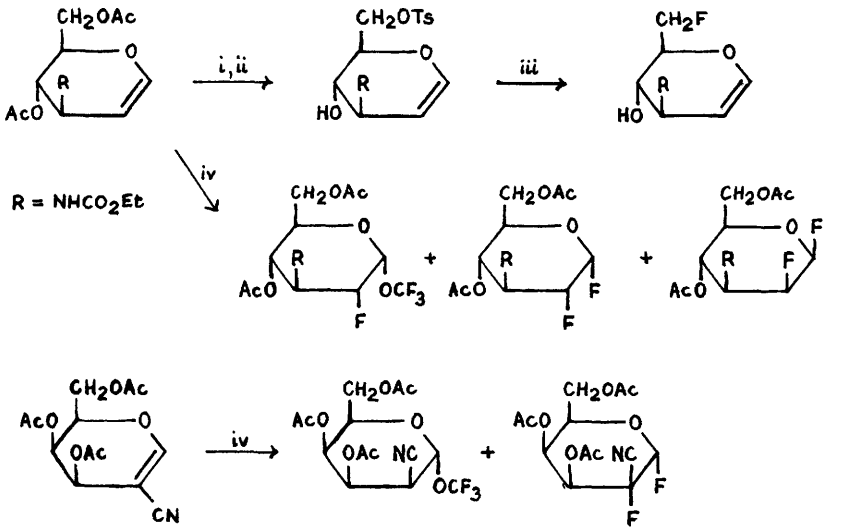


(2)



(3)

using Amberlite-A26 resin in its fluoride form on the other.[11] Direct displacement of hydroxy groups at C-4 and C-6 of methyl α-D-glucopyranoside using diethylamine-sulphur trifluoride gave the crystalline 4,6-dideoxy-4,6-difluoro-galactoside (2) in 60% yield.[12]



Reagents: i, NH_3-MeOH; ii, TsCl-C_5H_5N(1 mol); iii, Bu^n_4NF-DMF; iv, CF_3OF-CH_2Cl_2

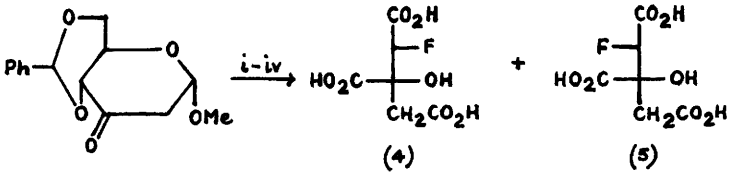
Scheme 1

The synthesis of 4-deoxy-4-fluoro- and 6-deoxy-6-fluoro-derivatives of 2-amino-2-deoxy-D-glucose and -D-galactose has been achieved by tetrabutylammonium fluoride displacements of the appropriate sulphonate esters.[13] 6-Deoxy-6-fluoro-L-ascorbic acid (3) has been prepared in five steps from 2,3:4,6-di-O-isopropylidene-2-oxo-L-gulonic acid.[14]

The two epimers (4) and (5), of which the latter is the enantiomer of the fluorocitric acid formed biosynthetically from oxaloacetic acid and fluoroacetyl-CoA, have been synthesized by the route outlined in Scheme 2.[15]

A series of α-D-galactopyranosyl chloride derivatives has been prepared containing selectively cleavable substituents as building blocks for the synthesis of oligosaccharides containing β-linked galactosyl units.[16] A reinvestigation of the reaction between β-

cellobiose octa-acetate and phosphorus pentachloride has specified conditions under which 3,6,2',3',4',6'-hexa-O-acetyl-2-O-(trichloroacetyl)-β-cellobiosyl chloride can be produced. The product



Reagents: i, Zn-$CHBrFCO_2Et$; ii, H^+; iii, $KMnO_4$-$\bar{O}H$; iv, H^+

Scheme 2

is useful in synthesis since it can be anomerized to the α-chloride and the trichloroacetyl group can be selectively removed.[17] Reaction of glycals with chlorine azide in the presence of benzoyl peroxide gave mainly the 2-azido-2-deoxy-glycosyl chlorides whereas in the absence of light and radical initiators the products were mainly the 2-chloro-2-deoxy-glycosyl azides, presumably formed by ionic addition. Thus 3,4,6-tri-O-acetyl-D-galactal gave mainly the 2-chloro-2-deoxy-D-galactosyl azide and the corresponding D-glucal gave the 2-chloro-2-deoxy-D-glucosyl azide.[18]

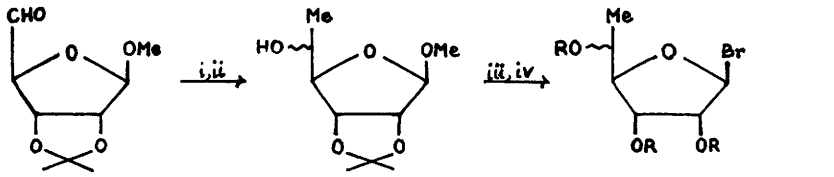
The ^{35}Cl-NQR frequencies for three anomeric pairs of methyl 2-chloro-2-deoxy-D-glucopyranoside derivatives have been measured, and reveal that the α-anomers have higher frequencies than the β-anomers by 0.4 - 1.1 MHz. A similar effect was observed for the ^{79}Br-NQR frequencies in methyl 2-bromo-2-deoxy-D-galactopyranosides (the α-anomer being 13.9 MHz higher than the β). Application of the Townes and Dailey formula indicates differences in the orbital population on the chloro or bromo atoms between anomers with axial or equatorial aglycones. Possible implications on chemical reactivity have been experimentally tested by attempted nucleophilic substitutions with sodium azide. Thus while methyl 3-O-benzyl-4,6-O-benzylidene-2-chloro-2-deoxy-β-D-glucopyranoside gave a 70% yield of the normal, inverted, 2-azido-2-deoxy-β-D-manno product, none could be obtained from the α-anomer under the same conditions. Other results were complicated by factors such as steric effects and neighbouring group participation.[19] The antiviral effects of phenyl 6-chloro-6-deoxy-β-D-glucopyranoside have been further investigated.[20]

Reaction of methyl 1,3-O-isopropylidene-α-D-fructofuranoside with thionyl chloride gave the corresponding 6-chloro-6-deoxy

derivative.[21]

Chloro-substituted unsaturated furanose derivatives obtained by Wittig reactions are described in Chapter 12, and the use of chloro-derivatives for preparing deoxy-sugars is mentioned in Chapter 8.

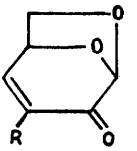
The synthesis of 6-deoxy-2,3,5-tri-O-(p-nitrobenzoyl)-β-D-allo- and α-L-talo-furanosyl bromide (6) has been accomplished by the route shown in Scheme 3. The two epimers (7) were separable by crystallization of their 5-p-nitrobenzoates.[22]



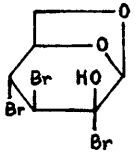
Reagents: i, MeMgBr; ii, aq-HCl; iii, $pNO_2C_6H_4COCl$-Py; iv, HBr-HOAc

Scheme 3

The use of imidazole-triphenylphosphine reagents has been extended to the preparation of bromo-deoxy sugars directly from the corresponding hydroxy compound ; e.g., methyl 3,4,6-tri-O-benzyl-α-D-mannopyranoside with triphenylphosphine, tribromoimidazole and imidazole gave methyl 3,4,6-tri-O-benzyl-2-bromo-2-deoxy-α-D-glucopyranoside in 73% yield. Steric factors are important in the reaction since 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose gave only 30% of the 3-bromo-D-allofuranose, the main products being alkenes. Methyl α-D-glucopyranoside gave high yields of the 3,6-dibromo-3,6-dideoxy product, thereby giving an excellent route to methyl 3,6-dideoxy-α-D-ribo-hexopyranoside. Several other selective brominations were described.[23] Bromination of laevo-glucosenone (8) gave good yields of 3-bromo-laevoglucosenone (9)



(8) R = H
(9) R = Br

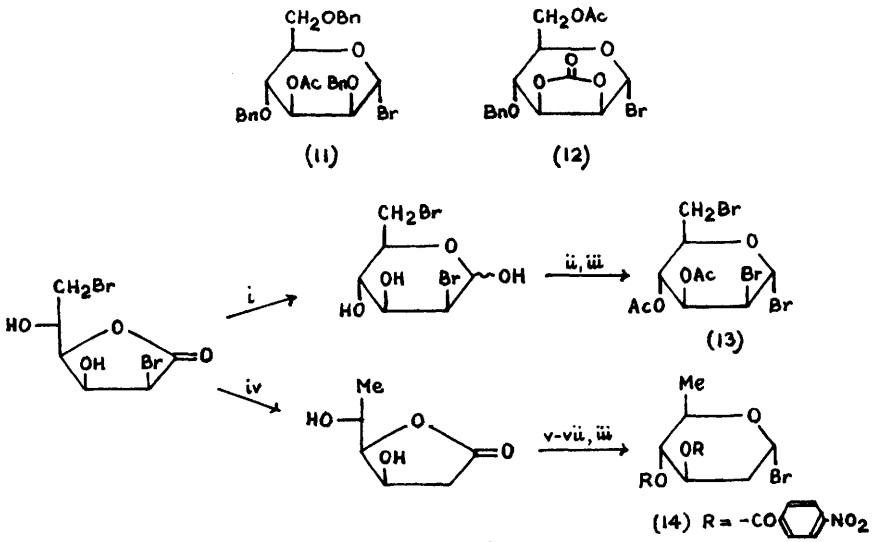


(10)

via the crystalline intermediate (10).[24]

2,3-Anhydropyranosides gave vicinal bromohydrins in high yield

on treatment with magnesium bromide etherate, the products resulting from the expected diaxial ring opening. 2,3-Diequatorial regio-isomers were obtained as well as the diaxial products with some α-glycosides.[25] The synthesis of the glycosyl bromides (11) and (12) has been reported,[26] and the 2-bromo-2,6-dideoxy-glycosyl bromides (13) and the 2,6-dideoxy-glycosyl bromide (14), potentially useful as glycosylating agents have been prepared as shown in Scheme 4.[27]

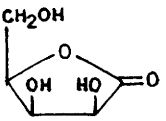


Reagents: i, $NaBH_4$-Resin(H^+); ii, Ac_2O-H^+; iii, HBr-HOAc; iv, Pd/C-Et_3N; v, $(Me_2CHC(Me)H)_2BH$; vi, MeOH-H^+; vii, p-NO_2-C_6H_4COCl-Py

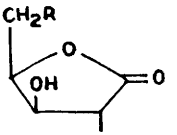
Scheme 4

Hydrogen bromide in acetic acid caused sequential replacements of the 2- and 5-hydroxy-groups of D-lyxono-1,4-lactone (15) giving, first, 2-bromo-2-deoxy-D-xylono-1,4-lactone (16), then 2,5-dibromo-2,5-dideoxy-D-xylono-1,4-lactone (17). Hydrogenolysis caused selective dehalogenation at C-2 in (16) and (17), the latter giving the 6-bromo-lactone (18). Similar reaction with D-ribono-1,4-lactone was accompanied by competitive epimerization at C-2 and C-4.[28]

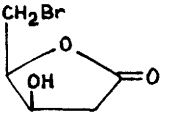
trans-Diaxial addition of iodine monochloride to 3,4,6-tri-O-acetyl-D-galactal, achieved using the reagent combination silver imidazolate-mercuric chloride-iodine, gave a 5:1 mixture of 2-deoxy-2-iodo-α-D-talo- and -β-D-galacto-pyranosyl chlorides (19)



(15)

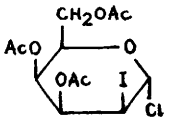


(16) R = OH
(17) R = Br



(18)

and (20). When used for glycosylation these mixed chlorides gave 1,2-trans-substituted products due to neighbouring group participation by iodine; thus the 2-deoxy-2-iodo-α-D-talopyranosyl galactoside (21) was the major product on reaction with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose.[29] An improved method for the synthesis of 3-deoxy-3-iodo-D-glucose (22) uses iodide dislacement of the tosyl group in (23), obtained in three steps from D-glucose, with concomitant iodide epimerization brought about by self-displacement.[30]



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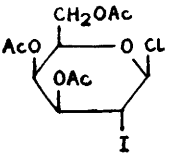

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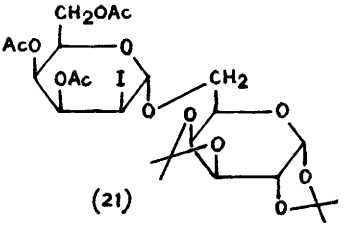

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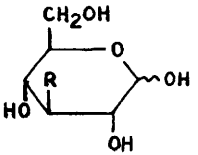

(22) R = I
(23) R = OTs

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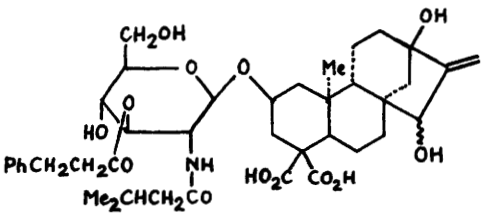
8

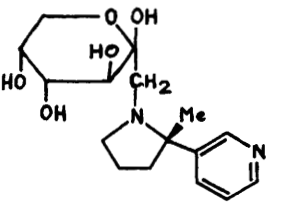
Amino-sugars

1 Natural Products

2,3-Diacetamido-2,3-dideoxy-D-glucuronic acid was identified as a constituent of the O-specific polysaccharide of *Pseudomonas aeruginosa*,[1] while O(3)-(2-acetamido-2-deoxy-β-D-glucopyranosyl) oleanolic acid, the first triterpene glycoside to contain an amino-sugar moiety, was isolated from a *Pithecellobium* species.[2] The major toxic constituent of the plant *Wedelia asperrima* was the diterpene aminoglycoside Wedeloside (1). The cyclohexyl glycoside of the constituent acylated amino-sugar was obtained by standard methods.[3] The Amadori compound (2) was isolated from flue-cured tobacco leaves.[4]



(1)



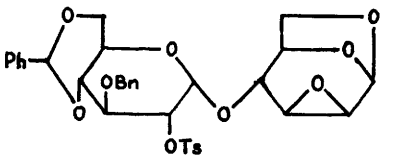
(2)

2 Synthesis

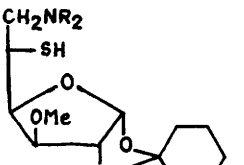
Synthetic aminoglycosides and the problems associated with their industrial preparation have been reviewed.[5] Sixteen Amadori- and Heyns-rearrangement products derived from D-glucose or D-fructose on treatment with amino-acids, *i.e.*, *N*-substituted 1-amino-1-deoxy-D-fructoses and 2-amino-2-deoxy-D-glucoses, respectively, were characterized by ^{1}H-n.m.r. spectroscopy (220 MHz) of their D_2O solutions, in which their acyclic, furanose, and pyranose forms are in equilibrium. The Amadori compounds were essentially in the β-pyranose form with a $^2C_5$ conformation at pH $\geq$7, while at pH 3 the acyclic and furanose (mainly β) forms were also present. The 2-

amino-2-deoxy-glucose derivatives existed essentially as anomeric pyranoses.[6]

In a new synthesis of N-acetylmaltosamine [2-acetamido-2-deoxy-4-O-(α-D-glucopyranosyl)-D-glucopyranose], the 2-amino-function was introduced by trans-diaxial opening of the epoxide ring in the dianhydride (3) with azide.[7] 6-Amino-5-thio-derivatives (4) were obtained by opening a 5,6-epithio-ring with primary and secondary aliphatic amines, and with 2-aminoacid ester.[8]

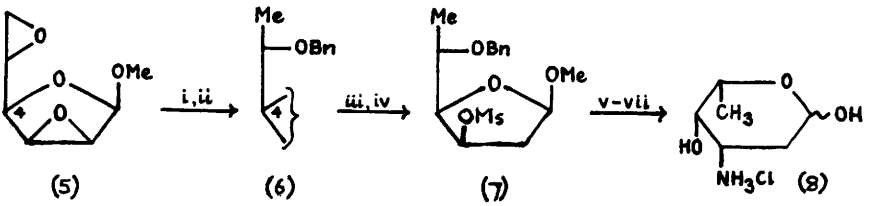


(3)



(4)

Displacement of a sulphonate ester group by a nitrogen nucleophile constituted a key step in several syntheses. L-Daunosamine (8) was obtained from D-glucose by three routes. The most successful (11 steps, 5% overall yield, no chromatographic purification) began by converting 1,2-O-isopropylidene-α-D-glucofuranose to the α-L-gulo-diepoxide (5) through benzoylation, methanolysis, then sequential introduction and displacement of a 2- then a 5-O-sulphonate group. Key steps in the remaining transformation (Scheme 1) were selective reduction of the 5,6-epoxide in diepoxide (5), specific C-2 reduction of 2,3-epoxide (6), and facile azide substitution on 3-O-mesylate (7). An attempted azide substitution



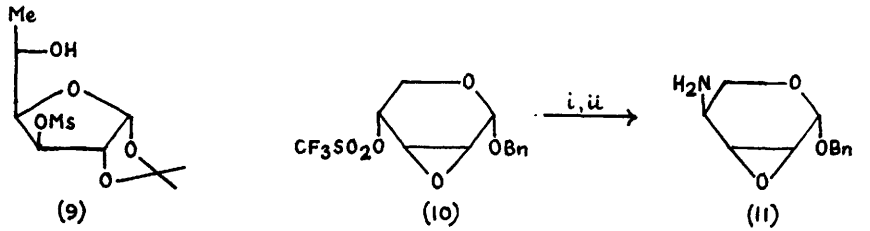
(5) (6) (7) (8)

Reagents: i, $NaBH_4$; ii, BnCl-KOH-DMF; iii, $LiAlH_4$; iv, MsCl-Py; v, NaN_3-DMF; vi, Pd/C-H_2; vii, H_3O^+

Scheme 1

on 3-O-mesylate (9) proceeded only slowly and in low yield due to steric hindrance by the isopropylidene group.[9] Azide displacement

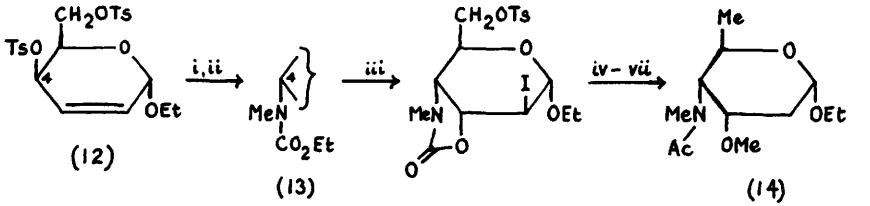
on 4-O-triflate (10) proceeded under mild conditions and led to the synthesis of 2,3-anhydro-4-amino-glycoside (11) (Scheme 2); other



Reagents: i, NaN_3; ii, PtO_2-H_2

Scheme 2

configurational isomers of compound (10) behave similarly.[10] In the synthesis of the holacosamine derivative (14) (Scheme 3) displacement of the allylic 4-O-sulphonate group in compound (12) by methylamine introduced the required 4-amino functionality. Overall 3,4-cis-oxyamination was then achieved by iodocarbamoylation

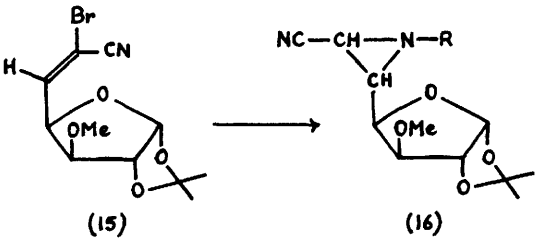


Reagents: i, $MeNH_2$-DMSO; ii, $ClCO_2Et$; iii, $I^+ClO_4^-$-dicollidine; iv, NaI-Me_2CO; v, Bu_3SnH; vi, KOH-EtOH; vii, Ac_2O-MeOH; viii, MeI-NaH-Bu_4NI

Scheme 3

of allylic amine (13).[11] Displacement reactions leading to amino-sugar derivatives are also referred to in Chapters 6, 9, 11, and 18.

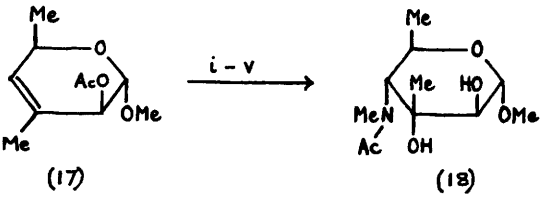
The addition of ammonia and primary amines to bromocyano-olefins e.g., (15), yields aziridines, e.g., (16), as shown in Scheme 4.[12]



Scheme 4

The stereochemistry of this addition was determined, relevant circular dichroism results being referred to in Chapter 21.

cis-Oxyamination of alkenes using osmium tetraoxide-chloramine T has again been utilized in amino-sugar synthesis. Thus, the glycoside (18) of the branched-chain amino-sugar sibirosamine, a component of sibiromycin, was obtained from 3-ene (17) (Scheme 5),[13]

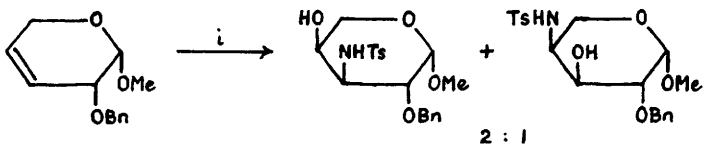


(17) (18)

Reagents: i, OsO_4-chloramine T; ii, MeONa-MeOH; iii, MeI-$KOBu^t$; iv, Na-NH_3; v, Ac_2O

Scheme 5

the synthesis of which is outlined in Chapter 13. Further, the cis-oxyamination of a variety of branched and unbranched ald-2- and 3-enopyranoside derivatives has been reported,[14] an example being shown in Scheme 6. Oxyamination has been postulated to be an

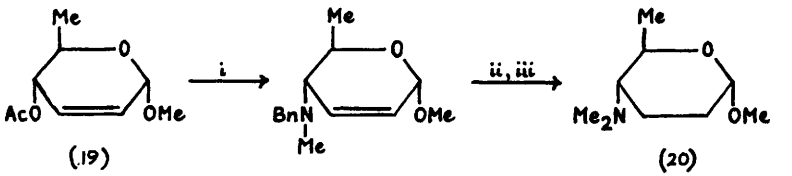


Reagent : i, OsO_4-chloramine T

Scheme 6

orbital-overlap controlled [3+2]-cycloaddition process from a study on model alkenes.[15] It was concluded, on the basis of work involving oxyamination of 15-methyl 3,4-dideoxy-α-DL-threo- and erythro-hex-3-enopyranoside derivatives, that the presence of an allylic acyloxy group suppresses oxyamination in favour of cis-dihydroxylation.[16]

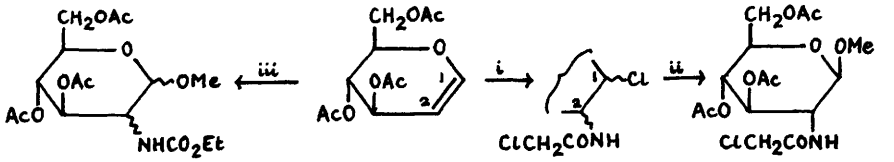
The methyl α-glycoside (20) of forosamine was obtained by palladium-catalysed allylic amination of 2-ene (19) as shown in Scheme 7.[17] Epimeric 3-acetamido-2,3-dideoxy-α-D-hexopyranosides, and their 2,3,6-trideoxy-analogues, have been synthesized from epimeric 3-azido-glycals, which were produced by the known BF_3-catalysed addition and allylic rearrangement of azide with acetylated glycals.[18] Other allylic amine derivatives are referred



Reagents: i, $BnNHMe-Pd(PPh_3)_4-PPh_3$; ii, $Pd/C-H_2$; iii, $HCHO-MeOH-NaBH_4$

Scheme 7

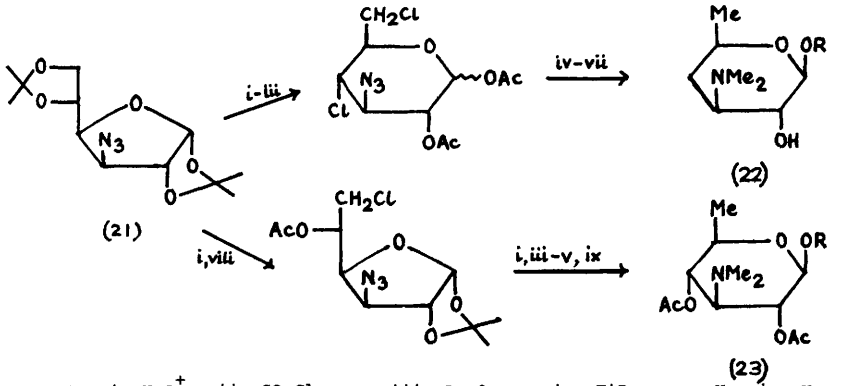
to in Chapters 12 and 13. 2-Amino-2-deoxy-D-hexopyranoside derivatives resulted from photochemical addition of N-chloro-chloroacetamide[19] or nitrenes[20] to tri-O-acetyl-D-glucal or D-galactal illustrated in Scheme 8, the latter reaction involving 1,2 -aziridine intermediates. Methyl 2-acetamido-2-deoxyhexo-



Reagents: i, $ClCH_2CONHCl-MeOH-h\nu$; ii, Ag^+-MeOH; iii, $EtOCON_3-h\nu$

Scheme 8

furanosides were obtained from furanoid glycals by nitrosyl chloride addition, methanolysis, and lithium aluminium hydride reduction.[21]

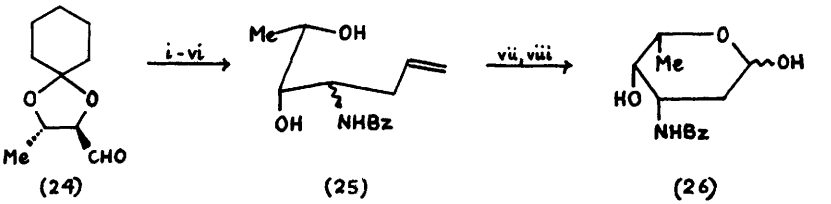


Reagents: i, H_3O^+; ii, SO_2Cl_2-py; iii, Ac_2O-py; iv, $TiBr_4$; v, Koenigs-Knorr glycosidation; vi, MeONa-MeOH; vii, Bu_3SnH; viii, acetylsalicyloyl chloride; ix, $HCHO-H_2-Pd/C$

Scheme 9

Glycosides of β-D-desosamine (22)[22] and of β-D-mycaminose (23)[23] were synthesized from the known 3-azido-3-deoxy-D-glucose derivative (21) as outlined in Scheme 9, two related approaches to compound (23) also being described.[23]

Non-carbohydrate starting materials, both chiral and achiral, have been employed in amino-sugar synthesis. N-Benzoyl-L-daunosamine (26) was synthesized as shown in Scheme 10 from the chiral aldehyde (24) which was available from D-threonine. The desired isomer in the epimeric mixture (25) was the major component,

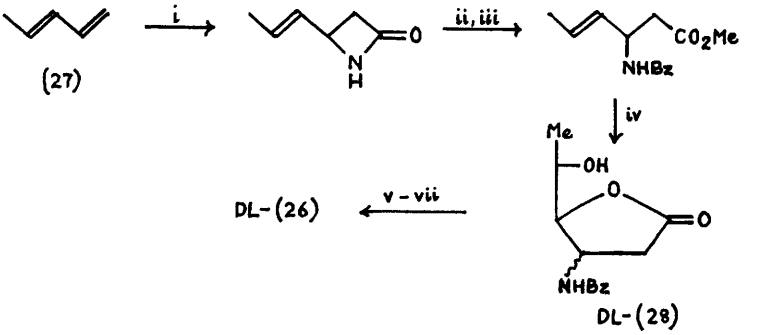


(24) (25) (26)

Reagents: i, CH_2=$CHCH_2MgBr$; ii, TsCl-Py; iii, NaN_3; iv, $LiAlH_4$; v, HOAc, vi, BzCl; vii, O_3; viii, Me_2S

Scheme 10

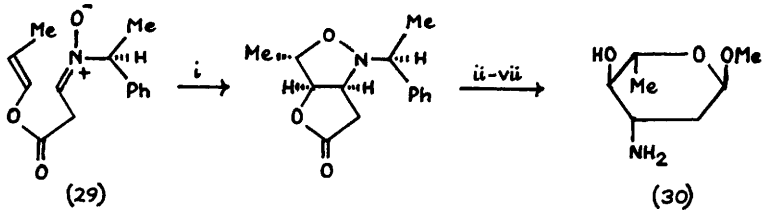
and was separated by crystallization.[24] The racemic DL-daunosamine derivative (26) was synthesized from (E)-1,3-pentadiene (27) and chlorosulphonyl isocyanate as shown in Scheme 11, a separation of racemic lyxo- and xylo-lactones (28) being necessary.[25] The



Reagents: i, $ClSO_2NCO$; ii, HCl-MeOH; iii, BzCl-Py; iv, OsO_4-$Me_3N\rightarrow O$; v, Ac_2O-Py; vi, $(Bu^i)_2AlH$; vii, NH_3-MeOH

Scheme 11

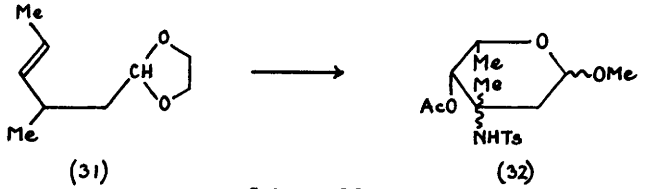
methyl glycoside of L-daunosamine was obtained from the β-L-acosamine analogue (30) by inversion at C-4 through sulphonate displacement, the latter having been synthesized (Scheme 12) from the chiral nitrone (29), whose intramolecular 1,3-dipolar cycloaddition



Reagents: i, Δ; ii, Zn-HOAc; iii, $ClCO_2Me$; iv, $(Bu^i)_2AlH$; v, MeOH-Resin(H^+) vi, Na-NH_3; vii, OH^-

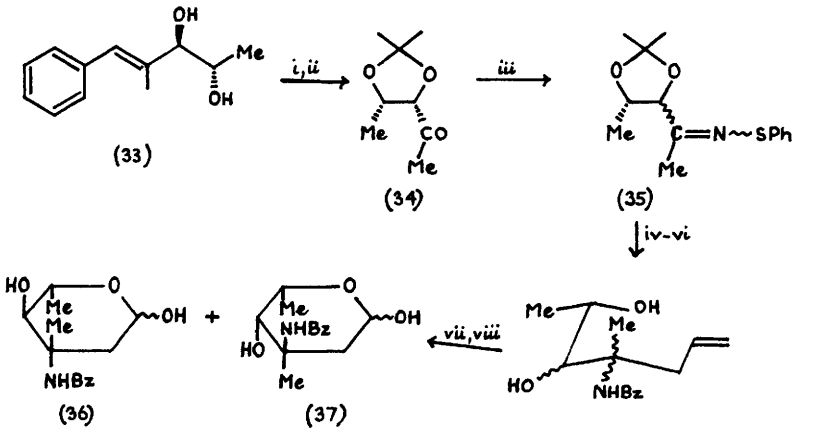
Scheme 12

relayed the desired chirality from (S)-α-methylbenzylamine to the atoms which become C-3, -4, and -5 in (30).[26] Racemic 2,3,6-trideoxy-3-C-methyl-3-amino-hexose derivatives (32) were obtained following allylic amination and cis-hydroxylation of (31),[27] Scheme 13, while the free sugars with the L-arabino-(36) and L-



Scheme 13

xylo-(37)-configurations were obtained from the yeast produced cinnamaldehyde-acetaldehyde adduct (33) by way of the chiral diol derivative (34) [c.f. (24) in Scheme 10] as shown in Scheme 14.



Reagents: i, O_3; ii, Ph_3P: iii, NH_3-PhSSPh-$AgNO_3$-MeOH; iv, CH_2=$CHCH_2MgBr$; v, H_3O^+; vi, BzCl; vii, O_3; viii, Me_2S

Scheme 14

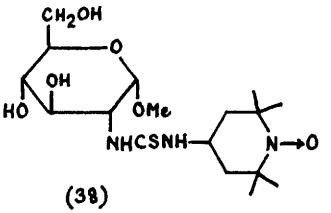
α-Epimerization occurred during the formation of sulphenimine (35). N-Benzoyl-L-vancosamine was synthesized from (36) by a mesylate-mediated inversion at C-4.[28] Other references to branched-chain amino-sugars appear in Chapters 12 and 13, while glycosides containing hexosamine residues appear in Chapter 3.

3 Reactions

The quantitative methylation analysis of aminosugars has been reviewed.[29]

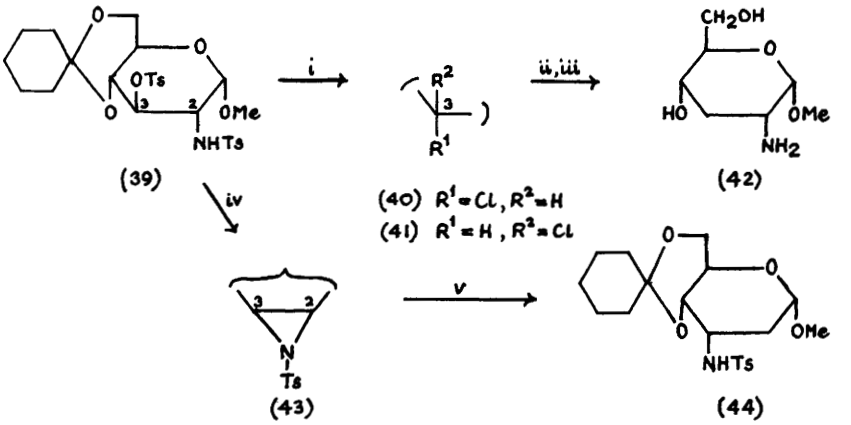
A Japanese group has synthesized a large number of N-acetylmuramoyl-L-alanyl-D-isoglutamine (MDP) analogues by conventional modification of 2-amino-2-deoxy-D-glucose and N-acetylmuramic acid derivatives, and have tested their immunoadjuvant activity, revealing many with greatly enhanced activity relative to MDP. Thus MDP-analogues bearing different dipeptide residues,[30] N-fatty acyl moieties,[31] N-(quinonylalkanoyl)-aminoacid ester residues linked through O-6,[32] or 2-NHMe, $-NH_3Cl$, or -N(Me)Ac moieties,[33] as well as the 4,6-dideoxy, 4-deoxy-, 4-deoxy-6-amino-, 4,6-dichloro-, and 4-chloro-analogues were prepared.[34]

Monosaccharide analogues of Lipid A, a constituent of bacterial lipopolysaccharides, namely 2-deoxy-2-(acylamino)-α-D-glucopyranosyl phosphates[35] and 2-deoxy-2-(D- and L-3-hydroxytetradecanoylamino)-D-glucose,[36] were synthesised by conventional procedures. 2-(Bromo-, chloro-, and fluoro-acetamido)-2-deoxy-D-mannoses and their tetra-O-acetylated β-pyranose derivatives were obtained by N-acylation of mannosamine, the O-acetylated derivatives displaying antitumor activity.[37] The spin-labelled compound (38) was synthesized conventionally from the amino-sugar and a spin-labelled isothiocyanate.[38]



(38)

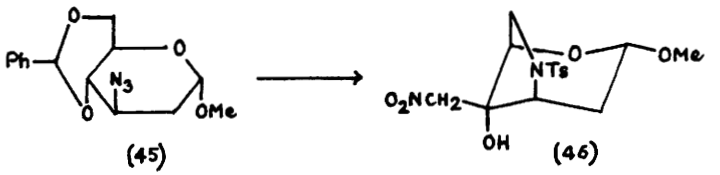
N-Tosylation activated 3-tosyloxy groups in 2-amino-2-deoxy-α-D-glucopyranosyl derivatives towards nucleophilic displacement by halide ions (Scheme 15). Thus the ditosylate (39) initially gave



Reagents: i, LiCl-DMF; ii, Na-NH_3; iii, Resin(H^+); iv, NaOBz; v, $LiAlH_4$

Scheme 15

the 3-chloro-alloside (40) which underwent a second S_N2 displacement with chloride ion to give the thermodynamically more stable 3-chloro-glucoside (41), from which methyl 2-amino-2,3-dideoxy-α-D-ribo-hexopyranoside (42) was obtained. Other nucleophiles acting on the ditosylate (39) resulted in the formation of the 2,3-epimino-derivative (43). Reduction of either (39) or (43) yielded the 3-amino-2,3-dideoxy-α-D-ribo-hexopyranoside (44).[39] The 3,6-epimino-4-C-nitromethyl-2,3,6-trideoxy-α-D-arabino-hexopyranoside (46), a potential chiral intermediate in the synthesis of 9-azaprostaglandins, was obtained from the known 2,3-dideoxy-3-azido-derivative (45) by conventional procedures (Scheme 16), using 6-

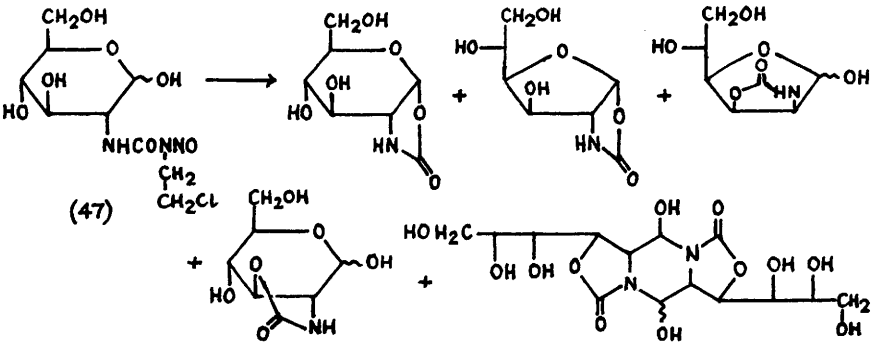


Scheme 16

bromo and 4-ulose intermediates.[40] Benzyl and methyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside have been converted to their allo-isomers by a conventional oxidation–reduction sequence.[41] Other synthetic modifications of amino-sugars are

reported in Chapters 3, 10, 15, and 16.

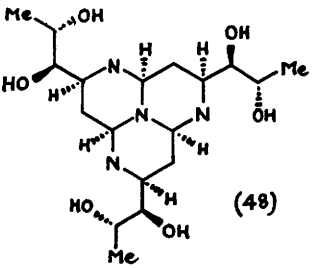
Chlorozotocin (47), a potential anti-cancer agent, degraded in buffer at pH 7.4 to give the products shown in Scheme 17.[42] When



(47)

Scheme 17

the hydrolyzate from the L-ristosamine (3-amino-2,3,6-trideoxy-L-*ribo*-hexopyranose) containing glycopeptide antibiotic avoparcin was exposed to ammonia on a strong base resin (NH_4^+ form), the major product was (48), formed by condensation of one ammonia with three L-ristosamine molecules.[43]



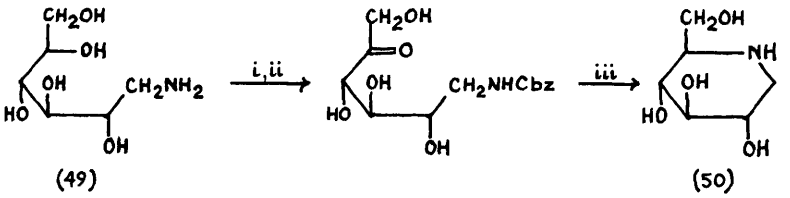
(48)

2-Acetamido-2-deoxy-D-glucopyranosyl disaccharides linked through secondary hydroxy groups in the reducing unit undergo Smith degradation with limited amounts of periodate to give 2-*O*-substituted glycerols; the α- and β-linked compounds were separable by g.c., allowing the anomeric configuration to be determined.[44] Radical deamination of amino-sugars is referred to in Chapter 11.

N-Acetyl-neuraminic acid underwent deuteration at *C*-3 in alkaline deuterium oxide, with H_{3a} being replaced faster than H_{3e}.[45] The C.D. of neuraminic acid derivatives is referred to in Chapter 21.

1-Deoxynojirimycin (50) was synthesized by the microbiological-

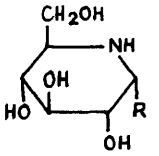
chemical method shown in Scheme 18 from 1-amino-1-deoxy-D-glucitol



Reagents: i, $ClCO_2Bn$; ii, Acetobacter suboxydans; iii, $Pd/C-H_2$.

Scheme 18

(49).[46] α-C-Glycosides containing a ring nitrogen atom (51) were obtained from the trimethylsilylated derivative of 1-α-cyano-1-deoxynojirimycin by use of Grignard reagents, the cyano group being



(51) R = n-alkyl, Ph, Bn, or C_4H_3S

completely exchanged, and ⩽ 5% of the β-anomers being formed.[47]

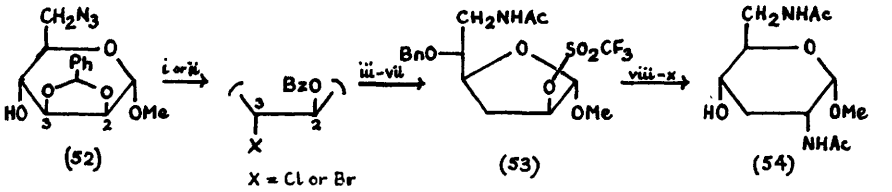
Titration (potentiometric and ^1H-n.m.r.) and optical rotation studies have shown that fully protonated chito-oligosaccharides with 2,3,4,5 and 7 sugar units adopt similar conformations. The ^1H-n.m.r. study indicated an α:β ratio of 0.87 in aqueous solution for chitobiose, which changed to 2.33 on protonation, and suggested that the reducing moieties of the protonated oligosaccharides provide higher proportions of the α-anomer than is found in the monomer, 2-amino-2-deoxy-D-glucose hydrochloride. The ^{13}C-n.m.r. spectrum of protonated chitobiose was fully assigned.[48]

Peptide esters of a series of 2-acetamido-2-deoxy-hexoses derived from D-2-propanoyl-L-alanyl-D-isoglutamine have been prepared in order to assess their immunoadjuvant activity.[49]

4 Diamino-sugars

The synthesis of diamino-sugars has been reviewed, with particular reference to 2,3- and 2,4-diaminopentoses, and 2,4-diamino-hexoses.[50]

The tobrosamine derivative (54) has been synthesized from the 6-azido-mannoside (52) (Scheme 19). The furanoside ring in (53) arose by a Tischenko-type ring contraction on treating the 2,4-diol

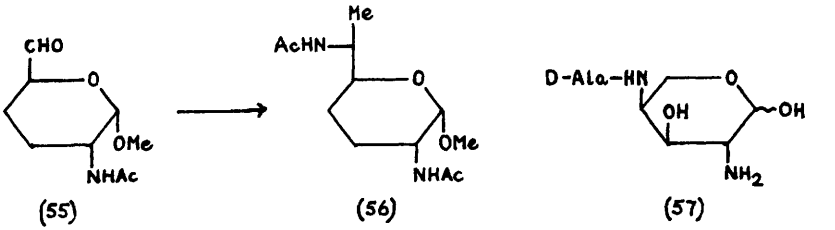


Reagents: i, NBS; ii, $PhC(Cl)=NMe_2HCl$; iii, $LiAlH_4$; iv, Ac_2O; v, PhCHO-$AlCl_3$-$ZnCl_2$; vi, NaOMe-MeOH; vii, $(CF_3SO_2)_2O$-Py; viii, NaN_3; ix, Pd-H_2; x, Ac_2O

Scheme 19

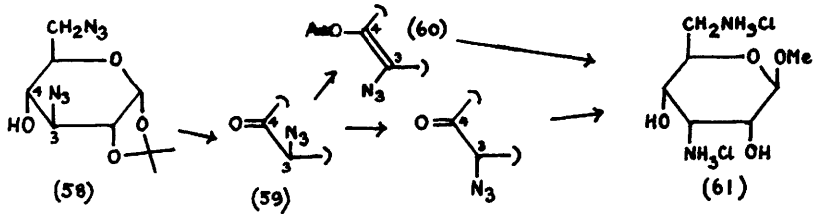
precursor in benzaldehyde in presence of Lewis acid catalyst.[51] The products of ammonolysis and azidolysis of four benzyl 2,3-anhydro-4-azido-4-deoxypentopyranosides and the relative rates of reaction have been reported.[52]

Methyl 2,6-di-*N*-acetyl-α-purpurosaminide (56) and its 6-epimer have been synthesized from the corresponding dialdose derivative (55) using a 6,7-epimine intermediate.[53] The D-*arabino*-, D-*ribo*-, L- and D-*lyxo*-stereoisomers of prumycin (57) were synthesized from



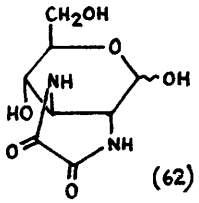
4-azido-2-benzyloxycarbonylamino-2,4-dideoxypentopyranosides by conventional methods. These and other isomers were tested for their antimicrobial activity, with only the L-*lyxo*-isomer displaying any significant activity.[54]

3,6-Diamino-3,6-dideoxy- and 3,4,6-triamino-3,4,6-trideoxy-D-galactose derivatives have been synthesized from the 3,6-diazido-D-*gluco*-derivative (58) by standard transformations involving mesylate displacements at C-4. A double inversion sequence at C-4 led to 3,4,6-triacetamido-3,4,6-trideoxy-D-glucose. The D-allose isomer of the 3,6-diamino sugar was obtained by C-3 epimerization of the 3-azido-4-ulose intermediate (59), followed by stereoselective reduction of the keto group. Alternatively, the ulose could be converted to the corresponding enol acetate (60), which gave the alloside (61) on borohydride reduction (Scheme 20).[55]



Scheme 20

2,3-Diamino-2,3-dideoxy-2,3-*N*-oxalyl-D-glucose (62) has been synthesized from benzyl 2,3-diamino-2,3-dideoxy-4,6-*O*-benzylidene-α-D-glucopyranoside and oxalyl chloride and its reactions were investigated. The diamide ring did not withstand acetylating conditions.[56]



A variety of amido-compounds related to "chord factor" have been prepared by acylation of 6,6'-diamino-2,3,4,2',3',4'-hexa-*O*-benzyl-6,6'-dideoxy-α,α-trehalose with complex carboxylic acids.[57]

References to other di- and higher-amino sugars appear in Chapters 6, 12, and 18.

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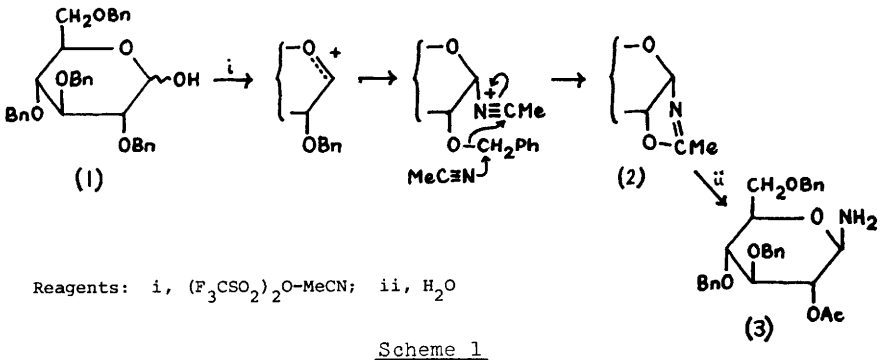
9

Miscellaneous Nitrogen Derivatives

1 Glycosylamines

The preparation of glycopyranosylamines by amination of free sugars has been outlined, the synthesis of β-D-mannopyranosylamine using ammonia-ammonium chloride in methanol being detailed. Such derivatives could be O,N-acetylated and then O-deacetylated.[1] The ^{1}H-n.m.r. spectra of some N-acetylglycofuranosylamines and their acylated derivatives have been reported.[2] The long-known "ribose anilides" have been shown to be N-phenyl-α-D-ribopyranosylamine (isomer A of Ellis and Honeyman) and a mixture of this and its β-anomer (isomer B).[3] The mutarotation of N-D-glucopyranosyl-p-bromoaniline in methanol solution has been examined as a function of pH. An acid-catalysed mechanism was observed at pH<13, but at pH>13 base-catalysis was observed.[4]

The O-protected β-D-glucopyranosylamine (3) was synthesized from 2,3,4,6-tetra-O-benzyl-D-glucose (1). As shown in Scheme 1, debenzylation at O-2 led to the formation of oxazoline (2), from which (3) was produced on hydrolysis.[5]

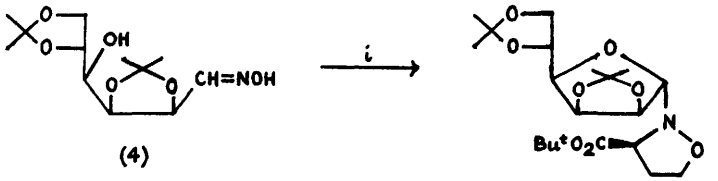


Reagents: i, $(F_3CSO_2)_2O$-MeCN; ii, H_2O

Scheme 1

Diastereomeric N-glycosyl isoxazolidines were obtained by 1,3-dipolar cycloaddition of ethylene to N-glycosyl nitrones formed in situ from sugar oximes and glyoxylic esters. Thus, as shown in

Scheme 2, the D-mannose oxime derivative (4) gave a mixture of N-α-D-mannosyl-3(R,S)-tert-butoxycarbonyl-isoxazolidine derivatives (90%) from which the predominant (3S)-isomer (5) crystallized in 43% yield. Analogous treatment of a D-ribose oxime derivative similarly gave a mixture of N-β-D-ribosyl-isoxazolidine derivatives.[6]

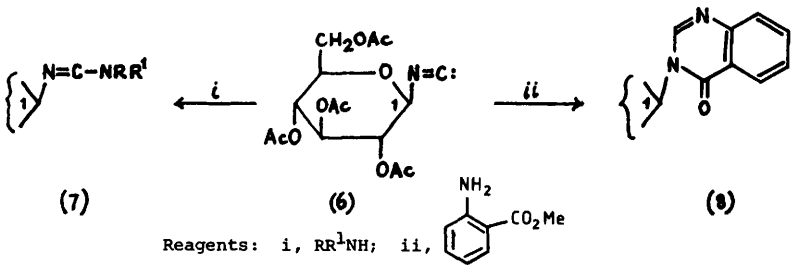


(4) (5)

Reagent : i, OHC•CO$_2$Bu^t – CH$_2$=CH$_2$

Scheme 2

Glycosyl isonitriles, when complexed with metal ions (e.g. silver), react with alcohols to give mixtures of alkyl glycosides and 1,2-orthoesters (where there is a participating group at C-2). With amines they give formamidines in high yield [e.g. (6) → (7)], and with methyl anthranilate they give glycosyl quinazolinones [e.g. (6) → (8)] (Scheme 3).[7]



(7) (6) (8)

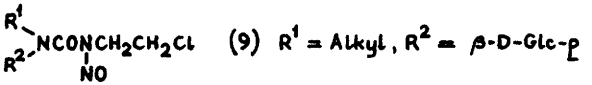
Reagents: i, RR^{1}NH; ii,

Scheme 3

Glycopeptides containing N-linked glycosyl moieties have been synthesized. β-D-Glucosylamine and 2-acetamido-2-deoxy-β-D-glucosylamine derivatives linked to the amino-acid sequence 5 to 9 of somatostatin were obtained by carbodi-imide coupling a suitably protected amino-acid sequence to a peracetylated β-D-glycopyranosylamine,[8] while other somatostatin analogues were prepared by solid phase methods utilizing N-(peracetylated β-D-glycosyl)asparagine derivatives as the source of the sugar moiety.[9] O-α-D-Gluco-

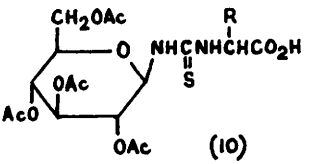
pyranosyl-(1→6)-O-β-D-glucopyranosyl-(1→6)-N-L-β-aspartyl-α- and β-D-glucopyranosylamine were synthesized by reduction (PtO_2-H_2) of the corresponding triosyl α-azide (synthesized itself by two routes employing standard glycosylation procedures) to a 2:1 mixture of α- and β-glycosylamine derivatives, which were separated and condensed with an aspartic acid derivative.[10] The Peoc (2-triphenylphosphonioethoxycarbonyl) group has been utilized for the protection of an amino-function in the synthesis of an N-(2-acetamido-2-deoxy-β-D-glucosyl)asparagine derivative; it is readily removed under mildly basic conditions (5% Et_2NH in Bu^tOH), allowing the peptide chain to be elongated from the liberated amine function.[11]

Forty-two variously 3-alkylated 1-(2-chloroethyl)-3-(β-D-glycopyranosyl)-1-nitrosoureas (9) have been synthesized using standard procedures from crude hexosylamine mixtures (containing products differing in ring size and anomeric configuration) obtained on treatment of D-galactose, D-glucose, or D-mannose with primary amines. Many of these nitrosoureas were remarkably active antitumor agents.[12]



(9) R^1 = Alkyl, R^2 = β-D-Glc-p

Enantiomeric amino-acids have been separated by h.p.l.c. (reversed phase) following conversion to their diastereomeric glycosyl thiourea derivatives [e.g. (10)] by reaction with either 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl or 2,3,4-tri-O-acetyl-α-D-arabinopyranosyl isothiocyanate.[13]



(10)

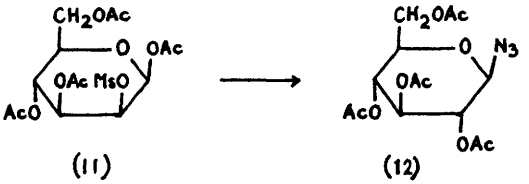
Glycosyl isothiocyanates have also been condensed with a variety of amidines, hydrazines and diazo compounds and then cyclized to yield N-glycosylated heterocycles.[14-17] Similar reactions of D-gluconyl isothiocyanate pentaacetate are covered in section 6 of this chapter, and other N-glycosylated heterocycles are referred to in Chapters 18 and 19.

The melanoidins produced from the Maillard reaction of D-glucose and D-fructose with glycine have been investigated,[18,19] and the

Maillard reaction between D-glucose and lysine hydrochloride has been analysed thermally.[20]

2 Azido-sugars

Reaction of 2-O-methanesulphonyl derivatives of hexopyranose acetates with sodium azide gave glycosyl azides, e.g. (12), rather than 2-azido-sugars, the D-mannose derivative (11) undergoing complete inversion at C-2 (Scheme 4), while the D-galacto-isomer gave both galacto- and talo-products.[21]



Scheme 4

The photo-catalysed addition of chlorine azide to glycals provided 2-azido-2-deoxy-glycosyl chlorides which were isolated as the corresponding glycosyl acetate (13). In addition to the major products, small amounts of 1,2-regio- and stereo-isomeric products were also isolated.[22]

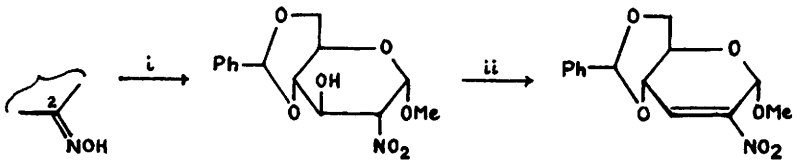
The expected addition products were obtained from the reaction of 3,4,6-tri-O-acetyl-D-glucal and iodine trifluoroacetate, iodine isocyanate, or Simmons-Smith reagent, while mercury(II) diazide gave the unsaturated derivative (14), and nitryl iodide and diazomethane failed to react.[23]

Azido-sugar synthesis and reduction are referred to in Chapters 6 and 8, while other azido-sugars appear in Chapters 3 and 12.

3 Nitro-sugars

The 2-deoxy-2-nitro-α-D-glucopyranoside derivative (16), obtained by

oxidation of the corresponding 2-oximino-derivative (15), can be converted to the 2-nitro-2-ene (17) by sulphonate elimination (Scheme 5).[24] The synthesis of an analogous 3-nitro-2-ene derivative is reported in Chapter 12. Based-catalysed condensation of a 7-deoxy-7-nitroheptose compound derived from D-glucofuranose with an aldehydo-D-arabinose derivative yielded an isomeric mixture of 7-deoxy-7-nitrododecose products of interest as intermediates for the synthesis of tunicamycin nucleoside antibiotics.[25]

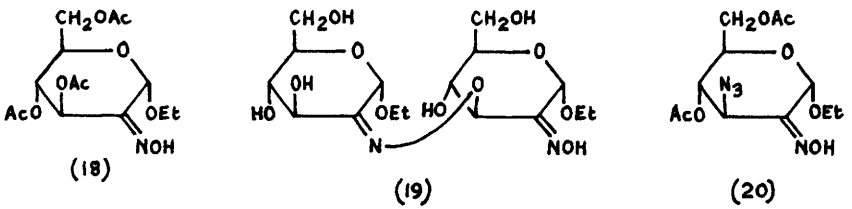


Reagents: i, CF_3CO_3H-$NaHCO_3$-$(NH_2)_2CO$; ii, MsCl-Et_3N

Scheme 5

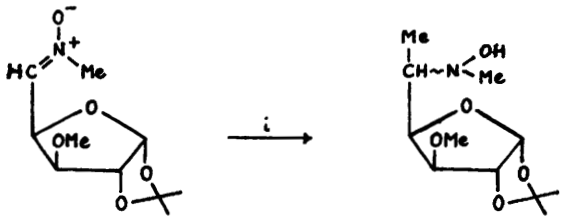
4 Oximes and Hydroxylamines

Deacetylation of the 2-oximino-derivative (18) gave the expected product but also the dimer (19) and an analogous trimer. This led to the development of reactions involving the displacement of the 3-acetoxy-group of (18) by nucleophiles {azide [gave the azido sugar (20)], phthalimide, hydride, and thiophenoxide}, and thence to the synthesis of 3-deoxy, 3-amino-3-deoxy-, 2-amino-2,3-dideoxy-, 2,3-diamino-2,3-dideoxy- and 2-amino-2,3,4-trideoxy-α-D-glycopyranosides.[26]



The generation of a 3-oximino-derivative from an unsaturated sugar is referred to in Chapter 12.

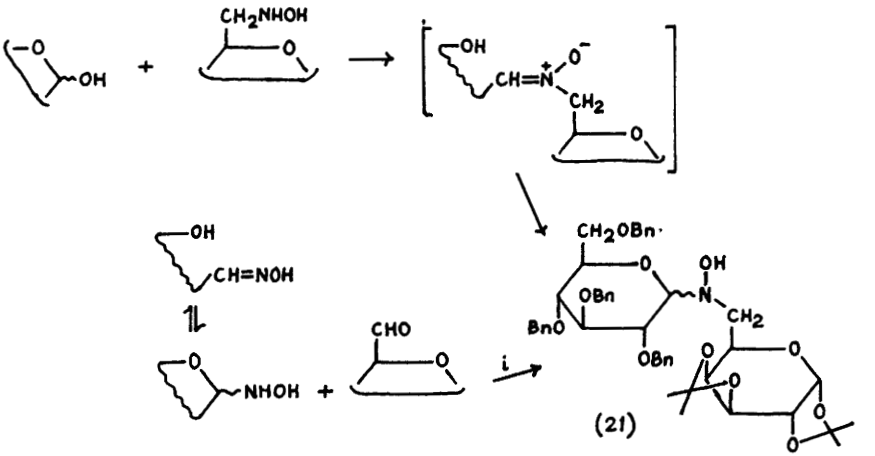
Treatment of sugar aldonitrones with Grignard reagents or with cyanide leads to deoxy-hydroxylamino-derivatives (e.g. Scheme 6).[27]



Reagent: i, MeMgBr

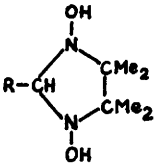
Scheme 6

The same communication extends earlier work on the synthesis of disaccharides in which the interglycosidic oxygen is replaced by a hydroxyamino-group. The two approaches outlined in Scheme 7 have been used, in which an aldehydo-sugar is condensed either with a deoxy-hydroxylamino sugar or a sugar oxime to give a disaccharide such as (21).[27] The same group obtained the 1,3-dihydroxy-imidazolidine derivative (22) by condensation of an aldehydo-sugar with 2,3-bis(hydroxyamino)-2,3-dimethyl-butane.[28] Oxidation of these deoxy-hydroxylamino and dihydroxyimidazolidine derivatives gave nitroxide radicals, whose e.s.r. spectra were recorded.[27,28]

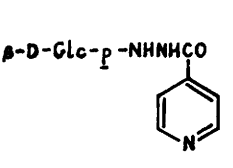


Reagent: i, $NaBH_4$

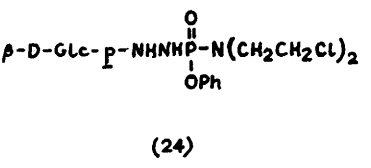
Scheme 7



(22)



(23)

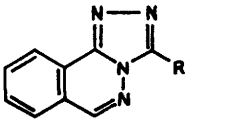


(24)

5 Hydrazones, Osazones and Derived Heterocycles

The condensation products from aldoses and isonicotinylhydrazine exist in solution mainly as the β-pyranosyl isomers, e.g. (23), whereas glyceraldehyde and glycolaldehyde gave the expected hydrazones.[29] Similarly, aldoses and phosphorus acid hydrazides gave cyclic hydrazones, e.g., (24), in good yield.[30] Various hexose and pentose hydrazones have been prepared using p-substituted α-phenoxyacetylhydrazines.[31] Condensation of aldoses with 1-hydrazinophthalazine gave hydrazones that underwent dehydrogenative cyclization to 3-(polyhydroxyalkyl)-1,2,4-triazolo[3,4-a]phthalazines (25) on exposure to a palladium catalyst, or on acetylation.[32]

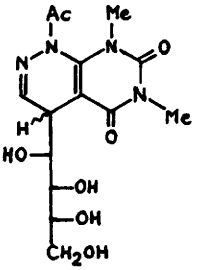
Likewise, D-mannose condensed with 6-hydrazino-1,3-dimethyluracil to give a hydrazone which underwent cyclodehydration to give the nucleoside analogue (26) as an epimeric mixture. Other sugars gave single diastereomers.[33]



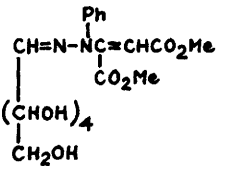
(25)

R = -(CHOH)$_n$CH$_2$OH

n = 3 or 4



(26)

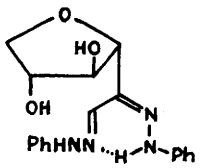


(27)

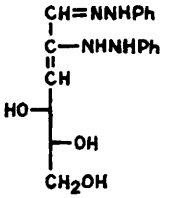
Hexose phenylhydrazones reacted with dimethyl acetylenedicarboxylate to give derivatives (27) with the E-configuration about both double bonds. These resisted cyclization to pyrazoles.[34]

Dehydrative cyclization (H_2SO_4-MeOH) of both D-lyxo- and D-xylo-

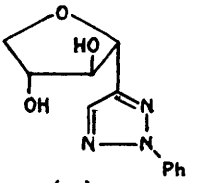
hexulose phenylosazones gave 3,6-anhydro-D-lyxo-hexulose phenylosazone (28) as the predominant product, consistent with the intermediacy of a 2-(phenylazo)-2-ene (29).[35] Cyclization ($CuSO_4$) of the osazone moiety in (28) yielded the C-nucleoside analogue (30). Analogous results were obtained with D-altro-2-heptulose phenylosazone.[36]



(28)

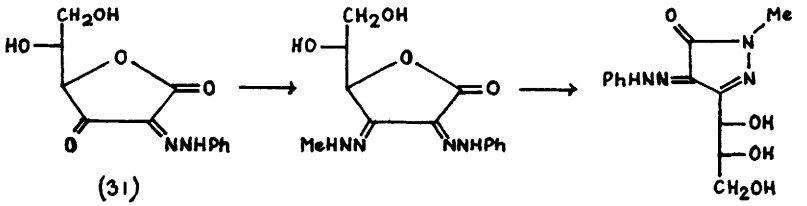


(29)



(30)

The heterocyclic derivative (32) was isolated from the reaction of dehydro-D-erythro-ascorbic acid 2-phenylhydrazone (31) with methylhydrazine as shown in Scheme 8.[37]



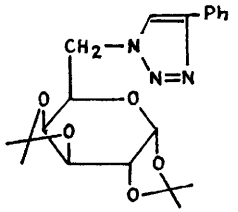
(31) (32)

Scheme 8

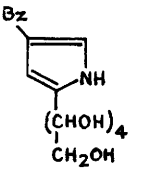
Sugar acid hydrazides are covered in Chapter 15, while other hydrazones are referred to in Chapter 14.

6 Other Heterocyclic Derivatives

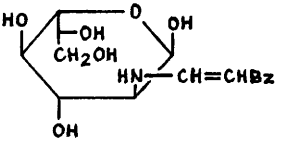
Condensation of 6-azido-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose with phenylacetylene gave the 6-triaza-heterocyclic derivative (33), an analogous derivative being obtained from 1-azido-1-deoxy-2,3:4,5-di-O-isopropylidene-α-D-fructopyranose.[38] Reaction of α-benzoylacetaldehyde with 2-amino-2-deoxy-D-glycero-D-talo- and D-glycero-D-ido-heptose gave the D-manno- and D-gluco-isomers of (34), respectively, whereas the D-glycero-L-gluco-analogue gave the amino-sugar Schiff-base tautomer (35).[39]



(33)



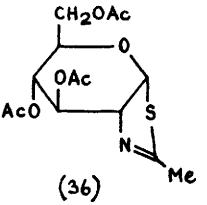
(34)



(35)

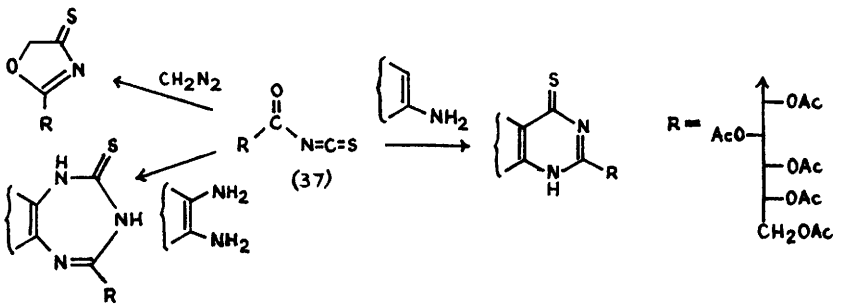
Treatment of 5-(D-galacto-pentitol-1-yl)tetrazole with nitric acid gave 5-(4-carboxy-D-galacto-tetritol-1-yl)tetrazole, from which ester and amide derivatives were synthesized.[40]

The thiazoline derivative (36) of D-glucose was synthesized conventionally from the corresponding 2-acetamido-2-deoxy-α-glucosyl chloride; bromination of (36) gave both 2-bromomethyl- and 2-dibromomethyl-thiazoline analogues.[41]



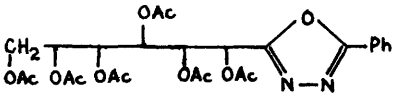
(36)

D-Gluconyl isothiocyanate penta-acetate (37) condensed with various nitrogen-containing compounds to give the heterocyclic derivatives shown in Scheme 9.[15,42]



Scheme 9

The 1,3,4-oxadiazole derivative (38) was obtained by simultaneous acetylation-cyclization of D-glycero-D-gulo-heptonic benzoyl-hydrazide using trifluoroacetic acid - acetyl bromide.[43]



(38)

Other heterocyclic derivatives are referred to in Chapters 12, 18, and 19.

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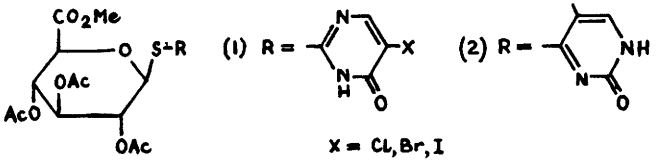
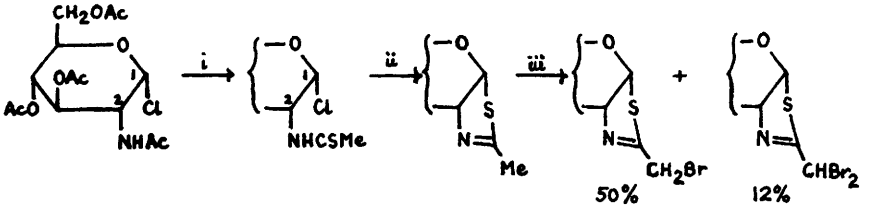
10

Thio- and Seleno-sugars

Ligand exchange and redox disproportionation reactions of aurothioglucose have been studied by ^{13}C-n.m.r. A novel oxidation-reduction reaction with β-D-thioglucose was discovered, leading to metallic gold and a product tentatively identified as the sulphuric acid derivative of thioglucose.[1] S-Glucuronides of 5-halo-2-thiouracils (1) and 5-halo-4-thiouracils (2) have been prepared by reaction of methyl 1,2,3,4-tetra-O-acetyl-β-D-glucuronate with thiouracil.[2] Thiazoline derivatives of D-glucose have been



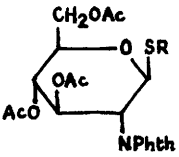
synthesized by the route shown in Scheme 1.[3] Derivatives of



Reagents: i, P_2S_5; ii, $Et_3BnN^+Cl^-$; iii, NBS

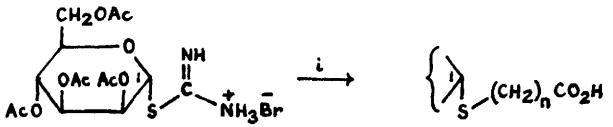
Scheme 1

1-thioglucosamine, such as (3), result from reaction of the



(3) R = Bu^t, Ph, Me

suitably blocked glucosaminyl chloride or 1-O-acetate with tributylalkyl(or aryl)thiotin (see also Chapter 8).[4] The reaction shown in Scheme 2 has been used to synthesize liposomes with 1-thiomannose side chains. A similar reaction was used to prepare the β-anomer.[5] The mass spectra of glucosinolates and desulphoglucosinolates have been recorded.[6] Conformational studies of ethyl 2-S-ethyl-1,2-dithio-α-D-mannofuranoside are described in

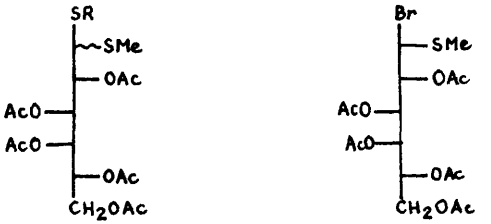


Reagent: i, $I(CH_2)_nCO_2H$

Scheme 2

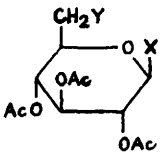
Chapter 20 and the preparation of S-α- and -β-D-gluco- and -galacto-pyranosyl thiophosphates is described in Chapter 6.

Thiocarbonates and thiocarbamates of the type shown in (4) were prepared from (5) by reaction with the appropriate potassium carbonate or xanthate salts.[7]



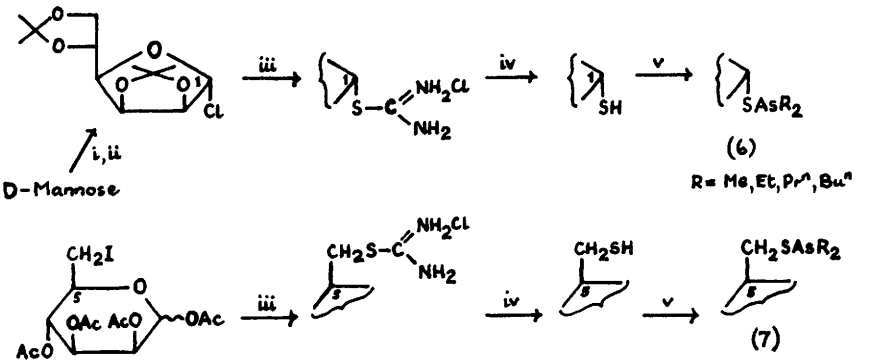
R = CO_2R^1, SCO_2R^1, SCSBu, $SCNR^1_2$
R^1 = Alkyl

Further studies on dialkylthioarsinous acid derivatives, some of which show carcinostatic activity, have appeared; in this case the 1- and 6-substituted mannose derivatives (6) and (7) were prepared as shown in Scheme 3,[8] and the 1- and 6-β-D-glucopyranosyl



(8) X = $SAsR^1R^2$, Y = OAc
(9) X = OAc, Y = $SAsR^1R^2$

R^1, R^2 = alkyl groups



Reagents: i, Me_2CO-H^+; ii, Ph_3P-CCl_4; iii, $SC(NH_2)_2$; iv, $NaHSO_3$; v, R_2AsI; vi, TsCl-C_5H_5N; vii, Ac_2O; viii, NaI

Scheme 3

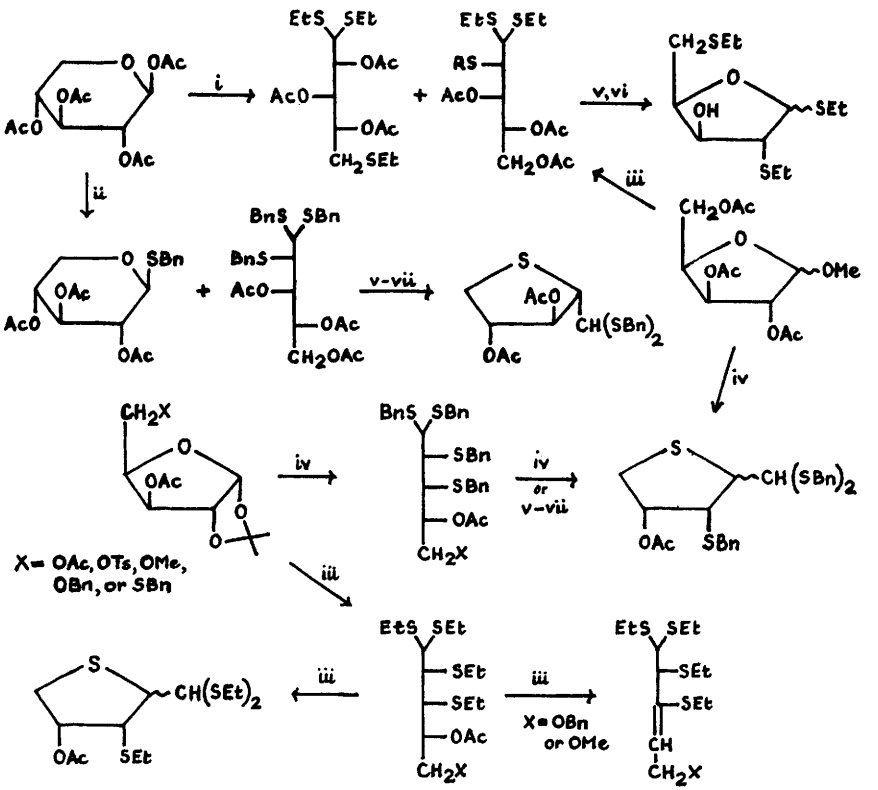
thioarsenites (8) and (9) by reaction of the tetra-O-acetylthioglucopyranoses with dialkylhaloarsines.[9]

A sequence of thiolyses carried out on pentose derivatives leading to dithioacetals and 2,5-epithio compounds is depicted in Scheme 4.[10]

Reaction of the 2,3-anhydro-mannoside (10) with the phosphoro-dithioic acid derivative (11) led exclusively to the diaxial product (12); whereas similar treatment of the corresponding 2,3-anhydro-alloside (13) gave a 2:1 mixture of the diaxial and diequatorial products (14) (debenzylidenated) and (15) as a result of selective debenzylidenation of the diaxial product under the reaction conditions. Treatment of the epoxides (10) and (13) with the triethylammonium salt of (11) gave the known epithio derivatives (16) and (17), respectively.[11]

Triflate displacements at C-2 in methyl 3-O-benzoyl-4,6-O-benzylidene-2-O-trifluoromethylsulphonyl-α-D-glucopyranoside using methanethiolate or phenylthiolate ions gave the corresponding 2-thio-mannoside derivatives[12] (see also Chapter 6 for other displacement reactions of this sugar derivative).

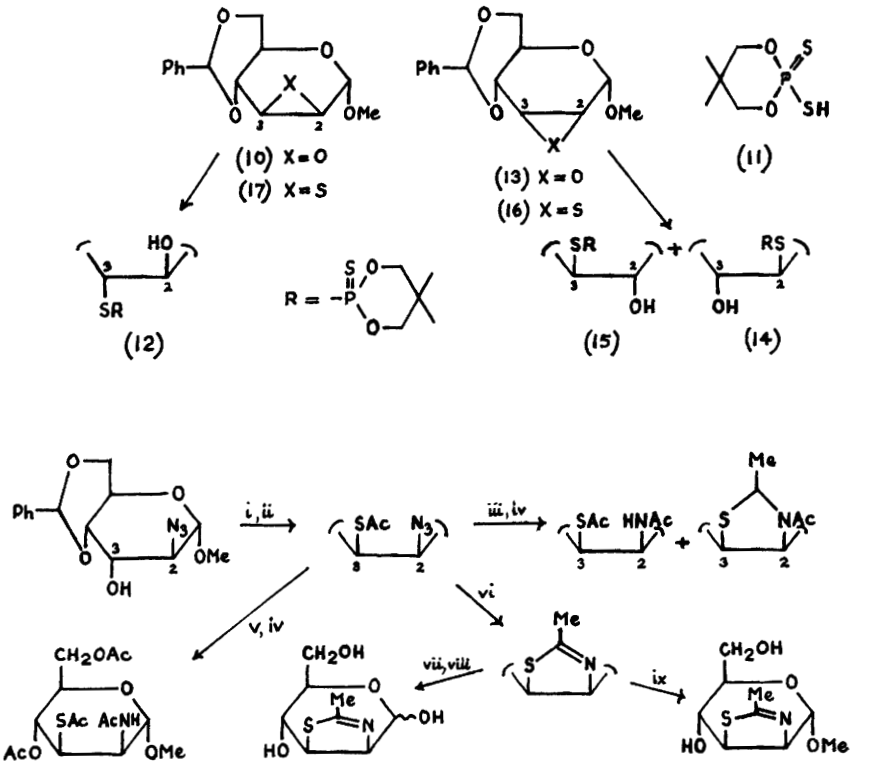
3-Thio-D-glucose and -D-allose have been synthesized by displacement of the triflate group of 1,2:5,6-di-O-isopropylidene-3-O-trifluoromethylsulphonyl-α-D-allo- and -gluco-furanose respectively by thiocyanate ion, followed by reduction with lithium aluminium hydride.[13] Displacement of triflate by potassium thioacetate has



Scheme 4

also been used to prepare 2-amino-2-deoxy-3-thio-D-mannose. Preparation of the thiazoline ring which is very resistant to acids provides an excellent protecting group for cis-amino-thio-sugars. These and other conversions are depicted in Scheme 5.[14]

Condensation of methyl 4-thio-α-D-glucopyranoside with 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide in HMPT, followed by deblocking, yielded 4-S-(β-D-galactopyranosyl)-4-thio-D-gluco-

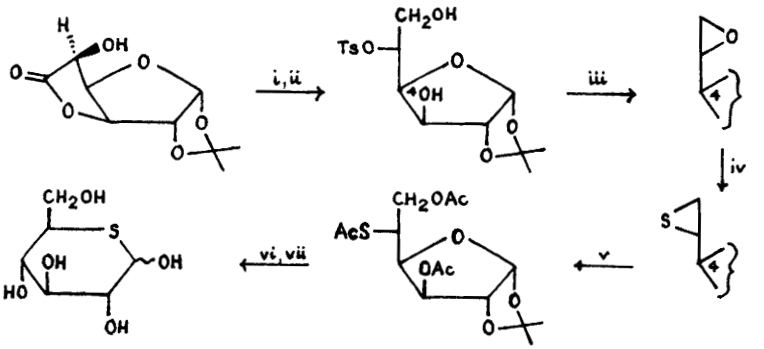


Reagents: i, Tf_2O; ii, KSAc-DMF, -15°; iii, $LiAlH_4$; iv, Ac_2O; v, $Na-NH_3$; vi, PPh_3; vii, $Ac_2O-H_2SO_4$; viii, NaOMe; ix, HCl, -15°C

Scheme 5

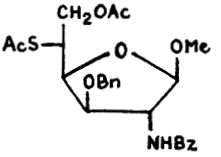
pyranose (thiolactose).[15]

5-Thioglucose has been synthesized from 1,2-O-isopropylidene-5-O-toluene-p-sulphonyl-∝-D-glucofuranurono-6,3-lactone (Scheme 6).[16] The anomeric ratio of 5-thio-D-glucopyranose in water has been shown to be 85:15 in favour of the ∝-anomer by means of ^1H- and ^{13}C-n.m.r.[17] Three syntheses of 2-acetamido-2-deoxy-5-thio-D-glucose have been published: methanolysis of the thio-acetate (18) followed by deblocking procedures,[18] and the two routes depicted in Scheme 7, sulphur being introduced by inversion of 5,6-anhydro-derivatives using methanolic thiourea.[19]

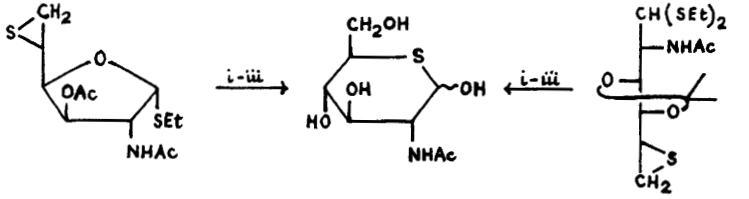


Reagents: i, TsCl-Py; ii, $LiBH_4$; iii, NaOMe-MeOH; iv, $(NH_2)_2CS$; v, HOAc-Ac_2O-NaOAc, 130°C; vi, TFA; vii, NaOMe

Scheme 6



(18)



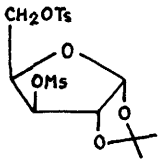
Reagents: i, KOAc-Ac_2O-AcOH; ii, Ac_2O-AcOH-H_2SO_4; iii, NaOMe-MeOH

Scheme 7

Opening of 5,6-epithio-sugars with secondary amines is referred to in Chapter 8, and n.m.r. studies of 5-thio-aldopyranosides and their derivatives are discussed in Chapter 20.

The synthesis of sultone derivatives has been achieved by proton abstraction from mesylates using organometallic carbanions as bases.

Thus the mesylates (19) and (20) with lithium acetylide gave the sultones (21) and (22) respectively.[20]



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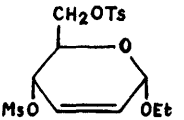
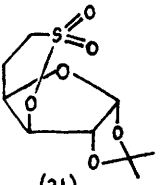


(20)



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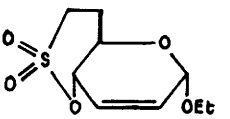

(22)

Glycosyloxy-selenation procedures for synthesis of 2-seleno-disaccharides giving ready access to 2-deoxy-disaccharides utilize the reaction of glycals with phenylselenyl chloride to provide the intermediate for condensation.[21]

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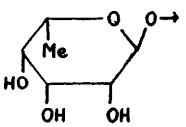
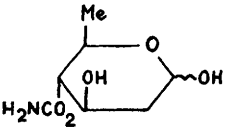
11

Deoxy-sugars

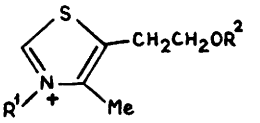
The 6-deoxy-α-L-talopyranosyl unit (1) was identified as a component of tri- and tetra-saccharide saponins from Zizyphus jujuba fruits.[1] A 4-O-carbamoyl-2-deoxy-β-D-rhamnopyranosyl unit was found to be a constituent of the macrolide antibiotic concanamycin A, and the free sugar (2) was isolated following alkaline degradation.[2] Evidence has been produced to indicate that 1-deoxy-D-threo-



(1)

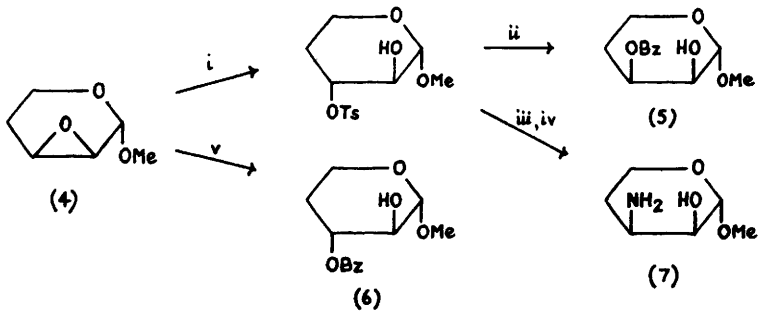


(2)



(3)

pentulose is incorporated without carbon-carbon bond cleavage in the biosynthesis of the thiazole part (3) of thiamine.[3] Iridoid diglycosides containing both D-glucosyl and either β-D-allo-pyranosyl, β-D-quinovopyranosyl (i.e., 6-deoxy-D-glucosyl), or 4-deoxy-α-L-erythro-pentopyranosyl (named mentzelosyl) residues were isolated from Mentzelia species.[4] This is the first report of mentzelose occurring in nature, although a useful synthesis of the racemic



(4) (5) (6) (7)

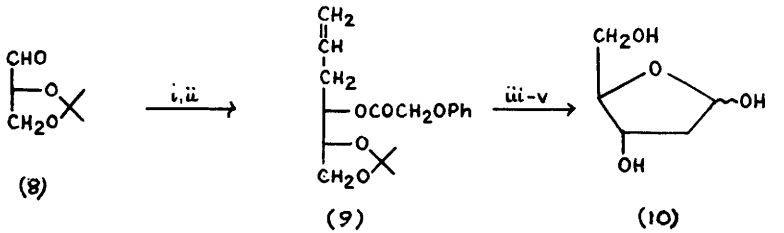
Reagents: i, TsOH-HMPT; ii, NaOBz; iii, NaN_3; iv, H_2-catalyst; v, BzOH-HMPT

Scheme 1

methyl glycoside (5) of this sugar from epoxide (4) has been reported(outlined in Scheme 1). The racemic 2,3-epoxide (4) could also be converted to the 4-deoxy-DL-erythro-pentopyranoside (6), or to the 3-amino-3,4-dideoxy-DL-erythro-pentopyranoside (7).[5]

The synthesis of deoxy-sugars by radical deoxygenation of esters and radical deamination of amines has been reviewed,[6] while an application of such a deoxygenation of O-(imidazolylthiocarbonyl) derivatives (readily prepared from sugars possessing a single free hydroxy group using commercially available N,N'-thiocarbonyldiimidazole) by the use of tributyltin hydride has been described. In some cases, side reactions were observed, while in others, high yields of deoxy products were obtained.[7]

A convenient synthesis of 2-deoxy-D-erythro-pentose (10) by elaboration of O-isopropylidene-D-glyceraldehyde (8) is shown in Scheme 2. The six-carbon adduct obtained in the first stage was a mixture (81:19) of the erythro-(9)- and threo-isomers which were separated chromatographically.[8]



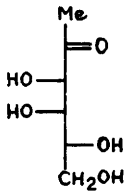
(8) (9) (10)

Reagents: i, CH_2=$CHCH_2I$-SnF_2; ii, $PhOCH_2COCl$-1,3-dimethyl-2-imidazolidinone-DMF; iii, HOAc-H_2O; iv, O_3; v, Me_2S

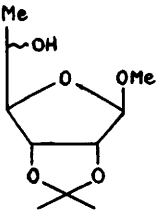
Scheme 2

A synthesis of 2-deoxy-D-arabino-[1-^{11}C]hexose has been developed, using labelled hydrogen cyanide.[9] A three-step synthesis of 1-deoxy-D-tagatose (i.e., 1-deoxy-D-lyxo-hexulose) (11) in 35% yield from 2-amino-2-deoxy-D-galactose hydrochloride involved diethyl dithioacetal formation, Raney nickel desulphurization, and oxidative deamination with 3,5-di-tert-butylbenzoquinone.[10]

Reaction of methylmagnesium bromide with a pentodialdose derivative gave the 6-deoxy-β-D-alloside and -α-L-taloside derivatives (12), which were separated by crystallization of their 5-O-p-nitrobenzoates.[11]

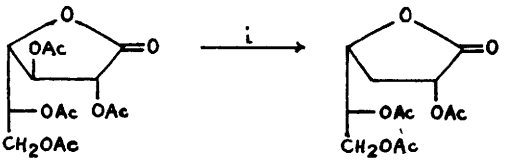


(11)



(12)

3-Deoxygenation of peracetylated hexono- and pentono-1,4-lactones occurred on hydrogenolysis, through base-catalysed β-elimination of acetic acid and hydrogenation of the resulting double bond. Thus

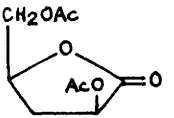


(13) (14)

Reagent : i, H_2-Pd/C-Et_3N

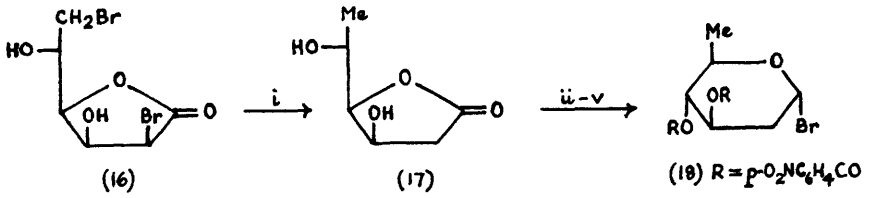
Scheme 3

2,3,5,6-tetra-O-acetyl-D-galactono-1,4-lactone (13) gave the 3-deoxy-lactone (14) (Scheme 3), while all four D-pentofuranolactones gave the same isomer (15).[12]



(15)

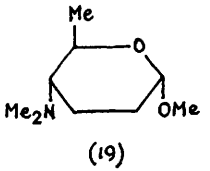
The same group has isolated and characterized a variety of halogenated derivatives from the action of hydrogen bromide on sugar acids and their lactones (see Chapter 7). Dehalogenation led to deoxy-sugar derivatives. Thus the 2,6-dibromide (16), derived from calcium gluconate, yielded the 2,6-dideoxy-1,4-lactone (17) from which the potentially useful 2,6-dideoxy-D-arabino-hexopyranosylating agent (18) was obtained (Scheme 4).[13]



Reagents: i, H_2-Pd/C-Et_3N; ii, bis(1,2-dimethylpropyl)borane; iii, H^+-MeOH; iv, p-$NO_2C_6H_4COCl$-py; v, HBr-HOAc

Scheme 4

The methyl α-glycoside (19) of forosamine has been obtained by sequential allylic amination of a 2,3-unsaturated sugar (see Chapter 8) and hydrogenation of the double bond.[14]



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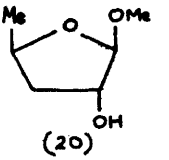

(20)

An attempted substitution of the 2-hydroxy group of the 3,5-dideoxy-derivative (20) by chlorine yielded di-, tri- and higher-saccharides.[15] (See Chapter 3).

Other references to deoxy-sugars are found in Chapter 4.

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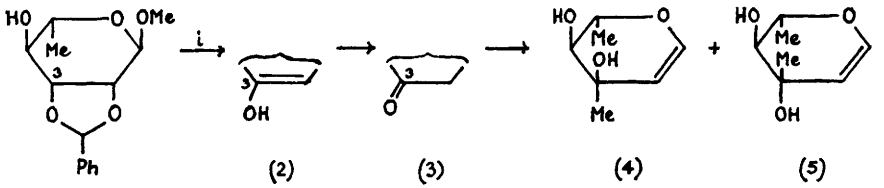
12
Unsaturated Derivatives

1 Glycals

A general method for converting epoxides into alkenes, involving the use of O,O-dialkylphosphoroselenoic acid salts, has been applied to give tri-O-acetyl-D-glucal from 3,4,6-tri-O-acetyl-1,2-anhydro-α-D-glucose in quantitative yield.[1] Treatment of the L-rhamnoside acetal (1) with methyl-lithium gave the branched-chain glycals (4) and (5) in 21 and 72% yield, respectively, presumably by way of (2) and (3) (Scheme 1), and the tetrahydropyranyl ether

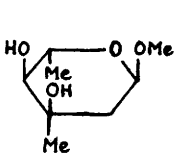


(1) (2) (3) (4) (5)

Reagent: MeLi

Scheme 1

of the starting material with butyl-lithium afforded the glycosid-3-ulose from which methyl mycaroside (6) was made.[2] 4,6-O-Benzylidene-D-allal, treated with benzoic acid and diethyl azodicarboxylate and triphenylphosphine, underwent direct nucleophilic displacement to afford 3-O-benzoyl-4,6-O-benzylidene-D-glucal, and also the anomeric 1-benzoates of the corresponding 2,3-unsaturated compound which were produced by allylic rearrangement. The mixed



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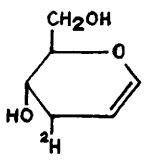

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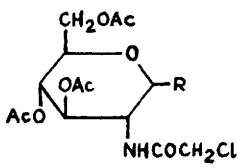
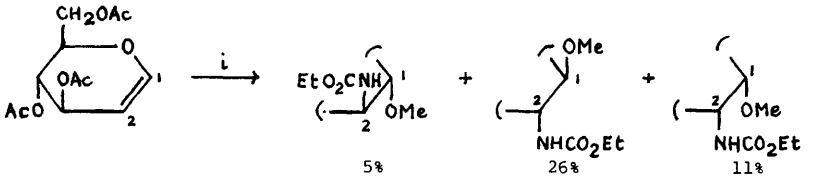


(8) R = α,β-Cl

(9) R = β-OMe

products with sodium methoxide gave 4,6-O-benzylidene-2-deoxy-3-O-methyl-D-arabino-hexose by methanol addition to the 2,3-unsaturated free sugar.[3] The practical details of the rearrangement whereby ethyl 2,3-dideoxy-α-D-erythro-hexo-2-eno-pyranoside can be converted into D-allal or the labelled analogue (7) with lithium-aluminium hydride or deuteride have been reported,[4] as have those of the preparation of various glycal esters, their chlorination and subsequent conversion into enolones and γ-pyrones.[5]

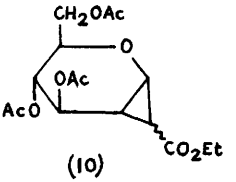
Photochemical addition of N-chlorochloroacetamide to tri-O-acetyl-D-glucal affords the 2-amino-2-deoxy-D-glucosyl chloride (8) and thence the β-glycoside (9).[6] An analogous photochemically induced nitrene addition, which is believed to proceed via aziridine intermediates, is illustrated in Scheme 2; tri-O-acetyl-D-galactal



Reagent: i, N_3CO_2Et, hν

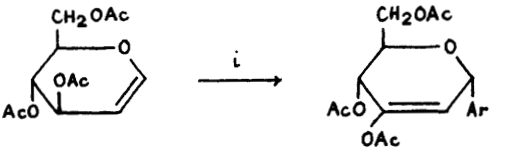
Scheme 2

was also studied.[7] Heating tri-O-acetyl-D-glucal with ethyl diazoacetate in ether in the presence of copper powder afforded 35% of the cyclopropane adduct (10).[8] Other addition reactions are noted in Chapter 3.



(10)

New reactions involving allylic migration in acylated glycals giving rise directly to 2,3-unsaturated C-glycosides are also noted in Chapter 3. The related reaction illustrated in Scheme 3 involves unusual hydrogen - rather than acetoxy - displacement. The products are obtained in about 50% yield and are efficiently converted into glycosid-3-ulose oximes with hydroxylamine hydrochloride.[9] Further work has been reported on the mixed products obtained from tri-O-acetyl-D-glucal and sodium azide in the presence of boron trifluoride, and their subsequent conversion into α-

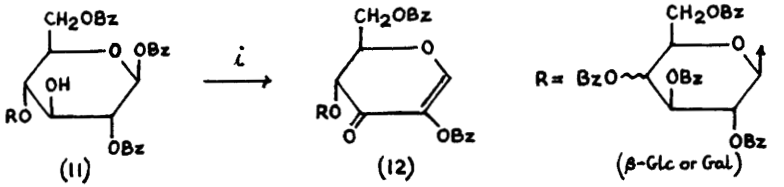


Reagents: i, $Pd(OAc)_2$-ArH Ar = Ph or $C_6H_3(OMe)_2$

Scheme 3

glycosides of 3-amino-2,3-dideoxy-D-*ribo*- and -D-*arabino*-hexopyranose by standard procedures.[10]

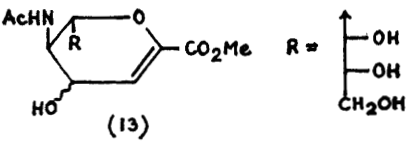
In the 2-hydroxyglycal series, photoirradiation of tetra-*O*-acetyl-2-hydroxy-D-glucal and -D-galactal in acetone with formamide gave mixed products with $C(OH)Me_2$ and $CONH_2$ groups at C-1 and different configurations at C-1 and C-2.[11] Oxidation of the 3-hydroxydisaccharides (11) gave high yields of crystalline enone products (12) (Scheme 4).[12]



Reagent : i, Ac_2O-DMSO

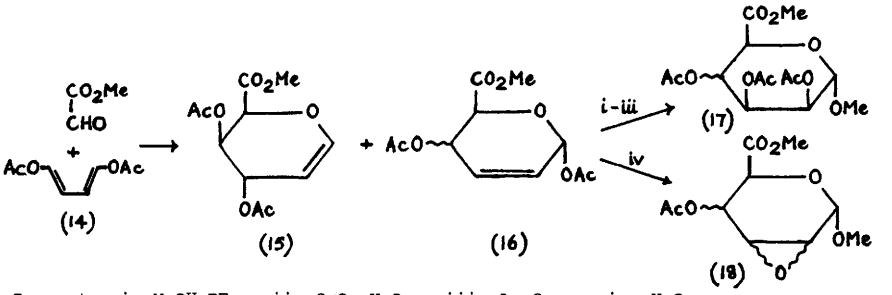
Scheme 4

Treatment of *N*-acetylneuraminic acid ethyl ester with acetic anhydride and sulphuric acid followed by sodium methoxide gave the 1-substituted glycal epimers (13) which are competitive inhibitors



of neuraminidase. The epimerization was discussed in terms of an oxazoline intermediate which was a minor reaction by-product.[13]

Diels-Alder reaction of methyl glyoxalate and the diene (14) gave racemic unsaturated uronic acid derivatives (15) and (16) which were converted into mannuronic acid and taluronic acid products (17) as well as epoxides (18) (Scheme 5).[14]



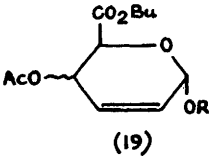
Reagents: i, MeOH-BF_3; ii, OsO_4-H_2O_2; iii, Ac_2O-py; iv, H_2O_2

Scheme 5

2 Other Unsaturated Derivatives

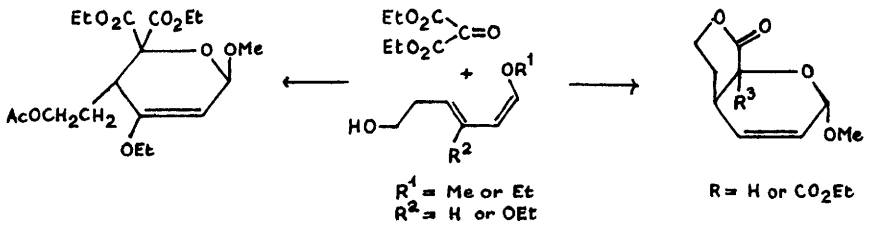
The reaction of epoxides with O,O-dialkylphosphoroselenoic acid salts which affords alkenes directly has been shown to be applicable to the synthesis of a range of unsaturated derivatives besides glycals.[1] Alkenes can also be prepared directly from *cis*- or *trans*-vicinal diols by treatment with iodoform, triphenylphosphine and imidazole, and methyl 4,6-O-benzylidene-α-D-hexopyranosides (*gluco*-, *altro*-, *manno*- and *ido*-isomers) gave the corresponding 2,3-alkene. The D-*galacto*-analogue failed to undergo this reaction.[15] An extensive discussion has appeared on factors affecting regioselective enolization and elimination processes in 4,6-O-benzylidenehexopyranosides and hexopyranosiduloses.[16]

Reaction of the diene (14) above with butyl glyoxalate in the presence of acetic acid gave the 1,2- and 2,3-unsaturated sugars analogous to (15) and (16) which, with alcohols and Lewis acids, afforded separable mixtures of the racemic epimeric unsaturated glycosides (19).[17]



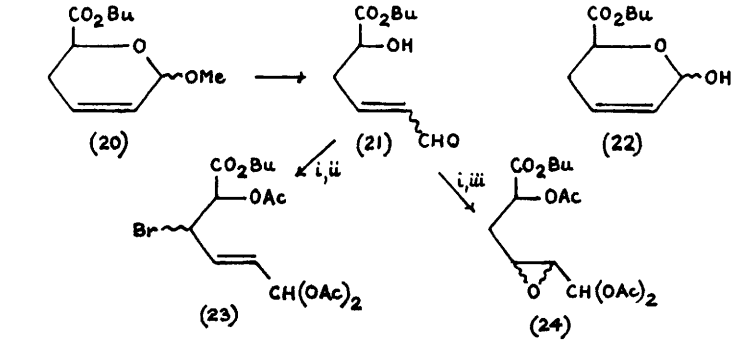
(19)

The same group of workers has extended this approach to the synthesis of an extensive range of branched-chain DL-hex-2-enopyranosyl derivatives exemplified in Scheme 6.[18] The racemic uronic acid



Scheme 6

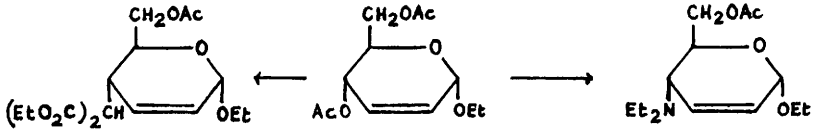
derivative (20) gave the E-alkene (21) when hydrolysed with acid, but a mixture of Z and E products (21) and (22) when hydrolysis was effected under neutral conditions. Surprisingly, the hydroxy-aldehydic form of compound (22) was also present to the extent of 20% in the products. Compound (21) was resolved by use of a camphor derivative and was converted into products (23) and (24) as indicated in Scheme 7.[19]



Reagents: i, Ac_2O-TsOH; ii, NBS; iii, MCPBA

Scheme 7

The methods outlined in Scheme 8 give means of making branched-chain sugars and amino-sugars by use of π-palladium complexes in which the metal is trans-related to the expelled ester groups. The metal is, in turn, displaced from the opposite side with net retention of configuration. In the α-D-erythro-series reactions are highly selective sterically and regiochemically; the β-anomer reacted less selectively but, again, mainly at C-4, while the α-D-threo-isomer behaved even less specifically. Very useful details

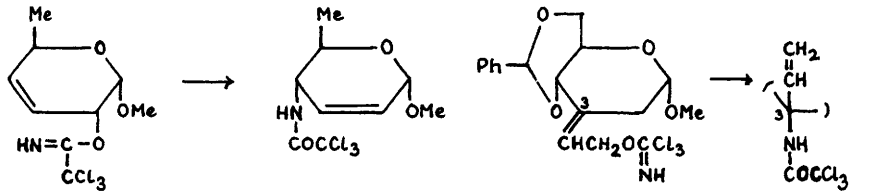


Reagents: i, $(Ph_3P)_4Pd$-Ph_3P-Et_2NH; ii, $(Ph_3P)_4Pd$-$CH_2(COOEt)_2$

Scheme 8

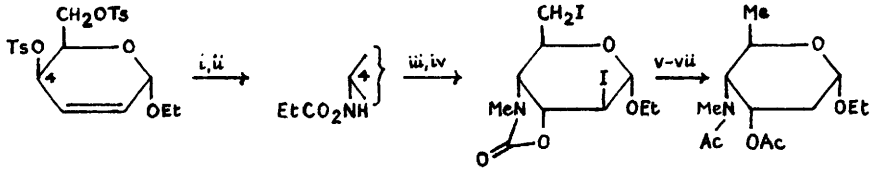
and discussion are provided on the mass spectra, ^{13}C and ^{1}H n.m.r. and optical rotations of the products.[20]

Allylic rearrangements have again been used to introduce C-N bonding into unsaturated derivatives, the reactions proceeding better when the allylic migrating groups were quasi-axial (Scheme 9)



Scheme 9

An interesting case of its application to the synthesis of a branched-chain amino-sugar is given in this Scheme.[21] Allylic amino-groups have been used to direct cis-hydroxylation (Scheme 10).[22]

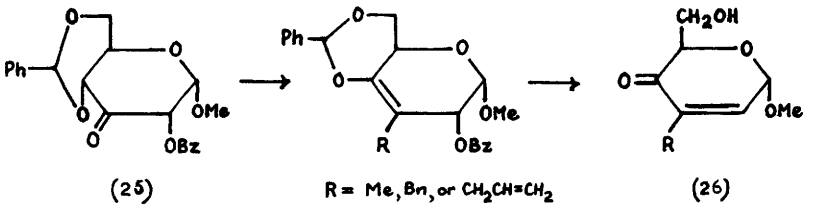


Reagents: i, $MeNH_2$; ii, $ClCO_2Et$; iii, $I^+ClO_4^-$; iv, I^-; v, Bu_3SnH; vi, OH^-, vii, Ac_2O-MeOH

Scheme 10

Specific 2,3-unsaturated compounds have been obtained as follows: methyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (together with 2-deoxy-3,4-O-isopropylidene-1-O-methyl-D-ribo-hex-1-enitol) on treatment of methyl 2-deoxy-2-iodo-3,4-O-isopropylidene-α-D-altro-pyranoside with butyl-lithium,[23] 2,3-dideoxy-D-glycero-pent-2-

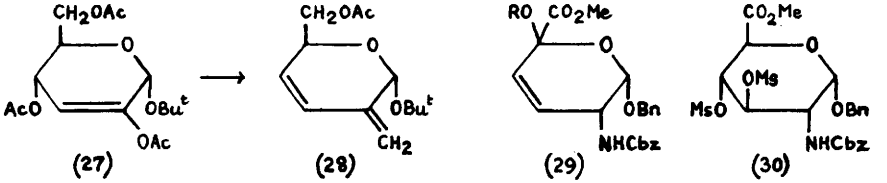
enonic acid γ-lactone from the corresponding D-ribono-γ-lactone,[24] phenyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-D-erythro-hex-2-enopyranoside from phenyl 4,6-O-benzylidene-2,3-dideoxy-3-nitro-β-



Scheme 11

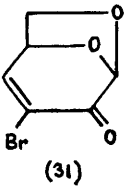
D-xylo-hexopyranoside by an α-selenation procedure,[25] and the enones (26) from the glycosidulose (25) by Grignard-based procedures (Scheme 11).[26]

The interesting conversion (27) → (28) was effected in high yield with a Wittig reagent[27] and the 3,4-unsaturated compounds



(29) were the products of treatment of uronic acid derivative (30) with base and alcohol. The 4,5-unsaturated sugar is initially formed, which then undergoes allylic substitution.[28]

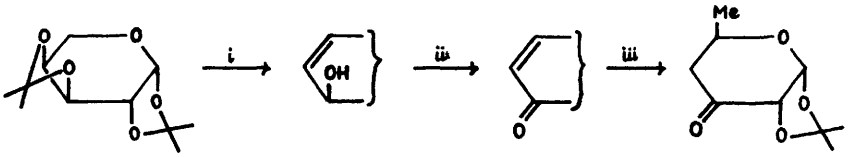
Bromination of levoglucosenone gives its 3-bromo-derivative (31),[29] and cis-oxyamination of various branched and unbranched



ald-2- and-3-enopyranosides (OsO_4, chloramine T) gives mixtures of cis-adducts.[30] In compounds containing allylic acyloxy groups the reaction can be suppressed, when cis-diols become major constituents of the product mixture.[31]

A further method of making 5'-deoxyadenosine with a 4',5'-double bond is mentioned in Chapter 19 (ref. 76) and 4,5-unsaturated

pyranose sugars are mentioned in the aminoglycoside section of Chapter 18 (refs. 31,42). The use of 4,5-unsaturated sugars in synthesis is illustrated in Scheme 12.[32] Hakamori methylation of

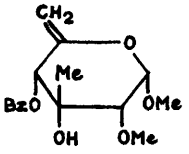


Reagents: i, $Pr^{i}_{2}NLi$; ii, CrO_3,py; iii, MeLi,CuI

Scheme 12

4-O-methyl hexuronic acid derivatives causes partial β-elimination of methanol whereas unmethylated derivatives are stable.[33]

Compound (32) has been used as the precursor of vinelose (6-deoxy-3-C-methyl-2-O-methyl-L-talose),[34] and in the furanose series novel 5,6-unsaturated nucleoside derivatives are noted in Chapter 19. Tronchet and co-workers have reported an extensive range of



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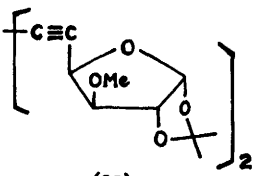
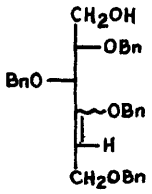


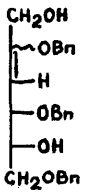
(33)

other 5,6-unsaturated furanoid compounds made basically by Wittig extensions of 5-aldehydes. 5,6-Alkynes and a large number of otherwise modified products were described[35-37] including the di-glycosyldiyne (33).[38]

An unexpected elimination reaction resulted when 2,3,4,6-tetra-O-benzyl-1,5-di-O-methanesulphonyl-D-glucitol was treated with potassium superoxide; the alkene (34) was formed in almost quantitative yield. Since the D-manno-epimer and the 1-(methoxy)-



(34)



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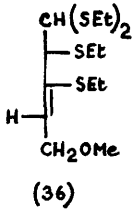

(36)

trityl ether gave quite different results, it was concluded that an initial C-1 peroxyanion carried out specific proton abstraction at C-4. 2,3,4,6-Tetra-O-benzyl-D-glucose with borohydride in propan-2-ol underwent unexpected elimination to give the enol ether (35).[39] Elimination also occurred when 4-O-acetyl-2,3-di-S-ethyl-5-O-methyl-2,3-dithio-D-ribose diethyl dithioacetal, produced from 3-O-acetyl-1,2-O-isopropylidene-5-O-methyl-α-D-xylofuranose, was treated with ethanethiol and trifluoroacetic acid; the product was the alkene (36).[40]

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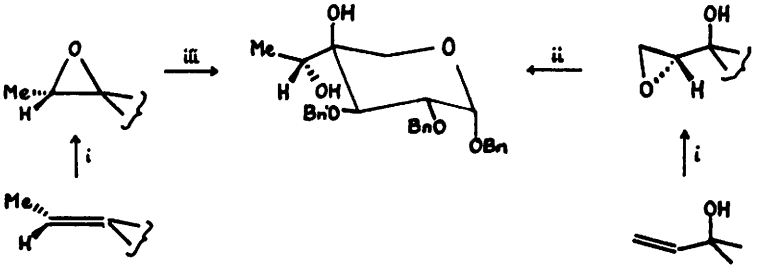
13

Branched-chain Sugars

β-D-Apiofuranosyl terminal residues have been detected in the oligosaccharide moeities of two presenegenin saponins isolated from the root of Polygala tenuifolia (a Chinese medicine).[1] The occurrence of a branched-chain tetronic acid lactone in legumes is referred to in Chapter 15.

Yoshimura has discussed the stereoselective synthesis of some branched-chain sugars in a review lecture,[2] and his group has reported syntheses of methyl virenoside (methyl 6-deoxy-3-C-methyl-β-D-gulopyranoside) from D-galactose via a glycosid-3-ulose intermediate,[3] and of L-nogalose (6-deoxy-3-C-methyl-2,3,4-tri-O-methyl-L-mannose) from a 4-O-methyl-L-rhamnose derivative utilizing a branch methylene intermediate sugar formed from a glycosid-3-ulose by Wittig synthesis; the D-enantiomer was also prepared, using a 3-C-methyl-D-mannose precursor.[4] They have also examined the stereoselectivity of addition of some Grignard reagents and 2-lithio-2-methyl-1,3-dithian to a number of pyranosid-4-ulose derivatives,[5] and determined the configuration of 1-hydroxyethyl branch chains by stereoselective epoxidation of unsaturated branched-chain sugars followed by alkaline hydrolysis or metal hydride reduction (Scheme 1).[6] Other groups have reported the

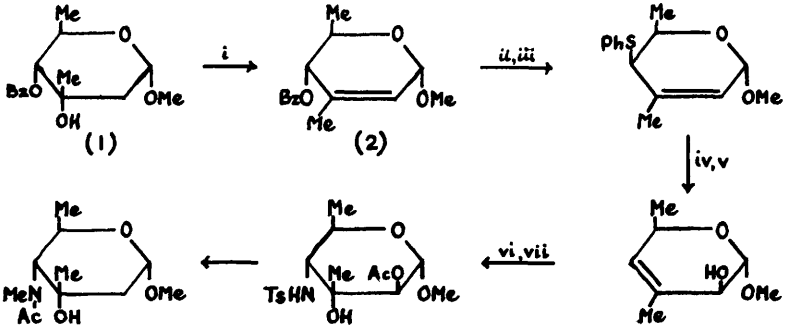


Reagents: i, MCPBA ; ii, LAH ; iii, NaOH

Scheme 1

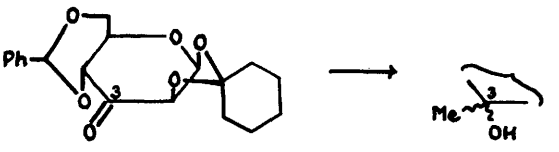
conversion of the 2,6-dideoxy-3-C-methyl-D-ribo-hexopyranoside derivative (1) to its 4-N-acetyl-N-methylamino-4-deoxy analogue (methyl sibirosaminide) by the sequence outlined in Scheme 2, which involves an allylic rearrangement of an unsaturated intermediate followed by Sharpless amination of the double bond,[7] and a synthesis of evalose (6-deoxy-3-C-methyl-D-mannose) from the same unsaturated sugar (2) by cis-hydroxylation stereospecifically from the β-face

of the molecule.[8] An alternative approach to evalose failed when Grignard addition to the glycosulose (3) gave a 1:1 mixture of stereoisomeric products (4).[8] Lukacs' group has also described the conversion of a known 3-C-methyl-D-allose derivative to



Reagents: i, $SOCl_2$-Py; ii, OH^-; iii, $COCH_2CH_2CONSPh$-Bu_3P; iv, MCPBA; v, $P(OMe)_3$; vi, Ac_2O-Py, vii, OsO_4 - Chloramine-T

Scheme 2

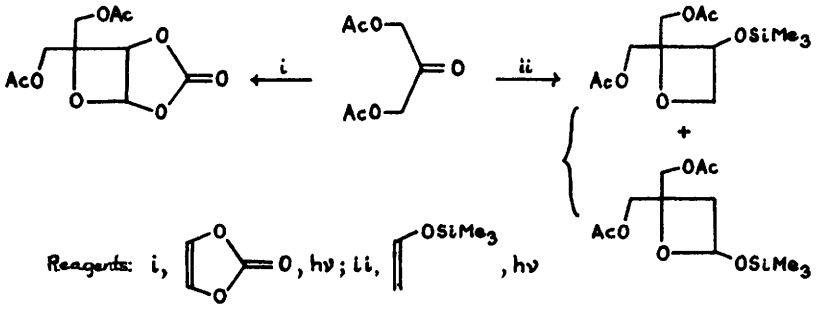


vinelose (6-deoxy-3-C-methyl-2-O-methyl-L-talose), the required C-5 inversion being achieved via a 4,5-unsaturated intermediate.[9]

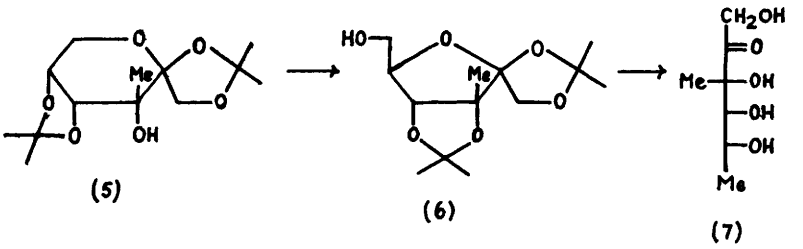
The photochemical cycloaddition of 1,3-diacetoxy-propanone with 1,3-dioxalenone gave an oxetan derivative of DL-apiose, and similar photochemical reaction with triethylsilyloxyethene gave a mixture of isomeric oxetans which are formally apiose derivatives (Scheme 3).[10,11]

The 3-C-methyl psicose derivative (5), obtained conventionally from a 3-keto precursor using MeLi, MeMgBr, or CH_2N_2-LAH, underwent acid-catalysed isomerization to the furanose form (6), which was then converted to 6-deoxy-3-C-methyl-psicose (7).[12]

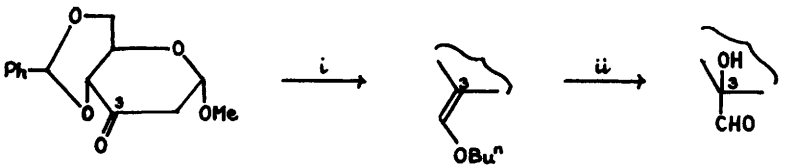
A new method for introducing a formyl branch group involves osmium tetraoxide oxidation of butoxymethylene sugar obtained from a keto sugar by Wittig synthesis (Scheme 4); this method stereo-



Scheme 3



chemically complements existing alkenyl-Grignard or dithian



Reagents: i, $Ph_3P{=}CHOBu^n$; ii, OsO_4

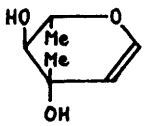
Scheme 4

procedures.[13] The preparation of a sugar with a fluoro-acetic acid side-chain by Reformatsky reaction is mentioned in Chapter 7.

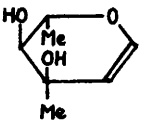
Factors affecting the formation of 2,4-di-C-(hydroxymethyl)-3-pentulose in the formose reaction have been studied; high selectivity was achieved using barium chloride-potassium hydroxide in methanol, the yield depending largely on pH, and further reduction to 2,4-di-C-(hydroxymethyl) pentitol was much slower in methanol than in aqueous media.[14] Another study showed that selective formation of 3-C-hydroxymethylpentofuranose occurs in the calcium hydride-catalysed reaction when most of the calcium ions

are removed at the end of the induction period and replaced by lead hydroxide ($Ph_2O(OH)_2$) adjusted to pH 10 with potassium hydroxide.[15]

Treatment of methyl 2,3-O-benzylidene-α-L-rhamnopyranoside with methyl lithium yielded the epimeric glycals (8) and (9) in a 7:2 ratio, a 2-deoxy-3-keto intermediate being assumed. Treatment of the corresponding 4-O-tetrahydropyranyl ether with butyl-lithium gave an analogous keto sugar without subsequent 1,2-elimination, which was used to prepare methyl mycaroside.[16]



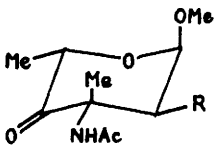
(8)



(9)

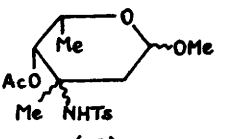
Cycloaddition reactions of unsaturated branched-chain sugars leading to glycosyl heterocycles are mentioned in Chapter 12.

Reduction of the 4-ulose derivatives (10) and (11) with L-selectride gave mainly the axial alcohols, the former being a vancosamine derivative; sodium borohydride regenerated the equatorial alcohol.[17] The derivatives (12) of vancosamine and its

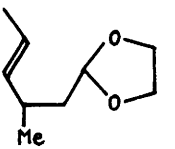


(10) R = H

(11) R = OMe



(12)

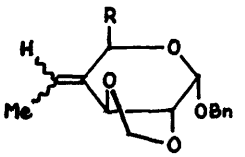


(13)

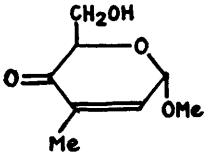
3-epimer have been prepared from the enacetal (13) by an allylic amination procedure.[18]

The EZ-isomers of the unsaturated branched-chain sugars (14) have been obtained by Wittig reaction from the corresponding 4-ulose; only the Z isomer resulted from the 2,3-di-O-benzyl analogue of (14). Epoxidation and hydride reduction or osmium tetraoxide hydroxylation led to stereoisomeric mixtures of the 1-hydroxyethyl branched-chain sugars, and the stereoselectivities of these reactions were discussed.[19]

The branched-chain sugar enone derivative (15) has been prepared by standard conversions from D-glucose.[20] The cyano-glycal (16) gave the fluorinated branched-chain sugar (17) with trifluoromethyl hypofluorite.[21]



(14) R = H or Me



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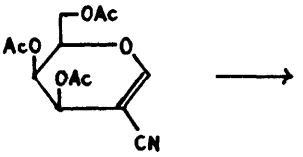

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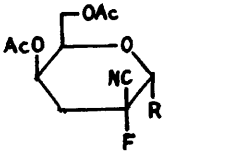
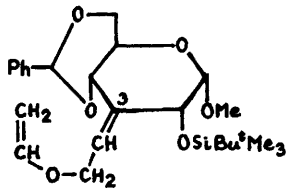
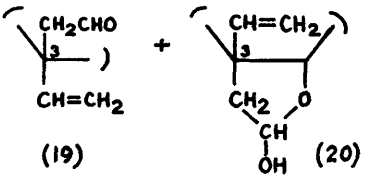


(17) R = F or OCF_3

Claisen rearrangement of the ethenoxy unsaturated sugar (18) (prepared conventionally from the corresponding 3-ulose) followed by desilylation led to the isomeric, geminally double branched-chain sugars (19) and (20); similar results were obtained with pyranosid-

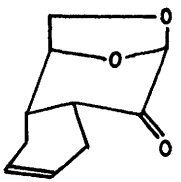


(18)



(19) (20)

2-and 4-uloses.[22] Novel double branched-chain sugars result from the Diels-Alder addition of dienes to laevoglucenone, e.g. the compounds (21) and (22) were obtained using butadiene and cyclopentadiene, respectively.[23]



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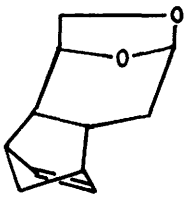
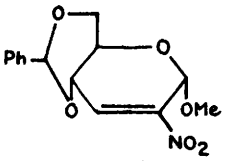


(22)

Reaction of the unsaturated nitro-sugar (23) with enolate anions led to the Michael adducts (24), which were mixtures of D-altro, D-gluco, and D-manno isomers, the ratios depending on the solvent; the 1,2-elimination product (25) was also obtained.[24]



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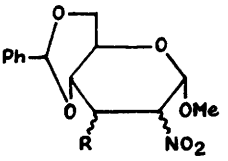
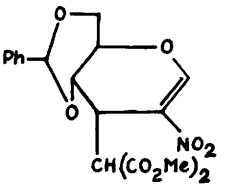
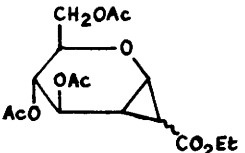


(24) R = $CH(CO_2Et)_2$, $CH(CO_2Me)_2$, $CHAc_2$



(25)

Tri-O-acetyl-D-glucal reacts with diazoacetic ester to give the cyclopropyl carbohydrate (26).[25]



(26)

The reduction of tetronic acid derivatives to branched-chain tetroses is mentioned in Chapter 15, and the use of double branched-chain sugars for the synthesis of macrolide segments is covered in Chapter 23. Branched-chain sugar nucleosides are referred to in Chapter 19.

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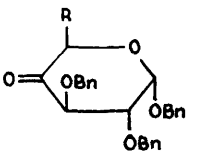
14

Aldosuloses, Dialdoses and Diuloses

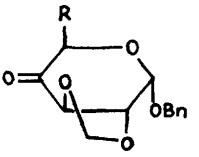
1 Synthesis

Under aerated conditions D-fructose, on irradiation in aqueous solution, gave D-arabino-hexosulose and D-threo-hexo-2,5-diulose amongst other products whereas, under aerobic conditions, 6-deoxy-D-threo-hexo-2,5-diulose and 4-deoxy-L-glycero-hexo-2,5-diulose were also identified.[1]

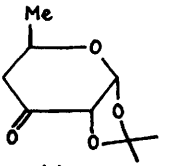
An improved synthesis of 3-deoxy-D-erythro-hexos-2-ulose is based on treatment of D-glucose with benzoylhydrazine to give the bis-hydrazone of the product sugar which can be recovered by exchange with benzaldehyde in the presence of acetic acid.[2] 2-Ketosucrose (β-D-fructofuranosyl α-D-arabino-hexopyranosid-2-ulose) has been isolated from the products of fermentation of sucrose by Agrobacterium tumefaciens. The 3-keto isomer, which is the primary product, was also obtained, and this was considered to give the 2-ketone by isomerization. Reduction of the latter with boro-deuteride gave [2-^{2}H] sucrose as sole product.[3] ^{13}C N.m.r. data for the methyl glycosides of α-D-arabino-hexopyranosid-2-ulose, α-D-ribo-hexopyranosid-3-ulose and α-D-xylo-hexopyranosid-4-ulose, their hydrates and their O-methyloximes have been reported.[4] The ketones (1) and (2) have been prepared as precursors of branched-



(1) R = H or Me R = H or Me



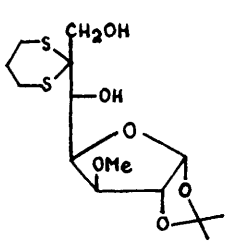
(2)



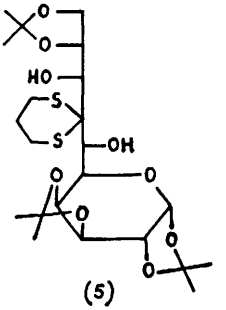
(3)

chain sugars. The synthesis of the 3-ulose derivative (3) by Michael addition to a 4-deoxypent-4-enose derivative[6] is outlined in Chapter 12 (Scheme 12).

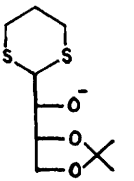
A set of heptose, octose, decose and undecose derivatives, for example (4) and (5), have been made by use of sugar-based dithianes, e.g. (6), applied to appropriate aldehydic compounds.[7] Related



(4)



(5)

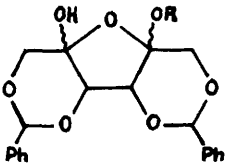


(6)

compounds have been produced following the application of Grignard reactions to analogous aldehydes, the initially-produced secondary alcohols being subsequently oxidized to the corresponding ketones.[8]

Treatment of D-galactose or 2-acetamido-2-deoxy-D-galactose with D-galactose oxidase gives aldehydes which, with indole in acid solution, afford coloured products useful for the quantitative assay of the two sugars. 2-Amino-2-deoxy-D-galactose and 2-deoxy-D-lyxo-hexose(2-deoxy-D-galactose) do not interfere.[9]

Oxidation of 1,3:4,6-di-O-benzylidene-D-mannitol gives the diacetal of threo-hexo-2,5-diulose which adds water or alcohols to give the tricyclic adducts (7). Reduction of the diulose to the

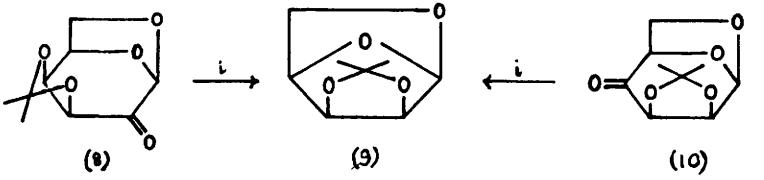


(7) R = H or Me

D-glucitol derivative and the products from treatment with aniline, phenylhydrazine, Grignard reagents and diazomethane were also reported.[10]

2 Reactions

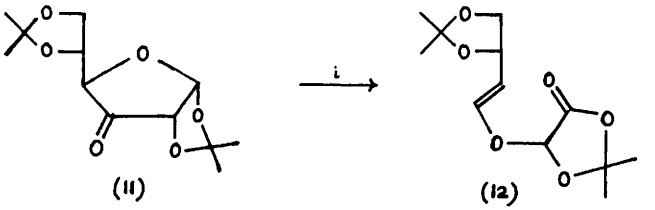
Photolysis of the anhydroaldosulose acetals (8) and (10) gives the D-lyxose derivative (9) (Scheme 1), and, likewise, the 1,5-anhydro-



Reagent: i, hν

Scheme 1

β-D-ribofuranose and 2,6-anhydro-β-D-psicofuranose acetals can be made (all in modest yields).[11] Similar treatment of the furanose ketone (11), however, gives the unexpected acyclic product (12) (Scheme 2).[12]



Reagent: i, hν

Scheme 2

Whereas reduction of glycopyranosidulose derivatives with sodium borohydride gives predominantly equatorial alcohol products, L-Selectride (tri-sec-butylborohydride) gives mainly the axial isomers. In Scheme 3 the reaction is illustrated in the synthesis of a L-vancosamine derivative.[13]

Reagent: i, L-Selectride

Scheme 3

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15
Sugar Acids and Lactones

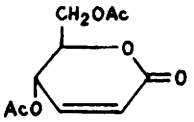
1 Aldonic Acids

Dehydrogenation of aldoses occurs in alkaline solution in the presence of platinum or rhodium catalysts to give aldonic acids and hydrogen gas. From a study of 25 mono- and disaccharides a mechanism was proposed which involves hydride abstraction from C-1 of an O-1 oxyanion species. Potassium lactobionate was produced in 80% yield from lactose.[1] Alkaline hydrogen peroxide in the presence of magnesium hydroxide oxidizes 2-deoxy-D-arabino-hexose to the aldonic acid, its γ-lactone and 1-O-formyl-D-arabinitol. 2-Deoxy-D-lyxo-hexose and 2-deoxy-D-erythro-pentose behaved similarly, the acids being isolated in 60-80% yield as the lithium salts.[2] A study of the oxidation of D-glucose with oxygen in the presence of platinum on charcoal indicated that oxygen chemisorbed on platinum was the active catalyst. The uronic acid was formed as a by-product.[3]

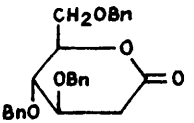
Further studies of the oxidation of monosaccharides to aldonic acids and lower acids by Cu^{2+}, Fe^{3+}, Ag^{+}, Hg_2^{2+}, Hg^{2+} and Ce^{4+},[4] and of various disaccharides by $Fe(CN)_6^{3-}$ in the presence of ammonia,[5] have been reported. Oxidation of D-glucose by a micrococcus grown on acetate as sole carbon source affords means of obtaining calcium D-gluconate in >90% yield.[6]

N-Chlorosuccinimide and tetrabutylammonium iodide afford excellent means for oxidizing reducing free sugars to lactones, 2,3:5,6-di-O-isopropylidene-D-mannose affording the corresponding γ-lactone in high yield.[7] Glycal derivatives can be converted to lactones in one step by use of pyridinium chlorochromate. Tri-O-acetyl- and O-benzoyl-D-glucal gave the unsaturated product (1), and the benzoyl analogue, but the tribenzyl ether gave the 2-deoxy compounds (2) - presumably by hydration followed by oxidation. No subsequent elimination took place in this case.[8]

D-Ribono-γ-lactone has been converted into the unsaturated derivative (3) (which is also obtainable by enzymic hydrolysis of



(1)



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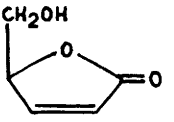
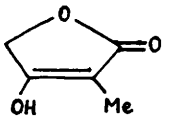


(3)

the natural glycoside ranunculin) by heating its 2,3-O-ethoxymethylidene derivative at 220°C.[9] The unsaturated lactone (4) has been reduced to the racemic branched-chain lactone (5) and the corresponding branched-chain sugar.[10]



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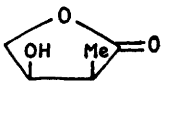
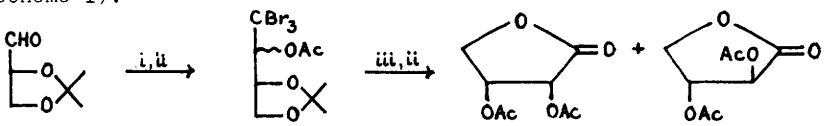


(5)

A synthesis of 2-deoxy-L-arabino-hexonic acid has been developed from 1-chloro-1-deoxy-L-fructose tetra-acetate which is available from L-arabinonic acid,[11] and D-glucono-γ-lactone has been converted into the L-ido-analogue by use of diethyl azodicarboxylate and triphenylphosphine.[12]

Reaction of aldehydes with carbon tetrabromide and tin(II) fluoride gives adducts formed by addition of the elements of bromoform across the carbonyl group which may be hydrolysed to acids. In this way, 2,3-O-isopropylidene-D-glyceraldehyde was converted into a mixture of D-erythro- and D-threo-tetronolactone (Scheme 1).[13]

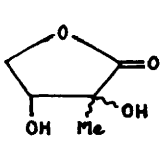


Reagents: i, CBr_4-SnF_2; ii, Ac_2O-py; iii, $AgNO_3$-H_2O

Scheme 1

The branched-chain tetronic acid lactone (6) of undetermined configuration has been isolated from water-stressed chickpea,[14] and it has been shown that L-arabinono-γ-lactone is tightly bound to α-L-arabinofuranosidase of Monilinia fructigena.[15]

Lactones react with trimethylsilyl ethers of vicinal diols to give spiro-orthoesters in the presence of trimethylsilyl trifluoromethanesulphonate. In this way the products (7) and (8) were obtained,[16] and in related fashion epoxides can react with lactones



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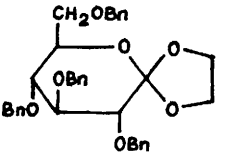

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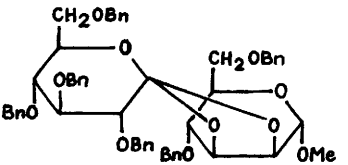
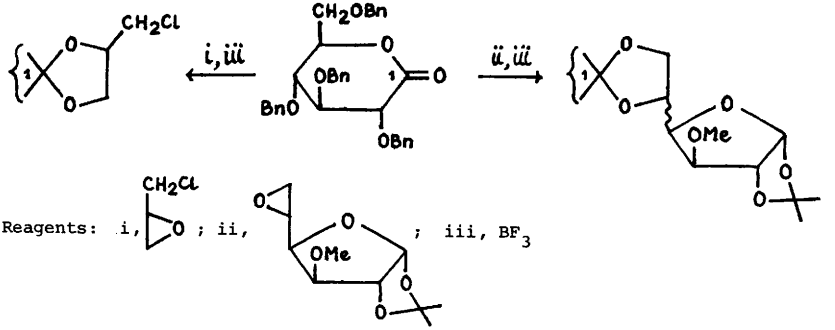


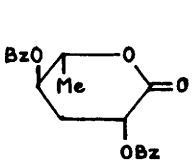
(8)

to give similar compounds of interest for orthosomycin antibiotic work e.g., (Scheme 2).[17]



Scheme 2

Ethanolysis of the lactone (9) gave the ester (10) which slowly converted to the γ-lactone (11) following benzoyl migration.[18]



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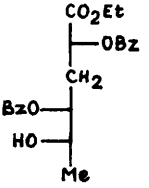

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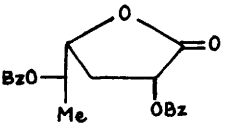
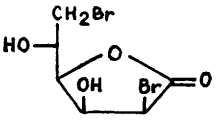


(11)

Borohydride reduction of the bromolactone (12) gave the corresponding dibromo free sugar leading to useful derivatives of 2,6-dideoxy-D-arabinohexose.[19] The same workers then showed that hydrogen bromide in acetic acid converted D-lyxono-1,4-lactone into



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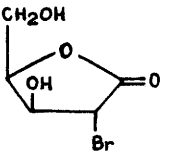

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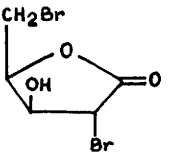

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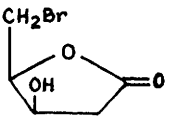
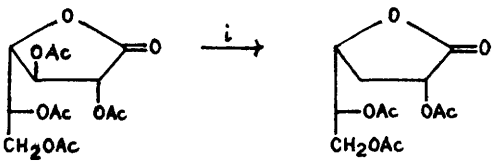


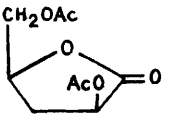
(15)

the 2-bromo- and then the 2,5-dibromo derivatives (13) and (14). Hydrogenolysis of (14) then gave the 2-deoxybromolactone (15).[20] Direct hydrogenolysis of esters of aldono-γ-lactones leads to 3-deoxy-analogues by elimination-addition processes (Scheme 3). All from D-pentofuranolactones gave compound (16).[21]



Reagent: i, H_2-Pd-Et_3N

Scheme 3



(16)

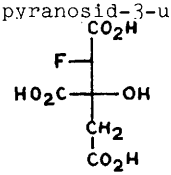
Thirteen aroyl- and six arylhydrazide derivatives of D-glycero-D-gulo-heptono-1,4-lactone have been synthesized, and the ionizability of the nitrogen-bonded protons was investigated.[22] Various peptide derivatives of 2-amino-4,6-O-benzylidene-2-deoxy-D-gluconic acid have been made by use of the corresponding acyl azide,[23] and other related derivatives, some having amino-acids bonded to the sugar amino-group, have also been reported.[24]

Ligands derived from D-gluconic acid and D-glucuronic acid have been used to solubilize platinum(II) complexes of 1,3-diamines and some of the products show high antileukemic activity.[25] Radiation-induced reaction of solid 2-deoxy-β-D-erythro-pentose gave 2,5-dideoxy-D-erythro-pentonic acid by a chain reaction, the nature of which was determined by consideration of the crystal structure.[26]

2 Aldaric Acids

A mixture of the caffeic acid esters of glucaric acid and its lactone has been isolated from tomato leaves,[27] and alkyl esters of D-glucarate have been converted into the 3,4-O-isopropylidene-2,5-dimethacryl derivatives which were polymerized.[28] Various metal salts of galactaric acid have been examined with respect to their compositions and physical properties,[29] and the aminolysis of the

diethyl ester has been found to proceed via the two possible 1,4-lactone intermediates in succession.[30] The branched-chain fluoro-acid (17), the enantiomer of fluorocitric acid formed biosynthetically from oxaloacetic acid and fluoroacetyl-CoA, has been synthesized from methyl 4,6-O-benzylidene-2-deoxy-D-erythro-hexopyranosid-3-ulose.[31]



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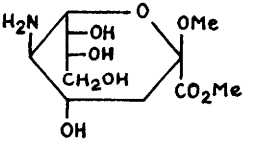
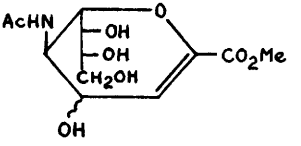


(18)



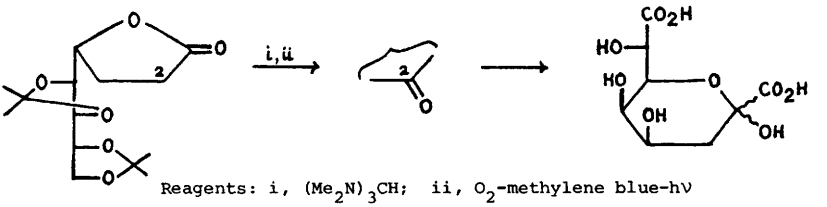
(19)

3 Ulosonic Acids

A two-stage automated continuous process for preparing di-O-isopropylidene-L-xylo-hexulosonic acid (the L-ascorbic acid precursor) has been described.[32]

Deamination with nitrous acid of methyl (methyl β-D-neuraminosidate) (18) gives mainly the corresponding alcohol with retained configuration at C-5,[33] and treatment of N-acetylneuraminic acid with acetic anhydride and sulphuric acid followed by sodium methoxide gives the epimeric unsaturated products (19). The inversion at C-4 was considered to arise from an oxazoline intermediate. The products are competitive inhibitors of neuraminidase.[34]

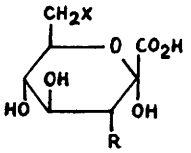
A new synthesis of 3-deoxy-D-manno-octulosonic acid is outlined in Scheme 4, the starting material being obtained from D-mannose by



Reagents: i, $(Me_2N)_3CH$; ii, O_2-methylene blue-hν

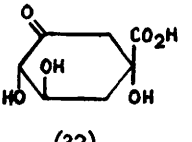
Scheme 4

a Wittig procedure.[35] The phosphono-heptulosonic and -octulosonic acids (20) have been prepared from suitably protected 6-bromo-6-deoxy-D-glucose and D-gluco-hexodialdose derivatives, respectively. All are competitive inhibitors of the enzyme which converts the pyranoid acid (21) to 3-dehydroquinate (22).[36]



(20) R = H or OH
X = $-PO_3H_2$ or $CH_2PO_3H_2$

(21) R = H, X = $-OPO_3H_2$

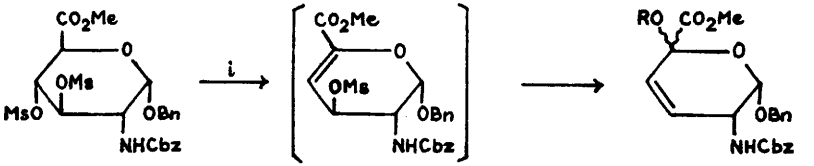


(22)

4 Uronic Acids

Syntheses of racemic hexuronic acid derivatives via unsaturated compounds in a Diels-Alder procedure are mentioned in Chapter 12. 5-Deoxy-D-xylo-hexofuranurono-6,3-lactone derivatives have been prepared from D-glucuronolactone using three deoxygenation procedures.[37]

Acid-catalysed degradation of a methyl heptosiduronic acid resulted in decarboxylation and the production of 5-(hydroxymethyl)-furfural; the course of the reaction was studied using ^{14}C labels.[38] Hexuronic acid esters with good leaving groups at C-3 and C-4 on treatment with base firstly give 4,5-enes which then solvolyse with allylic rearrangement, e.g., Scheme 5.[39]



Reagent: i, DBU-ROH

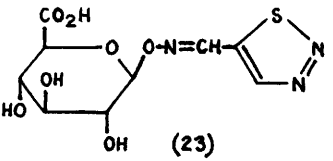
Scheme 5

Deuterium labelling at C-5 in methyl β-D-gluco- and -galacto-pyranosiduronic acid occurs without epimerization on treatment with deuterium oxide in aqueous sodium hydroxide.[40] Reaction of per-methylated hexopyranosiduronic acids with lead tetra-acetate affords epimeric 5-acetoxypentopyranosides by oxidative decarboxylation. The products, treated with sodium borohydride, undergo glycosidic cleavage and reduction to give partly methylated pentitols.[41] In related work, electrolytic decarboxylation of D-glucuronic acid has been used to convert D-glucuronic acid into D-xylo-pentodialdose and hence, by use of nitromethane, nitroinositols. The reaction can be applied to natural products which contain the acid.[42]

Heats and entropies of reactions of Cu^{2+} with D-glucuronate and -galacturonate have been interpreted in terms of bidentate ligands

bonded to the copper ions.[43]

D-Riburonic acid has been found as a component of an acidic polysaccharide of Rhizobium meliloti, being present as terminal α-D-furanuronosyl units.[44] The glucuronic acid conjugate (23) has



(23)

been isolated from urine of rabbits injected with the oxime,[45] and a related steroidal conjugate was converted into the uronamide with 1,6-diaminohexane for use in the immunological determination of estrogens in pregnancy urine.[46]

5 Ascorbic Acids

A method for determining L-ascorbic acid using 4,7-diphenyl-1,10-phenanthroline has been reported.[47]

The semi-empirical MINDO/3 and MNDO methods have been used in a theoretical study of the tautomers of ascorbic acid.[48]

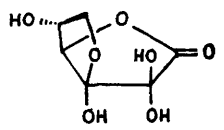
Reduction of L-ascorbic acid with hydrogen over palladium on charcoal gave L-gulono-1,4-lactone quantitatively.[49] A set of new acetal derivatives produced using α-ketoaldehydes have been tested in cancer work,[50] and 6-deoxy-6-fluoro-L-ascorbic acid has been prepared from 2,3:4,6-di-O-isopropylidene-L-xylo-hexulosonic acid by conventional procedures.[51] The 6-oleate of L-ascorbic acid has been described,[52] and the 5-palmitate potassium salt has been found by infrared methods to undergo a phase change in aqueous solution at 48 °C.[53]

Oxidation has been examined with thioureapentacyanoferrate,[54] polyamino acid–Fe^{3+} complexes,[55] tris(2,2'-bipyridine)ruthenium,[56] and pyruvic acid and quinones (radical studies).[57] L-Ascorbic acid acts as a reversible electron donor in a model photosynthesis system which generates hydrogen.[58]

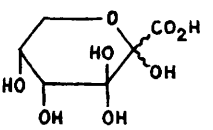
Ascorbate radicals disproportionate to give ascorbate ion and dehydroascorbic acid by way of a dimeric species,[59] and in a related study the oxidation of ascorbate radical to dehydroascorbic acid has been found to be anomalously difficult.[60]

Both ^{1}H and ^{13}C n.m.r. studies have shown that dehydroisoascorbic acid (D-erythro-2,3-hexodiulosono-1,4-lactone) exists in

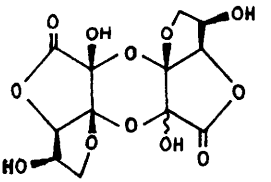
water initially as the bicyclic form (24) which then rearranges to the pyranoid anomers (25). In DMF the compound exists in epimeric dimer form (26).[61] ^{15}N N.m.r. spectroscopy has been used to study



(24)

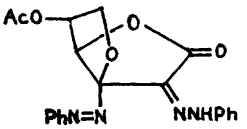


(25)

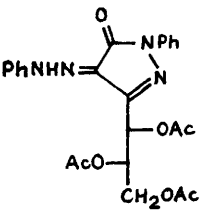


(26)

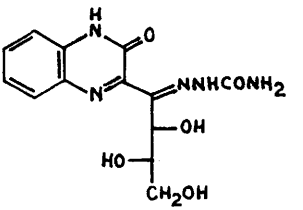
the acetylated derivatives (27) and (28) of products obtained from reaction of dehydro-L-ascorbic acid with phenylhydrazine followed by oxidation and base treatment, respectively.[62] Treated with o-



(27)

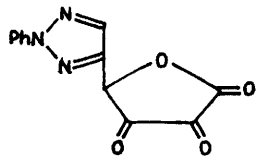


(28)

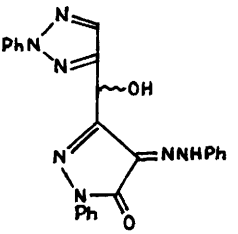


(29)

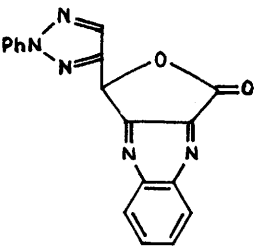
phenylenediamine followed by semicarbazide, dehydro-L-ascorbic acid gives compound (29) which was conventionally degraded with periodate to its formyl analogue,[63] and in similar work the dehydroascorbic acid analogue (30) was converted into the pyrazolone (31) and the quinoxaline (32).[64]



(30)

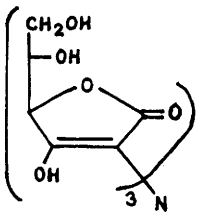


(31)

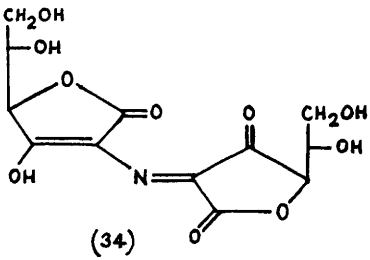


(32)

Reaction of dehydro-L-ascorbic acid with an amino acid gives the tris(2-deoxy-2-L-ascorbyl)amine (33) which is a stable, blue free radical species. On oxidation this dissociates into the known red pigment (34) and L-ascorbic acid.[65]



(33)



(34)

A kinetic study of the reaction of several Co^{3+} co-ordination complexes with L-ascorbic acid has been reported.[66]

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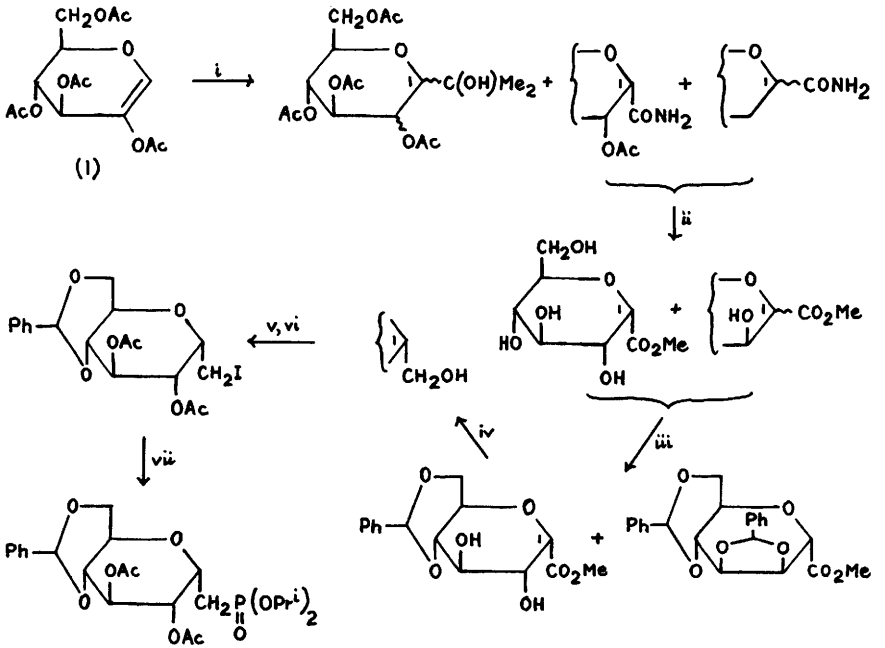
16

Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

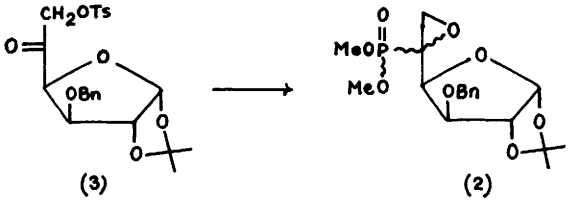
Two papers on the synthesis of C-glycosyl phosphonate analogues of α-D-gluco- and -galacto-pyranosyl phosphates, the second being a corrected version of the first, have appeared. The route to the glucose derivative is depicted in Scheme 1; a similar route from the C-4 epimer of (1) was used for the galactose-phosphonate analogue.[1,2]



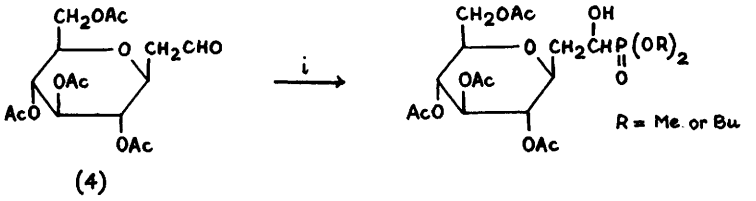
Reagents: i, $HCONH_2$-Me_2CO-hν; ii, HCl-MeOH; iii, PhCHO-$ZnCl_2$; iv, $NaBH_4$-THF-H_2O; v, NIS-Ph_3P-DMF; vi, Ac_2O-C_5H_5N; vii, $P(OPr^i)_3$

Scheme 1

α,β-Epoxyphosphinyl compounds, e.g., (2), were obtained as predominantly single isomers (stereochemistry not determined), from corresponding 6-O-tosyl-5-ulose derivatives, e.g., (3), by treatment with dimethyl phosphite-DBU. Such compounds are analogues of the antibiotic fosfomycin.[3] Acetylated aldehydo-sugars, e.g.,



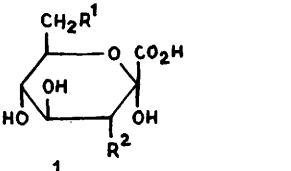
the anhydro-octose (4) derived from D-glucose, with dialkylphosphites in the Abramov reaction, under phase-transfer conditions to give the corresponding α-hydroxyphosphonates in yields up to 85% (Scheme 2). An analogue derived from rhamnose was similarly obtained.[4] The phosphonoheptulosonic and phosphono-octulosonic



Reagent : i, $(R'O)_2POH-C_6H_6-DMSO-Na_2CO_3-BnN^+Et_3Cl^-$

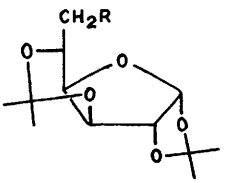
Scheme 2

acids (5) were prepared from suitably protected 6-bromo-6-deoxy-D-glucose and 6-aldehydo-D-glucohexodialdose derivatives, respectively. All are competitive inhibitors of the enzyme which effects the synthesis of 3-dehydroquinate from the phosphate (6).[5] Treatment of



(5) $R^1 = PO_3H_2$ or $CH_2PO_3H_2$, R^2 = H or OH

(6) $R^1 = OPO_3H_2$, R^2 = H

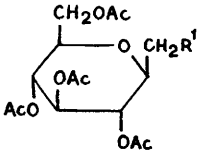


(7) R = PPh_2

(8) R = $OPPh_2$

1,2:3,5-di-O-isopropylidene-6-O-tosyl-α-D-glucofuranose with diphenylphosphine and sodium dihydrobis(2-methoxyethoxy)aluminate (to

generate in situ the diphenylphosphide anion) gave the diphenylphosphino-glucofuranose derivative (7) which was used to prepare Wilkinson-type catalysts for asymmetric hydrogenation. The corresponding oxy-linked compound (8) was also used. Optical yields varied between 2 - 14% for (7) and 29 - 67% for (8).[6] The Arbuzov reaction (trialkylphosphites and hydroxylamine on acid chlorides) has been applied to higher 2-deoxyaldonic acid chlorides, e.g., (9) to give the derivatives (10) and (11).[7]



(9) $R^1 = COCl$

(10) $R^1 = -C(=NOH)-P(=O)(OR^2)_2$ R^2 = Me, Et, or Bu

(11) $R^1 = -CHOP(=O)(OR^2)_2$ with $PO(OR^2)$

2 Other Carbon-bonded Compounds

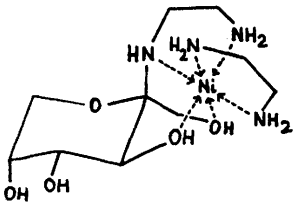
Aminosugar derivatives of ruthenocene and ferrocene have been reported. Glucosamine, galactosamine, and mannosamine react with ferrocene- or ruthenocene-carbaldehyde to give Schiffs bases which were reduced. Radiolabelled compounds were also prepared.[8]

3 Oxygen-bonded Compounds

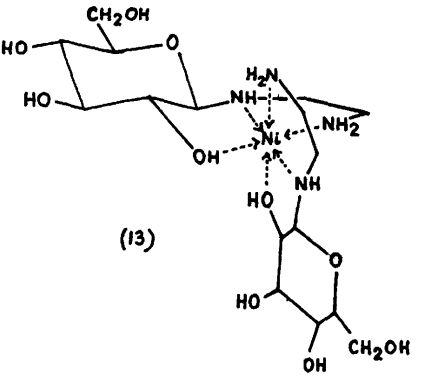
The reaction of D-xylose with ammonium molybdate gave a 1,2-complex in which the sugar portion was shown by X-ray analysis to be D-lyxose, formed by the molybdate-catalysed epimerization at C-2.[9]

Hexamethyldisilazane and trimethylsilyl chloride have been compared as reagents for the preparation of trimethylsilyl derivatives of sugars.[10] Stannylanes of diols have been shown to be dimeric in all physical states except, perhaps, in very polar solvents. The enhancement of oxygen nucleophilicity was ascribed to this structure, which persisted even in the vapour state.[11] The ^{13}C- and ^{119}Sn-n.m.r. spectra of seven tributylstannyl ethers and one dibutylstannyl ether of carbohydrates have been reported. Selective tributylstannylation of methyl 4,6-O-benzylidene-α-D-glucopyranoside gave mainly the 3-O-mono- and the 2,3-di-O-ethers with very little of the 2-O-(tributyl)stannyl compound.[12]

The text of the Haworth Memorial Lecture on sugar-cation complexes has been published.[13] Blue crystalline Ni(II) complexes of D-glucosylamine, D-mannosylamine, and D-fructosylamine have been obtained by treatment with tris(ethylenediamine)nickel(II) dichloride. X-Ray analysis showed that the fructose derivative had the 1:2 pyranose structure (12) while the aldoses had 2:1 structures, e.g., (13).[14]



(12)



(13)

3-Hydroxy-2-nitrophenyl β-D-galacto- and -fucopyranosides are able to chelate lanthanide metal ions and are useful as shift or relaxation probes for the active sites of β-D-galactosidase and the lac-repressor of E. coli.[15] A new mechanism involving a double ion exchange has been suggested for the precipitation of tricalcium saccharate from a calcium chloride-sucrose solution by addition of sodium hydroxide, on the basis of the finding that precipitation is initiated when calcium ion-sucrose ratio is 2-3:1, that $Ca(OH)_2$ and complex are precipitated when this ratio is 3-4:1, and when this ratio is >4 only $Ca(OH)_2$ is precipitated.[16]

D-Gluconato- and D-glucuronato-ligands impart better water solubility to platinum(II) complexes of 1,3-diamines, and these combinations have been tested for antitumour activity against leukaemia L1210. In particular [Pt(D-gluconato)(cis-1-2-(aminomethyl)-cyclohexylamine)] showed reduced toxicity and higher potency.[17] Palladium and rhodium complexes of amidophosphites of sugars, prepared by reaction of tetra-ethyldiamidophosphite derivatives of various mono- or di-O-isopropylidene sugars with alkenyl palladium chlorides or rhodium carbonyls, have been tested as asymmetric hydrogenation catalysts.[18,19]

Complexes between ATP, AMP, ribose 5-phosphate, glucose 1-phosphate, or glucose 6-phosphate and metal cations are thought to be responsible for the catalysis observed in reactions of acetic acid, glycine, β-alanine, alanine, lysine, glutamic acid, or histidine with hydroxylamine to give the corresponding hydroxamic acids in the presence of Ni^{2+}, Co^{2+}, Ca^{2+}, Mn^{2+}, Mg^{2+}, Zn^{2+}, or Be^{2+}. The reaction proceeds without release of inorganic phosphate.[20] Mixed complexes of platinum(II) with cyclic alkenes and adenosine, formed by interaction of adenosine with platinum(II) cyclic alkene complexes have been reported.[21]

Gadolinium(III) trinitrate-inositol is reported to be an effective paramagnetic relaxation reagent useful in highly polar solvents such as DMF ; e.g., the time required for ^{13}C-n.m.r. of adenosine in $[^{2}H_6]$DMSO was reduced from 4 to 2.5h with a signal-to-noise ratio of 32:1.[22]

An i.r. and ^{1}H-n.m.r. study of 2',3'-O-isopropylidene-6-mercaptopurine riboside (S,N)-tri-n-butyl tin showed that it is a five-co-ordinate complex with an Sn-S bond and N(7) co-ordination to tin. The molecules are associated via the primary alcohol-nitrogen(1) hydrogen bond.[23]

The use of stannylene protecting groups as regioselective agents is described in Chapters 4 and 6. The n.m.r. of cyclic sulphites is to be found in Chapter 20.

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17

Alditols and Cyclitols

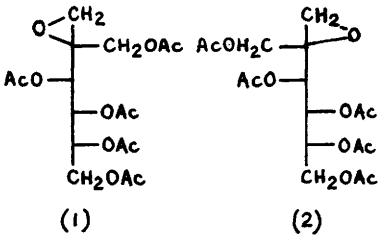
1 Alditols

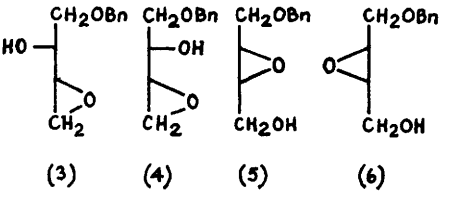
The synthesis and properties of xylitol have been reviewed,[1] and its crystallization from aqueous alcohol solution has been examined[2].

Studies using $^{14}CO_2$ have shown that D-glucitol is synthesized in the leaves, and metabolized largely by the root apices, of apple seedlings.[3]

D-Mannitol has been produced from D-glucose by hydrogenation in the combined presence of immobilized glucose isomerase (to establish a glucose-fructose equilibrium) and RuY zeolite catalyst (for conversion of fructose to glucitol and mannitol), the zeolite maintaining its catalytic activity better than conventional catalysts.[4] Raney nickel catalysed hydrogenation of D-glucose (>0.16M) was found to be first order with respect to hydrogen, and zero-order with respect to glucose. At 99-124 °C, the activation energy was 19.87 kcal mol^{-1}, and the reaction rate increased with stirring speed.[5] In the presence of two catalysts, one for hydrogenation and one for hydrolysis, hexitols were produced from several di-, oligo-, and poly-saccharides (e.g., sucrose, maltose, lactose, maltodextrins). Best yields were obtained with a ruthenium catalyst and Montmorillonite K10 or a Nafion-type resin. Fructose-containing saccharides hydrogenated at 120 °C, but other saccharides required higher temperatures (150 °C) and concomitant side reactions were observed.[6] The cathodic reduction of D-glucose using various cathode metals and different solution pH values has been examined, leading to the conclusion that a surface film forms on the cathode during reduction.[7] The ionization of various polyhydroxy-compounds in alkali was investigated by potentiometric titration. At hydroxide ion concentrations $\leq$0.4M D-galactitol and D-glucitol behave as monobasic acids, while D-mannitol and meso-inositol behave as dibasic acids.[8]

A re-investigation of the reaction of diazomethane with keto-D-fructose penta-acetate revealed that the epoxides (1) and (2) were formed in the ratio 85:15.[9] D- And L- tartaric acids have been used to prepare all four stereoisomeric forms of 2,3- and 3,4-epoxybutanediols, i.e., (3) to (6), as building blocks in the synthesis of chiral compounds.[10] The structure and conformation of some di-O-benzylidene derivatives of L-iditol have been determined by n.m.r. spectroscopy.[11]





A variety of quaternary ammonium derivatives have been synthesized by N-alkylation with various hydrophobic alkyl groups of 1-deoxy-1-methylamino-D-glucitol,[12] and 1,6-diazido-2,4-O-benzylidene-1,6-dideoxy-3,5-O-ethoxymethylene-D-glucitol has been prepared from 2,4-O-benzylidene-D-glucitol by standard procedures.[13]

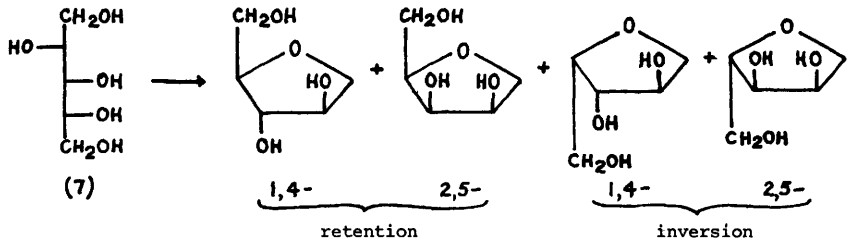
The action of a new α-glycol-cleavage reagent (Ph_3Bi-NBS-K_2CO_3-H_2O) was demonstrated by the synthesis of 2,3-O-isopropylidene-D-glyceraldehyde from 1,2:5,6-di-O-isopropylidene-D-mannitol.[14] Sequential lead tetra-acetate cleavage and borohydride reduction of 1,6-di-O-trityl-D-mannitol gave 1-O-trityl-sn-glycerol which was used to prepare 2,3-di-O-palmitoyl-sn-glycerol and its di-oleoate analogue.[15]

The formose reaction in the presence of calcium ions and D-fructose gave 2-C-(hydroxymethyl)glycerol, 3-C-(hydroxymethyl)-pentitol and 2,4-bis-C-(hydroxymethyl)pentitol with high selectivity, the ratio of formaldehyde to calcium ion being the dominant factor in controlling the selective production of these alditols.[16] The synthesis of alditol derivatives and phospholipids from vinyl carbonate telomers has been reviewed.[17]

Unsaturated alditols are mentioned in Chapter 12, while the g.l.c. analysis of alditol derivatives is covered in Chapter 22.

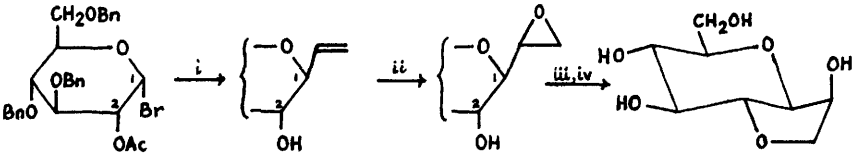
The dehydration of pentitols in aqueous sulphuric acid has been examined. Inversion of configuration can occur at C-2 or C-4 during 1,4- and 2,5-anhydride formation through S_N2 displacement of

protonated secondary hydroxy groups, but no inversion at C-3 was observed. Thus D-arabinitol (7) gave the anhydrides shown in Scheme 1.[18]



Scheme 1

1,5-Anhydro-3,4,6-tri-O-tosyl-D-mannitol was produced in low yield in the ditosylation of 3,4-di-O-tosyl-D-mannitol.[19] The 1,4:3,7-dianhydro-octitol (9) has been synthesized as shown in Scheme 2, using the vinyl C-glycoside (8); it has the trans-fused perhydrofuropyran ring system found in the ezomycins, the octosyl acids and certain antitumour terpenoids.[20]



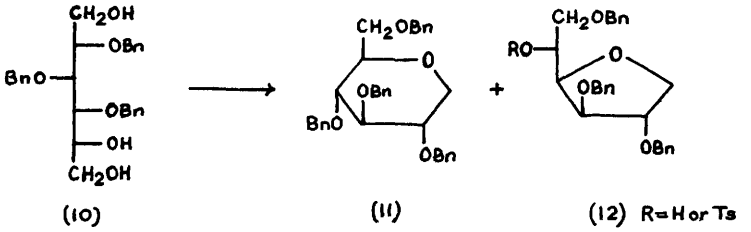
Reagents: i, CH_2=CHMgBr; ii, m-Cl-$C_6H_4CO_3H$; iii, camphorsulphonic acid-CH_2Cl_2; iv, Pd/C-H_2

Scheme 2

The selective esterification of 1,4;3,6-dianhydro-D-glucitol is referred to in Chapter 6 (ref.20).

Ether(10) gave the 1,5-anhydride (11) on 1-O-tosylation followed by base treatment, but with excess tosyl chloride in pyridine at 60 °C, the 1,4-anhydrides (12) were the predominant products, being formed through participation of the 4-benzyloxy-group (Scheme 3). This novel 1,4-anhydride formation was exploited in the synthesis of C-glycosides and α-showdomycin (Chapter 18).[21]

Crown ethers derived from 1,4:3,6-dianhydro-D-mannitol are referred to in Chapter 23, while other anhydro-alditol derivatives appear in Chapter 3 (C-glycosides), Chapter 8, and Chapter 19 (C-nucleosides).



(10) (11) (12) R=H or Ts

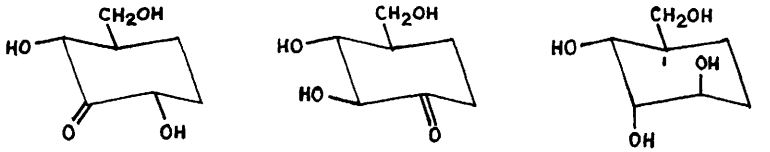
Scheme 3

2 Cyclitols

Comparitively high levels of myo-inositol were found in the cerebrospinal fluid of infants.[22] [^{14}C]Pinitol was obtained from soya bean extracts by use of an h.p.l.c. method capable of separating the various cyclitols present.[23] Only the aminocyclitol (13), from a selection of stereoisomeric aminocyclohexane tetrols, was utilized by Bacillus circulans in the biosynthesis of 2-deoxystreptamine (14).[24]

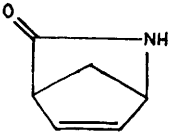
(13) (14)

Further degradation products of validomycin A produced by Flavobacterium saccharophilum include the deoxyinososes 3-keto-1-epi-validatol (15) and 4-keto-1-epi-validatol (16), and the tetrol 1,3,4-epi-validatol (17).[25]

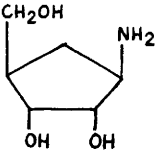


(15) (16) (17)

Racemic cyclopentane polyols have been synthesized, particularly for the preparation of carbocyclic analogues of furanoses and furanosyl nucleosides. Thus cis-hydroxylation of the bicyclic unsaturated amide (18) and subsequent conversion to the carbocyclic analogue(19) of β-DL-ribofuranosylamine has been reported by two groups, one group also preparing the α- and β-lyxofuranosylamine analogues,[26] while the other group used (19) in the synthesis of nucleoside analogues.[27]

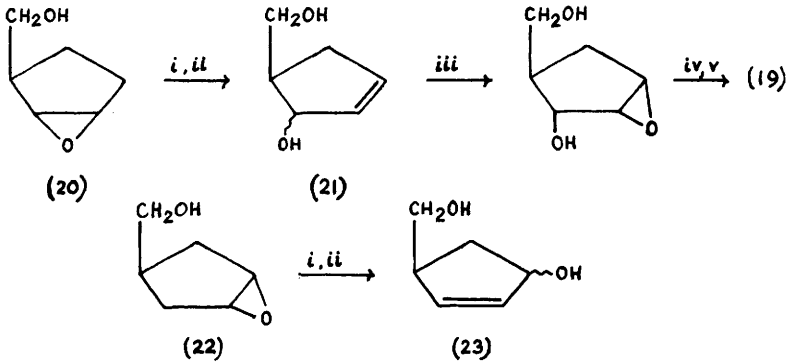


(18)



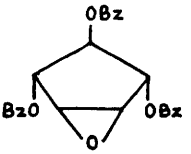
(19)

The same compound (19), isolated as its tetra-acetate, was also synthesized from epoxide (20) as shown in Scheme 4; addition-elimination of a phenylselenium reagent gave (21) as a stereoisomeric mixture requiring separation. The isomeric epoxide (22) yielded the unsaturated diols (23) in analogous fashion. Many related compounds were also described.[28] The racemic cyclopentane epoxide (24) was obtained by epoxidation [H_2O_2-$(CF_3CO)_2O$] of its cyclopentene precursor.[29] A cyclopentene nucleoside is referred to in Chapter 18.



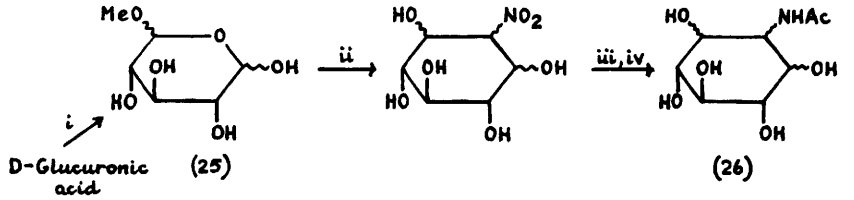
Reagants: i, $(PhSe)_2$-$NaBH_4$; ii, H_2O_2; iii, m-$ClC_6H_4CO_3H$; iv, NaN_3; v, Pd/C-H_2

Scheme 4



(24)

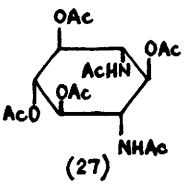
A Japanese group has developed an aminocyclitol synthesis based on the electrolytic decarboxylation of D-glucuronic acid and related derivatives, condensation of the resulting 1,5-dialdehyde derivatives (25) with nitromethane, and reduction (Scheme 5). The myo-, muco- and scyllo-isomers of (26) were thus isolated in 37, 8 and 6% yield, respectively, from D-glucuronic acid, while enantiomeric D- and L-neo-aminocyclitol derivatives were obtained following similar treatment of D-galacturonic acid and methyl α-D-mannopyranosiduronic acid, respectively. Since substituents at O-2, -3, and -4 remain unaffected by this process, glucuronide saponins yield aminocyclitol-oligoglycosides.[30,31] The same



Reagents: i, e^--MeOH-Et_3N; ii, $MeNO_2$-MeONa-MeOH; iii, Raney Ni-H_2; iv, Ac_2O-MeOH

Scheme 5

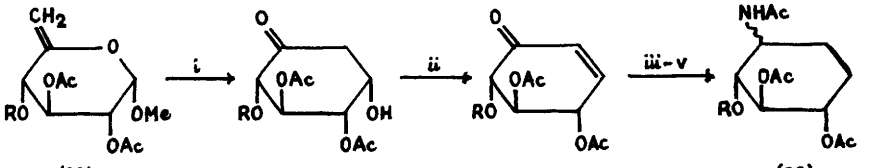
strategy was applied to the synthesis of hexa-acetyl-streptamine (27) from 2-acetamido-2-deoxy-D-glucose, which was first converted to its uronic acid methyl α-glycoside. Unfortunately, low yields were encountered in the nitromethane condensation-reduction sequence.[32]



(27)

Ferrier's mercury(II) ion-mediated conversion of 5,6-unsaturated pyranoses to cyclohexanone derivatives, when applied

to the disaccharide derivative (28) obtained from maltose, led to the synthesis of the α-D-glucopyranosylated aminocyclitols (29) (Scheme 6) which could be separated and de-O-acetylated.[33]

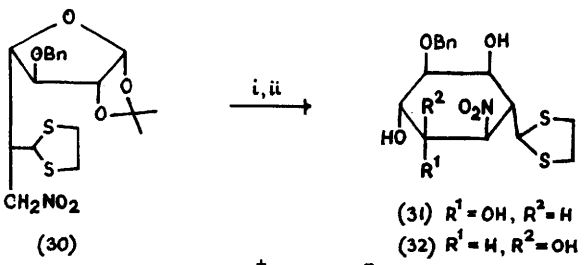


(28) R = 2,3,4,6-tetra-O-acetyl-α-D-Glcp (29)

Reagents: i, $HgCl_2$-H_2O-Me_2CO; ii, Ac_2O-py; iii, H_2-Pd/C; iv, $NaBH_3CN$-NH_4OAc; v, Ac_2O-MeOH

Scheme 6

Branched-chain cyclitols have been synthesized from branched-chain nitro-sugars. Thus the D-galacto-isomer (30) yielded the chiro-(31) and muco-(32)-cyclitols as shown in Scheme 7, while its D-altro-isomer yielded neo- and myo-cyclitols.[34]



(30)

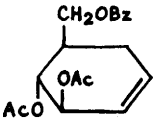
(31) R^1 = OH, R^2 = H

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

Reagents: i, H^+; ii, OH^-

Scheme 7

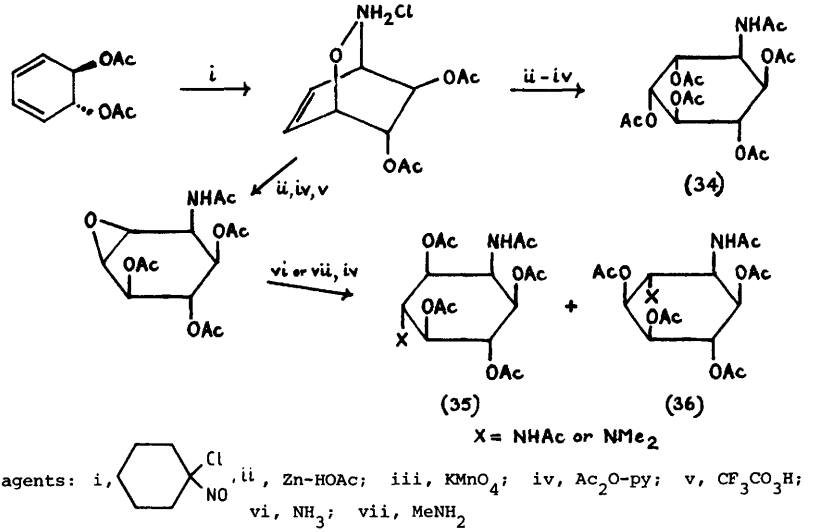
pseudo-Hexopyranoses with the α- and β-DL-gluco-configuration as well as their 2-amino-2-deoxy-analogues, have been synthesized from the cyclohexene (33) by hydroxylation or oxyamination reactions.[35]



(33)

A series of papers report syntheses of racemic aminocyclitols from products obtained on dipolar cycloaddition of cyclohexadienes and nitroso-compounds; Scheme 8 illustrates the formation of the racemic chiro-inosamine derivative (34)[36,37] or the

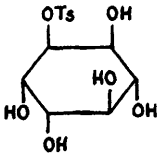
diaminocyclitols (35) and (36).[38] Related syntheses of dideoxy- and dicarbomethoxy-aminocyclitols were also reported.[39,40]



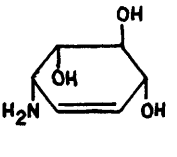
Scheme 8

The mono-tosylate (37) has been used to prepare conduritols (cyclohexene-tetrols) and the amino-analogue (38).[41]

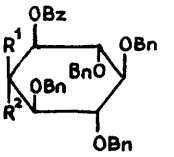
Kanamycin A has been used as a deoxystreptamine source for the synthesis of (1D)-1,3,5/2,4- and (1L)-1,2,4/3,5- 5-amino-cyclohexanetetrols using an oxidative-deamination and borohydride-reduction sequence.[42] Tetrahydropyranyl ether derivatives of myo-inositol have been synthesized by standard methods.[43]



(37)



(38)

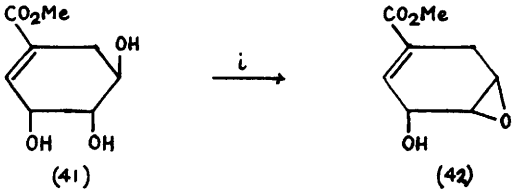


(39) R^1 = OH, R^2 = CH_2OAc

(40) R^1 = CH_2OAc, R^2 = OH

The fluorinating agent "DAST" (Et_2NSF_3) caused epimerization of the branched-chain cyclitol (39) at the quaternary carbon giving (40), which was alternatively synthesized by hydroxylation of an exocyclic methylene analogue of (39).[44] The epoxide (42) was obtained

on treatment of methyl shikimate (41) with the "DEAD-TPP" reagent[45] (Scheme 9) (see also Chapter 4).

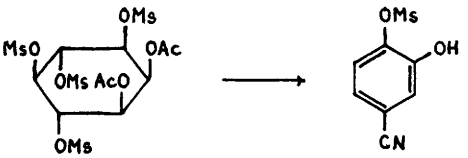


(41) (42)

Reagents: i, $EtO_2CN{=}NCO_2Et$-Ph_3P

Scheme 9

Reaction of the myo-inositol derivative (43) with cyanide ion did not give the expected substitution product, but instead aromatization occurred to give (44), for which a mechanism was postulated.[46]



(43) (44)

Aminocyclopentane triol-derivatives are referred to in Chapter 9 (ref. 41) as carbocyclic analogues of arabinonucleosides.

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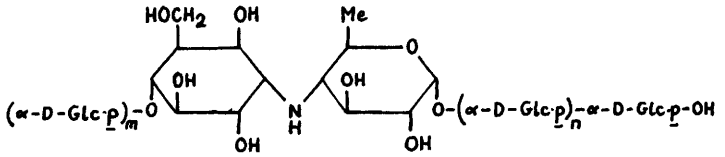
18
Antibiotics

1 Aminoglycoside Antibiotics

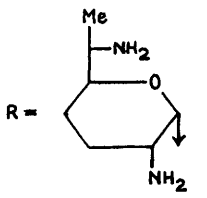
Recent progress in the chemistry of aminoglycoside antibiotics has been reviewed.[1]

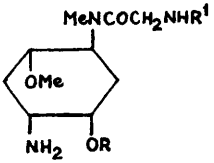
New oligosaccharide antibiotics, which are inhibitors of amylase, have been isolated from S. myxogenes. Oligostatins C-E have been shown to be pseudo penta-, hexa- and hepta-saccharides, respectively, in which an inosamine is N-linked to glucose units as shown in structures (1)-(3).[2]



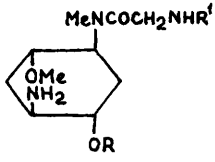
(1) Oligostatin C, $m=0, n=2$
(2) " D, $m=0, n=3$
(3) " E, $m=1, n=3$

New fortimicin relatives described include further components of the sporaricin complex produced by Saccharopolyspora hirsuta subsp. kobensis, sporaricins C(4) and D(5),[3] and dactimicin (6), elaborated by a strain of Dactylosporangium, an N-imino-formyl derivative of fortimicin A (6, R^1=H).[4] The structures of fortimicins having





(4) R^1 = $CONH_2$
(5) R^1 = CHO

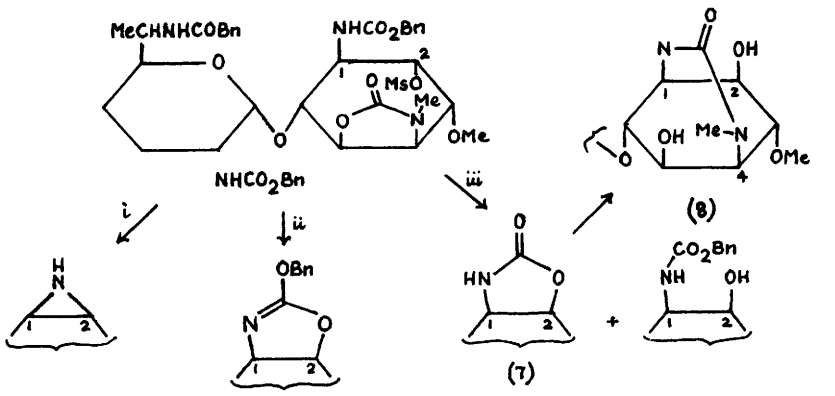


(6) R^1 = -CH=NH

double bonds in the purpurosamine moiety have been reviewed.[5]

Numerous analogues of fortimicin A and fortimicin B have been prepared by standard transformations on the parent compounds. Solvolysis of a 1-N-acetyl-2-O-methanesulphonyl fortimicin B

derivative led to 2-epi-fortimicin B involving neighbouring group participation by the acetamido group, whereas the corresponding 1-N-benzyloxycarbonyl-fortimicin B gave a variety of 2-epi-products depending on the conditions, resulting from O- or N-participation with or without benzyl or benzyloxy elimination,[6] illustrated in Scheme 1. Partial alkaline hydrolysis of the bis-carbamate (7) gave



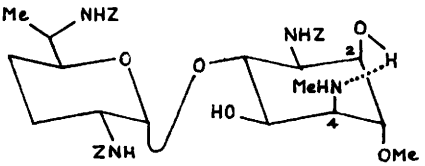
Reagents: i, Na_2CO_3-MeOH, ii, $NaHCO_3$-H_2O-THF; iii, NH_4OAc-$MeOCH_2CH_2OMe$

Scheme 1

the 1,4-urea (8), which was further hydrolysed to 2-epi-fortimicin B.[6] A number of 2-substituted fortimicins have been prepared conventionally from 1,2-aziridine or 2-methanesulphonyl derivatives analogous to those illustrated in Scheme 1.[7] 1-epi-Fortimicins A and B have been synthesized by epimerizing a 2-keto derivative of fortimicin A with subsequent borohydride reduction,[8] and fortimicin B has been used to prepare 6'-epi-fortimicin B and A by a sequence involving oxidative deamination at C-6' with N-chlorosuccinimide followed by reductive reamination using sodium cyanoborohydride.[9] Further fortimicin analogues have been prepared by glycosylation of suitably protected derivatives of fortamine, e.g., 6-O-(2'-amino-2'-deoxy-α-D-glucopyranosyl)-4-N-glycylfortamine and its 6'-amino-6'-deoxy isomer.[10]

Fortimicin B 1,2;4,5-bis-carbamate has been prepared, together with the three possible mono-carbamates; the 1,5-isomer can be prepared conveniently by rearrangement of the 1,2-carbamate.[11] Several 2'-N-substituted derivatives of 4-N-[(S)-4-amino-2-hydroxybutyl]-fortimicin B have been synthesized, which showed antibiotic activity comparable to fortimicin A.[12] The four amino groups have

been selectively blocked, leading to 2'-mono-, 6'-mono- and 2',6'-di-substituted benzyloxycarbonyl or t-butyloxycarbonyl derivatives, which were then converted to fortimicin A analogues by 4-N-glycylation.[13] Selective acylation of 1,2',6'-tri-N-benzyloxycarbonyl-2-epi-fortimicin B with N-(N-benzyloxycarbonylglycyloxy)-succinimide gave the 2-O,4-N-diacyl product, only N-acylation having occurred with the corresponding fortimicin B derivative; the acylation at O-2 was attributed to activation by intramolecular hydrogen bonding to the 4-amino group in the epi-isomer as shown in (9). Under basic conditions, 2-O to 1-N acyl migration predictably occurred with 2-O-glycyl epi-fortimicin A. Whereas 2-epi-fortimicin A showed similar antibacterial activity to fortimicin A, its 2-O-glycyl, 1-N-glycyl and 5-deoxy analogues were inactive.[14] Basic conditions can also lead 4-N-acyl fortimicins to rearrange

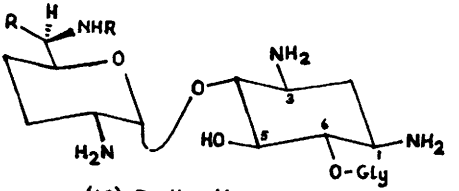


(9) Z = BnOCO-

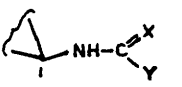
to 2'-N-acyl isomers, the acyl residue apparently being relayed by the 5-hydroxy group, since benzylation of this site prevents the migration.[15] Other reports describe the synthesis of 6'-N-methyl-fortimicins A and B and corresponding 6,6'-di-N-methyl derivatives, only the 6'-N-methyl fortimicin A derivative among these showing any antibiotic activity,[16] and the synthesis of 1-N-, 2'-N- and 6'-N-alkylated and acylated derivatives, and of these 2'-N-[(S)-4-amino-2-hydroxybutyl]fortimicin A was a more potent antibiotic than fortimicin A.[17] The 4-N-methyl group in fortimicin analogues appears to be essential for antibiotic activity, since a series of 4-de-N-methyl analogues of fortimicin A, as well as 4-N-demethyl-4-N-(β-aminoethyl)-4-N-ethyl fortimicin B, were inactive.[18] A number of 4-arenesulphonyl and 4-alkanesulphonyl derivatives of fortimicin B have been prepared, utilizing 2',6'-di-N-benzyloxycarbonyl fortimicin B 1,5-carbamate, in which the 4-methylamino group is rendered equatorial by the carbamate ring, and therefore more reactive than in uncyclized derivatives which resist 4-N-sulphonation.[19]

The biosynthesis of ^{13}C- and ^{14}C-labelled fortimicins using S-methyl-labelled L-methionine indicates that all the C-, N-, and O-methyl groups are derived from methionine.[20]

Mallams and his co-workers have reported extensive studies in gentamicin chemistry this year. A substantial paper analyses c.m.r. spectra of a wide range of natural and synthetic amino-glycoside antibiotics, revealing a wide range of well-defined conformations in solution dependent on both structure and pH. The limitations of the Nagabhushan-Daniels rule are discussed in the light of these observations.[21] Other papers report the synthesis of hexopyranosyl and hexofuranosyl derivatives of Gentamine C_1 and C_{1a} [general formula (10)],[22] corresponding pentopyranosyl and furanosyl derivatives of these amines, including some 5-O-glycosyl isomers,[23]

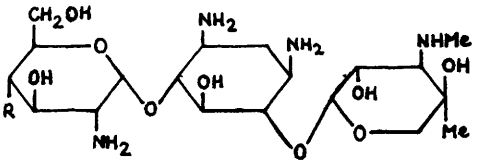


(10) R = H or Me



(11) X = O or S
Y = OR, NHR, SR

the synthesis of selectively N-trifluoro-acetylated gentamicin and sisomycin derivatives which were then converted to 1- and 3-oxo compounds using O-quinones and hence to deamino-and epi-gentamicin analogues by cyanoborohydride reduction in absence or presence of ammonia,[24] and finally the synthesis of a comprehensive series of 1-N-carbamoyl derivatives of sisomicin, gentamicins, and kanamycin A, including amino and thio analogues of the type shown in (11).[25] Paulsen's group has reported the synthesis of the gentamicin analogues (12) condensing the appropriate 2-azido-glycosyl chloride with a garosaminyl-deoxystreptamine derivative.[26]

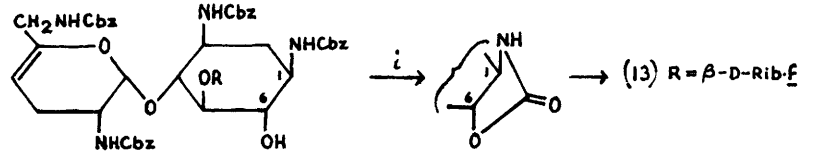


(12) R = OH, NH_2 or Cl

6-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)- and 5-O-(β-D-ribofuranosyl)-apramycins have been prepared, but these only showed similar rather than the hoped-for increased activity relative to apramycin itself.[27] (For apramycin, see Vol. 10, p. 130). Selective benzyloxycarbonylation of apramycin occurs in the presence of metal acetates, the nickel salt leading to the 2'-N-substituted derivative

and copper to the 3-N-substituted compound, whereas zinc gave mainly 1-N-benzyloxycarbonyl-apramycin; other 4-O-substituted 2-deoxystreptamines gave similar results.[28]

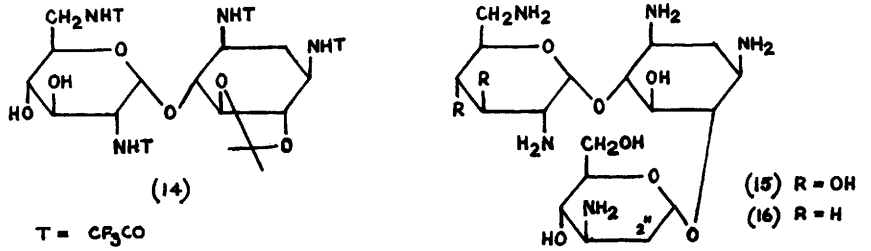
A new antibiotic, 10676, isolated from a Hunan soil sample, has been characterized as the 6'-amino analogue of paromomycin.[29] Ribostamycin and its 4"-thio-analogue have been made by glycosylating neamine with appropriate ribofuranosyl and 4-thio-ribofuranosyl derivatives.[30] Conversion of tetra-N-benzoyloxycarbonyl-sisamine (13) to the cyclic carbamate (13a) allowed Koenigs-Knorr ribosylation to give the sisomycin analogue shown in Scheme 2,[31]



Reagent : i, NaH-DMF

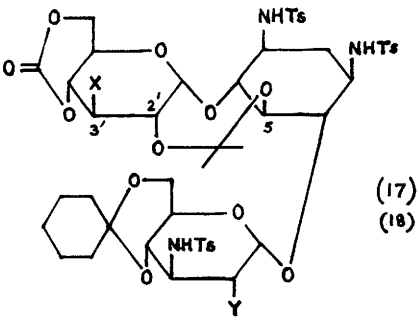
Scheme 2

and sisamine has also been used in Koenigs-Knorr glycosylations to prepare sisomycin D, sisomycin B and 5"-C-methyl-sisomycin B.[32] The substituted sisamine was prepared by periodate oxidation of the corresponding sisomycin derivative, and the analogous tetra-N-acetyl sisamine has similarly been prepared in high yield.[33] Treatment of tetra-N-trifluoroacetyl-neamine with dimethoxypropane in presence of trifluoroacetic acid gave the 5,6-mono-acetal (14), which could then be used to prepare 2"-deoxykanamycin B (15) and 2",3',4'-trideoxykanamycin B (16) by conventional procedures, the latter being a more effective antibiotic than kanamycin B against resistant strains of Pseudomonas aeroginosa.[34]

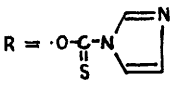


Many modifications of intact antibiotics have been reported.

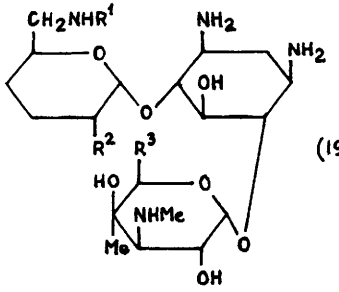
3'-Deoxy-kanamycin A has been prepared using Barton's tributylstannane deoxygenation procedure on the kanamycin A derivative (17), which undergoes selective deoxygenation at C-3 to give compound (18); compound (17) incorporates an inter-residue acetal function, implying the close proximity of the 2' and 5 positions in the kanamycin precursor.[35] An alternative synthesis of 3'-deoxy-kana-



(17) X = Y = R
(18) X = H, Y = R

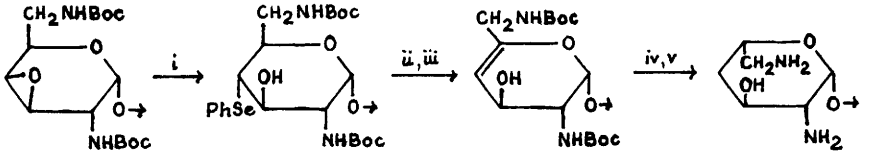


mycin A utilized a 3'-O-methanesulphonyl derivative which gave a mixture of 2',3'- and 3',4'-epoxide intermediates on treatment with base, and which on reduction yielded only the 3'-deoxy-isomer.[36] Likewise a 4'-O-methanesulphonyl-derivative led to a 3',4'-epoxide, which could be converted to 4'-deoxy-kanamycin A and 3',4'-dideoxy-kanamycin A by standard procedures.[37] Barton's deoxygenation procedure has also been applied to the 3"-O-imidazolylthiocarbonyl derivative of dihydrostreptomycin to give 3"-deoxydihydrostreptomycin.[38] 5,6"-Dideoxykanamycin B has been obtained by tributylstannane reduction of the corresponding dichloro compound.[39] An attempt to convert kanamycin A and B to 3',4'-dideoxy analogues by mutational biosynthesis using gentamicin-producing Micromonospora yielded combimicins, which are not only 3',4'-dideoxy but also 4"-C-methyl and 3"-N-methyl analogues of kanamycins, and relatives of gentamicin as well, indicated in structure (19).[40] Paromomycin has been converted to analogues modified at the 4',4''', and 5" positions (amino, deoxy, and epi-chloro derivatives), some of which showed useful antibiotic activity against Staphylococcus resistant to paromomycin itself.[41] The 2,6-diamino-2,6-dideoxy-D-glucose unit in kanamycin B has been modified to its 4-deoxy, 5-epimer by the part-sequence shown in Scheme 3; the resulting antibiotic analogue only showed weak activity however.[42] Standard methods have been used to convert 5,3',4'-trideoxy-kanamycin B to further deoxy, chloro and N-methyl derivatives, which were subsequently converted



(19) Combimicins, R^1 = H or Me, R^2 = NH_2 or OH, R^3 = CH_2OH

Gentamicin C, R^1 = H, R^2 = NH_2, R^3 = H



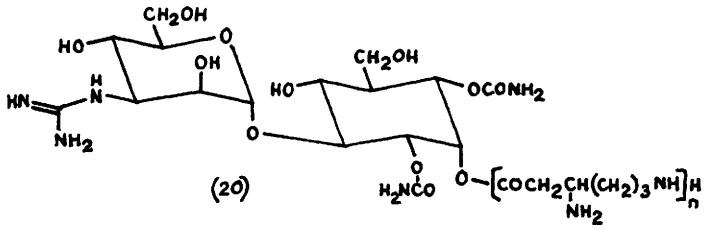
Reagents: i, $(PhSe)_2$-$NaBH_4$; ii, MCPBA; iii, NaOMe; iv, H_2-PtO_2; v, TFA

Scheme 3

to 1-N[(S)-4-amino-2-hydroxybutyryl]derivatives and shown to possess strong activity against Gram-positive and Gram-negative bacteria,[43] and to prepare 1-N-(2-aminoethoxycarbonyl) and 1-N-(3-aminopropoxycarbonyl)kanamycin A, the former showing similar antibiotic activity to amikacin (which contains a 1-N[(S)-4-amino-2-hydroxybutyryl] residue).[44] Treatment of tetrakis-N-benzyloxycarbonyl-6"-O-trityl-kanamycin A with sodium hydride leads to a number of cyclic carbamate derivatives.[45] Enzymes have been used to adenylate sisomicin, to phosphorylate kanamycin A (at oxygen), and to acetylate tobramycin (at nitrogen).[46]

6'''-Deamino-6'''-hydroxyneomycin and 6'''-deamino-6'''-hydroxyparomomycin have been obtained from strains of Streptomyces (fradiae and rimosus forma paromomycinus mutant,respectively); they are both obtained as mixtures of C-5''' epimers, and are suggested to be intermediates in the biosynthesis of the parent antibiotics.[47]

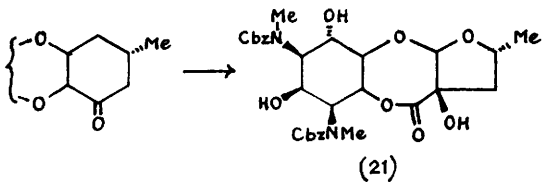
Three close relatives of the antibiotic myomycin have been isolated from a strain of Nocardia sp. (LL-BM782); they possess the same carbohydrate skeleton as myomycin (20, n=2), but differ in the number of attached β-lysine residues (20, n=3-5), which are linked to the myoinositol ring.[48] (The peptide chain was previously thought to be attached through the guanidino group). Antibiotic X-14847, produced by Micromonospora echinospora sp. X-14847, has



(20)

been identified as 1-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-myo-inositol.[49] Trans-4-amino-cyclohexyl α-glycosides of 2-amino-2-deoxy-D-glucose and 2,6-diamino-2,6-dideoxy-D-glucose have been prepared, using Lemieux's glucal chloronitroso-dimer route; these analogues of paromamine and neamine, respectively, showed little antibiotic activity.[50]

The 4-keto group in spectinomycin has been reduced to corresponding epimeric 4-amino analogues either via a hydroxy intermediate, leading to the [S]-isomer,[51] or by reduction of the oxime, giving both [R] and [S] isomers.[52] The axial [R]-epimer showed comparable activity to spectinomycin, whereas the equatorial [S]-epimer was inactive. 4-N-Acyl and 4-N-alkyl derivatives of the [R]-form were prepared; some showed useful activity, the N-ethyl derivatives being more active than spectinomycin.[53] N-Blocked spectinomycin undergoes electrophilically-catalysed α-keto rearrangement to yield the isomeric α-hydroxy-lactone (21), which could be degraded to the same 6-deoxy-D-isosaccharino-1,4-lactone (22) as that prepared from lactose.[54]



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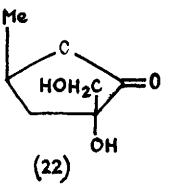
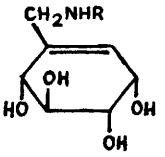


(22)

Stereoisomers of validoxylamine A have been synthesized by condensation of DL-validamine with bromo-cyclenitol derivatives giving compounds (23) and (24) in racemic form.[55] The partial conversion of maltose to cyclohexane analogues, which are α-linked pseudo-dissacharides of potential antibiotic interest, and cyclitol microbial degradation products of validomycin, are mentioned in Chapter 17.

The ^{13}C n.m.r. spectra of aminoglycoside antibiotics has been



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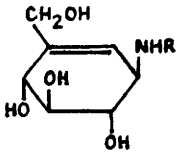

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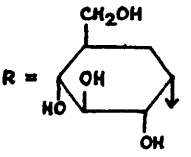
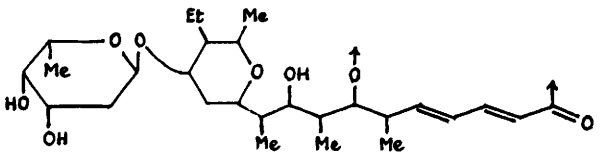


reviewed.[56] ^{13}C N.m.r. spectra of neomycin B and its 3'-phosphate, monomycin A, and kanamycin A at pH 1.0-10.0,[57] and of streptomycin and dihydrostreptomycin at pH 1.0-7.0,[58] have been recorded and signals completely assigned.

Emitter chemical ionization mass spectra of kanamycins have been recorded,[59] and fragmentation patterns from N-acetylated, O-methylated derivatives of 2-deoxy streptamine, neamine and ribostamycin discussed.[60]

2 Macrolide Antibiotics

The structure of a new macrolide antibiotic, cytovaricin, has been elucidated by X-ray crystal analysis; the compound, which shows both anti-tumour and anti-fungal activity, contains D-cymarose (2,6-dideoxy-3-O-methyl-D-ribo-hexopyranose) glycosidically β-linked to a complex 22-macrolide ring.[61] The 16-macrolide antibiotic acumycin contains mycaminose and 2,3,6-trideoxy-L-glycero-hexos-4-ulose (cinerulose) as sugar components.[62] Elaiophylin (azalomycin B), which contains 2-deoxy-L-fucose, is a 16-macrolide antibiotic formed by head-to-tail dimerization of the part structure (25).[63] Six metabolites of 9,3"-diacetylmidecamycin have been isolated and



(25)

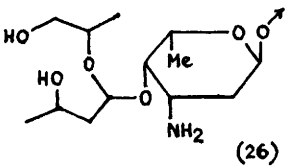
characterized; besides hydroxylation and deacetylation of the macrolide ring, they all had suffered deacylation of the 3- and 4-hydroxy groups in the terminal 2,6-dideoxy-α-D-ribo-hexopyranose ring.[64] Mycinamicin III, another component of the mycinamicin complex, has been characterized as a 3"-O-demethyl mycinamicin IV.[65]

Improved antibiotic activity resulted from the conversion of leucomycin A_5 to its 3"-O-propionyl derivative, involving esterification of the tertiary hydroxy group in the mycarose unit.[66] A standard sequence has been used to convert mycaminosyl tylonolide to its 4'-deoxy analogue.[67] The use of carbohydrates in the total synthesis of the aglycone tylonolide and of part-structures of other macrolides is referred to in Chapter 23.

C.i. mass spectra of a number of macrolide antibiotics have been reported; abundant molecular ions and ions arising from glycosidic cleavage were detected.[68]

3 Anthracycline Antibiotics

Components of the rubeomycin complex, isolated from a strain of Actinomadura, have been isolated and characterized. They contain daunosamine substituted at O-4 with a 3-hydroxybutanal acetal function shown in (26).[69] Seven new anthracycline analogues



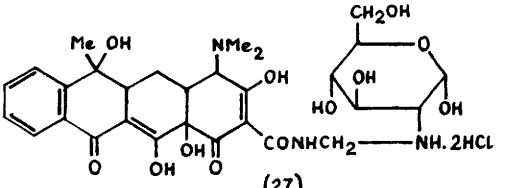
(26)

produced by mutant strains of S. galilaeus have been identified; they contain di- and tri-saccharide variants of the oligosaccharide side-chain in aclacinomycin.[70] Variants of auramycin and sulphamycin, containing 1-hydroxy substituted tetracycles, have been reported.[71]

Aklavin, the simplest representative of the aclacinomycin group of antibiotics, has been synthesized, using a glycal derivative of N-methyl daunosamine in the glycosylation step, followed by N-methylation to give the rhodosamine unit.[72] A total synthesis of 4-demethoxydaunomycin utilized an established glycosyl chloride for the glycosylation of the tetracycle.[73] A glycosyl chloride has likewise been used with a daunomycinone derivative to prepare 7-O-(3,4-di-O-acetyl-2,6-dideoxy-α-L-lyxo-hexopyranosyl)-adriamycinone, which was found to possess high anti-tumour activity.[73a]

Microbial glycosylations have also been employed. Treatment of 2-hydroxy-aclavinone, itself produced by a mutant strain of aclacinomycin-producing S. galilaeus, with an aclacinomycin-negative mutant strain gave 2-hydroxy-aclacinomycin,[74] and treatment of

carminomycinone and 13-dihydrocarminomycinone with a strain of S. galilaeus gave the 13-dihydrocarminomycinone trisaccharide, trisarubicinol, an active anti-tumour antibiotic containing the aclacinomycin A trisaccharide sequence, cinerulose → 2-deoxy-fucose → rhodosamine.[75] Incorporation of a 2-amino-2-deoxy-D-glucosyl residue into a tetracycline as shown in structure (27) rendered the tetracycline more effective towards Gram-negative bacteria.[76] Reduction of 2-hydroxyaclacinomycin A at the carbonyl group of the cinerulose



(27)

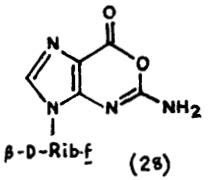
unit gave M and N variants, which showed similar cytotoxicity to the parent antibiotic.[77] Reductive amination of aclacinomycin A gave the [R] and [S] isomers of 4'''-deoxo-4'''-amino-aclacinomycin A, which were further modified to 4'''-alkylamino and 4'''-amide derivatives.[78]

A structure-activity study of 92 anthracycline compounds has been made, studying growth, nucleic acid and protein synthesis in L1210 leukemia cells. It was noted that the amino group on both the aglycone and sugar are essential for *in vitro* activity, that 3'-alkylamino compounds were more active than the unsubstituted 3'-amino analogues, and that di- and tri-saccharide side-chains gave more potent compounds than corresponding mono-saccharides, but that the length of the sugar chain did not correlate with *in vivo* antitumour activity.[79]

The synthesis of disaccharide units for anthracycline antibiotics is referred to in Chapter 3.

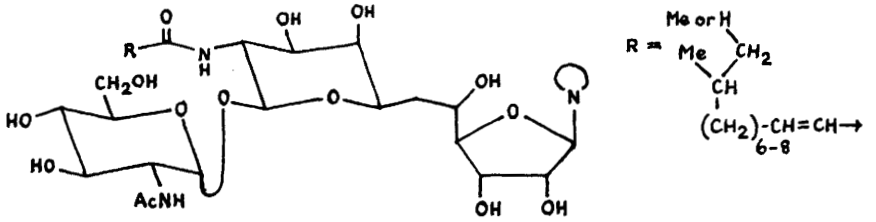
4 Nucleoside Antibiotics

Oxanosine, a new nucleoside antibiotic produced by a strain of S. capreolus, has been shown to have the structure (28)[80,81] Novel structures continue to be discovered. Further details on the structure analysis of mildiomycin have appeared.[82] (See Vol. 12, p.151). The structures of the streptovirudins A-D, relatives of tunicamycin, have been established; they may be considered to be pseudodisaccharides of amino sugars of uridine or dihydrouridine



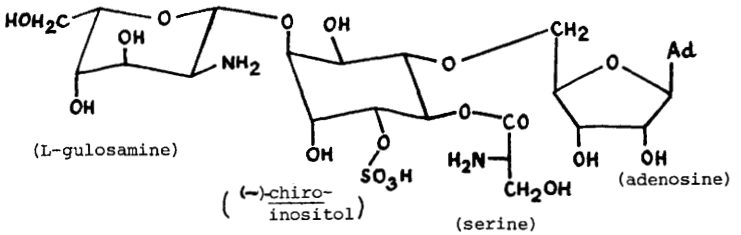
(28)

linked to a lipid residue, with general formula (29).[83] ^{252}Cf Plasma desorption mass spectrometry has been used to determine the



(29)

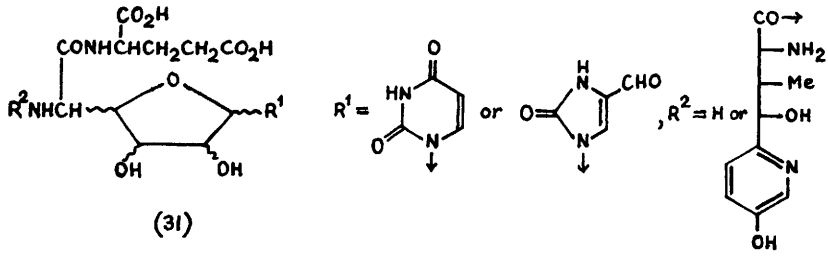
structure of the adenosine derivative adenomycin (30) which is elaborated by S. griseoflavus; conventional ionization techniques were unsuccessful.[84] Structure (31) represents the partial constitution of minor constituents of the nikkomycin complex produced by



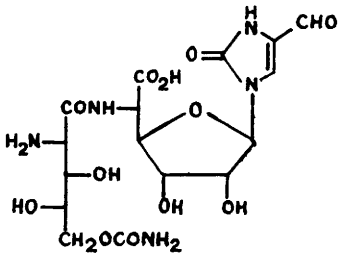
(30)

S. tendae; the configuration of the amino-hexuronic acid unit was not established.[85] Polyoxin N (32), a minor component occurring along with polyoxin L and M in the broth of S. piomogenus, is likewise an amino-hexuronic acid nucleoside analogue, closely related to other polyoxins.[86] (See Vol. 14, p.161).

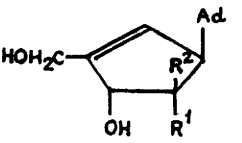
Neoplanocin A (33), a new antitumour antibiotic derived from Ampullariella regularis, has been characterized as a carbocyclic analogue of adenosine incorporating a cyclopentene ring; it is a more effective antibiotic than its relative aristeromycin.[87,88]



(31)



(32)

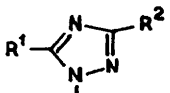


(33) $R^1 = OH$, $R^2 = H$

(34) $R^1 = H$, $R^2 = H, OH, OAc, SAc, NH_2, Cl, Br, or\ I$

2'-Epimeric analogues (34) of neoplanocin A have been synthesized by conventional sulphonate displacement on a neoplanocin derivative blocked at O-3' and O-5' by the tetraisopropyldisiloxane blocking group.[89]

Ara-tubercidin has been prepared by phase-transfer catalysed coupling of adenine with 2,3,5-tri-O-benzyl-D-arabinofuranosyl bromide; both anomers were obtained, separated after deprotection by ion-exchange chromatography.[90] Virazole (35) and its carboxamide isomer (35a), together with the parent triazole nucleoside, have been obtained from D-ribofuranosylhydrazine by standard conversions.[91]



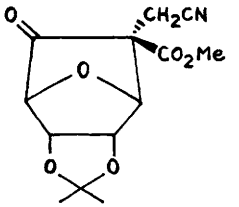
β-D-Rib-f

(35) $R^1 = H$, $R^2 = CONH_2$

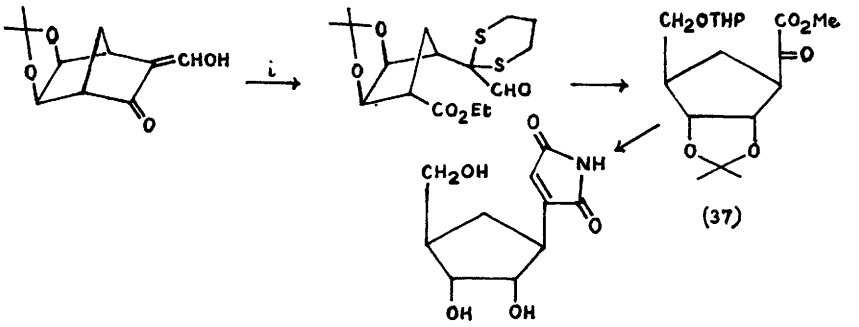
(35a) $R^1 = CONH_2$, $R^2 = H$

(±) - Carba-showdomycin (36) and carba-analogues of the related C-nucleosides oxazinomycin and pyrazomycin have been prepared from the common intermediate (37) obtained as shown in Scheme 4.[92] A synthesis of DL-showdomycin employed a Diels-Alder adduct as a source of the intermediate (38).[93] Chapter 3 contains references to the

synthesis of showdomycin from a C-glycoside (ref. 189) and the synthesis of analogues of pyrazomycin and bredinin (ref. 190).



(38)

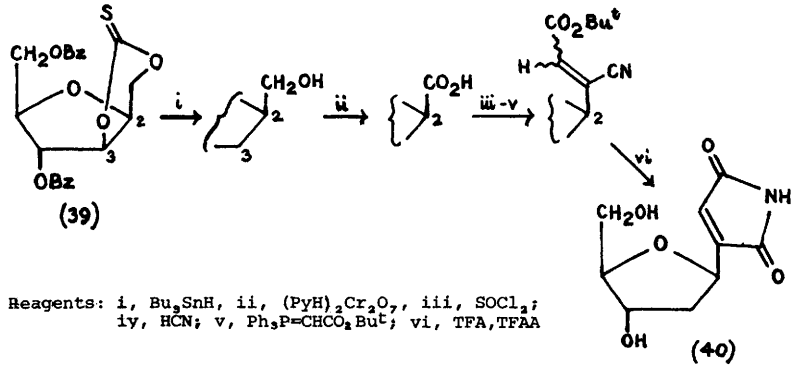


Reagent : i, $TsS(CH_2)_3STs$-KOH

(36)

Scheme 4

C-3 Deoxygenation of the 2,5-anhydro-glucitol derivative (39) gave a product which could then be converted to 2'-deoxyshowdomycin (40) as outlined in Scheme 5.[94] An improved synthesis of (2,3,5-



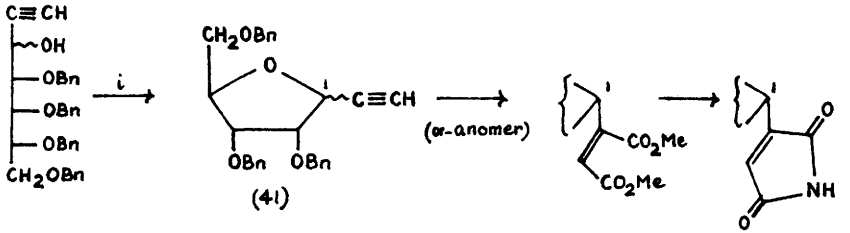
(39)

(40)

Reagents: i, Bu_3SnH, ii, $(PyH)_2Cr_2O_7$, iii, $SOCl_2$; iy, HCN; v, $Ph_3P{=}CHCO_2Bu^t$; vi, TFA,TFAA

Scheme 5

tri-O-benzyl-α- and -β-D-ribofuranosyl) ethyne (41), utilizing a newly-discovered benzyloxy participation reaction with loss of benzyl indicated in Scheme 6, has been applied to the preparation of showdomycin.[95] A new sythesis of pyrazofurin has also been



Reagent : i, TsCl-Py

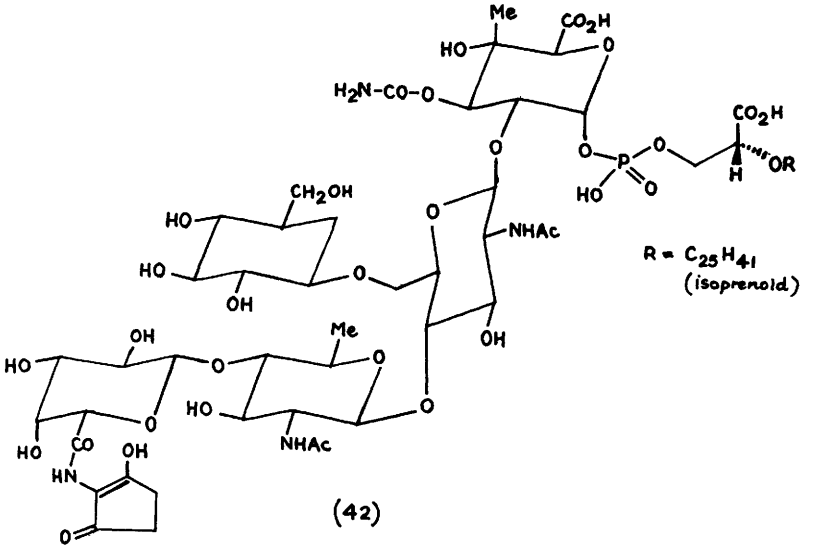
Scheme 6

described.[96] The synthesis of some prumycin diastereoisomers is mentioned in Chapter 8.

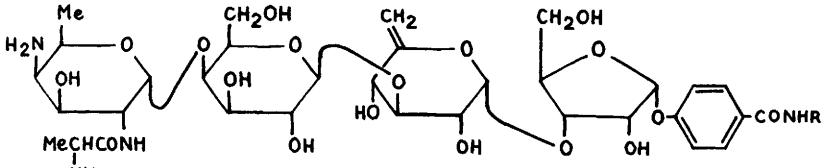
The conformation of nucleoside antibiotics has been reviewed; the similarity of these conformations to those of standard nucleosides suggests that they can easily be incorporated in growing DNA or RNA chains by mimicry.[97]

5 Miscellaneous Antibiotics

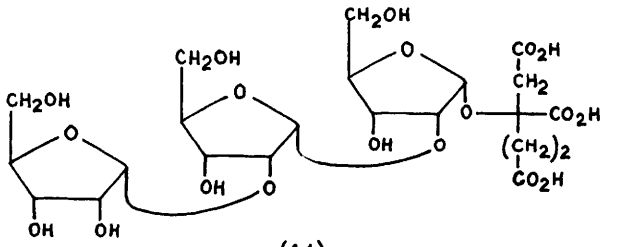
The structure of the oligosaccharide-lipid antibiotic moenomycin A has been established to be (42);[98] trifluoroacetic acid–catalysed alcoholysis yielded the disaccharide fragments obtained by cleavage from the terminal galacturonamide residue.[99,100,101] Another, new complex carbohydrate antibiotic, glysperin, produced by strains of *Bacillus cereus*, contains the tetrasaccharide unit (43) linked glycosidically through p-hydroxybenzoic acid to polyamines (spermine and spermidine);[102] these are basic, water-soluble compounds active against amino-glycoside-resistant organisms; one component contains D-glucose instead of the unsaturated sugar. Ribocitrin (44), an inhibitor of dextransucrase produced by S. strain MF980-CF1, is a ribose trisaccharide derivative of homocitric acid.[103] The antibiotic K-52B is an oligosaccharide derivative of an uncharacterized diamino sugar, for which the following partial structure is suggested: Glc-p(1→4)-Gal-p(1→4)-Fuc-p(1→4)-Glc-p(1→5)-Ara-f(1→4)-Gal-p(1→1)-Glc-p(4→)-Diamino sugar.[104,105] Details of the structure of the pentasaccharide segment (pseudo-olgose A)(45) in curamycin A have been deduced from ^{13}C n.m.r.


Me
CO2H
HO
O
H2N-CO-O
CO2H
O
O
P
O
OR
H
HO
O
CH2OH
HO
NHAc
HO
O
OH
OH
R = C25H41
(isoprenoid)
OH
Me
HO
O
O
HO
O
HO
NHAc
HO
CO
OH
HN
O

(42)

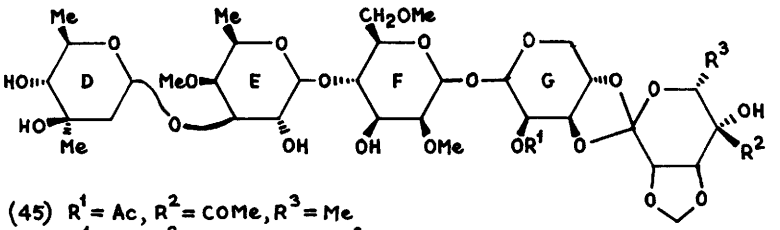

Me
H2N
O
CH2OH
O
CH2
O
CH2OH
OH
OH
O
O
HO
O
CONHR
MeCHCONH
NH2
OH
OH
OH
O
OH

(43)


CH2OH
O
CO2H
CH2OH
O
CH2
CO2H
CH2OH
O
O
OH
O
(CH2)2
OH
O
CO2H
OH
OH

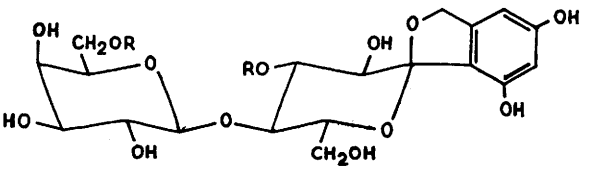
(44)

data;[106] for comparison, olgose, the corresponding pentasaccharide obtained from everninomicin D, has structure (46). (See also Vol. 13, p. 167). Microbial oligosaccharide inhibitors of α-glucosidases have been reviewed.[107] Deacylation of the antibiotics papulacandin



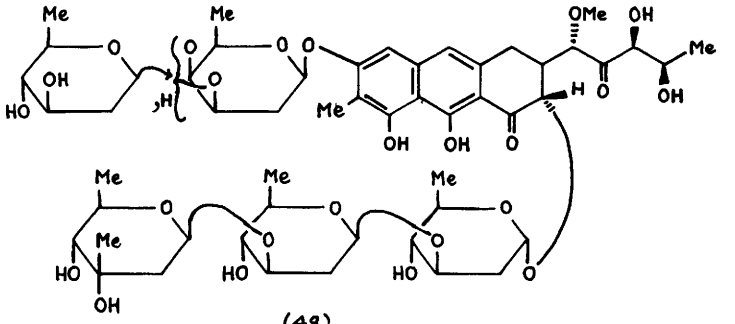
(45) R^1 = Ac, R^2 = COMe, R^3 = Me
(46) R^1 = Me, R^2 = CH(OMe)Me, R^3 = H

A, B, and C (47, R=fatty acid residues) yields the unusual disaccharide (47) (R=H).[108] A minor revision of the structure of olivomycin



(47)

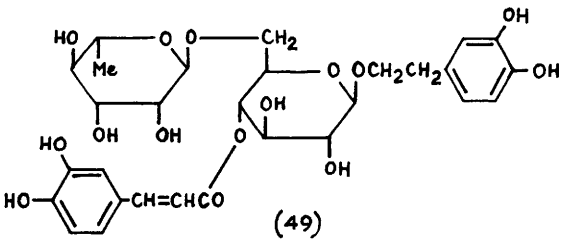
A has been proposed, (a change from α-1→4 to α-1→3 for the intra-disaccharide linkage) whereas substantial changes were suggested for the structure of mithramycin, now suggested to be (48).[109] An antimicrobial substance isolated from the leaves of Forsythia suspensa, forsythoside A, is considered to be the disaccharide derivative (49).[110]



(48)

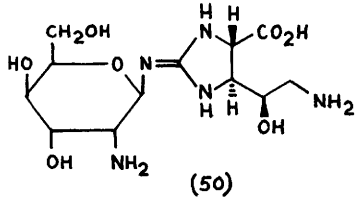
Gilvocarcins V and M, new antitumour antibiotics from S. gilvo-

tanareus, appear from chemical, spectral and X-Ray evidence to contain L-fucofuranose linked as an α-C-glycoside to a benzonaphthopyranone polycycle.[111]



(49)

The bud of Syzygium aromatica yields an antiviral substance identified as eugenin, a polygallic ester of β-B-glucopyranose.[112] (See Vol. 14, p. 53). A 1-(tri-O-methyl-galloyl) derivative of D-glucose shows useful neoplasm inhibitor activity.[113] A synthesis of the N-streptolidyl-gulosaminide (50) confirms this structure for streptothricin.[114] Two components of the antibiotic complex from



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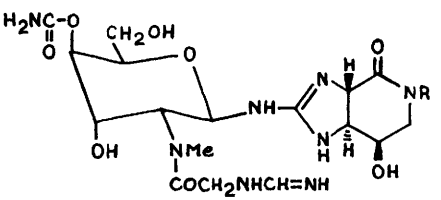
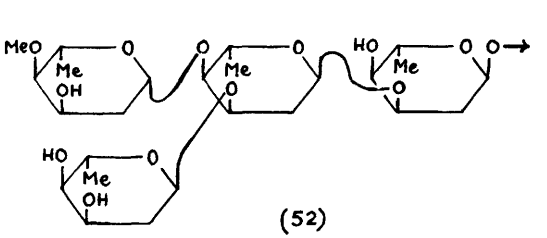


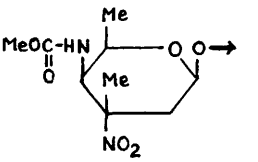
(51) R = H or Me

Streptoverticillium olivoreticuli have been identified as the 2-deoxy-2-N-methylamino-D-gulopyranosylamine analogues of streptothricin (51).[115]

Antibiotic Bu-2545 is a 7-O-methyl ether derivative of lincomycin incorporating N-methylproline rather than 3-propyl-N-methylproline.[116] The complete structure of kiganimicin, a major component of the antibiotic complex elaborated by Actinomadura kiganiata, has been elucidated from degradative,[117] ^{252}Cf plasma desorption m.s., and X-ray crystal structure analysis;[118] the antibiotic contains a polydeoxy tetrasaccharide (52) and the novel amino, branched-chain, nitro sugar (53) attached to a complex tetronic acid nucleus closely related to tetronolide.

Studies directed towards the total synthesis of ezomycins, octosyl acids and related antibiotics have been discussed in a review lecture.[119]





A series of N-glycosylthioureas, rhodanines and 2-amino-thiazoles have been prepared from D-glucose and D-ribose derivatives, of which N-(2,3,5-tri-O-acetyl-β-ribofuranosyl)rhodanine and glucosylamino-thiazole-4-carboxylate showed the broadest spectrum of antibiotic activity.[120]

Analogues of the polyether antibiotics leuseramycin and dianemycin elaborated by S. hygroscopicus TM-531 have been identified; instead of the 4-O-methyl-amicetose present in dianemycin, TM-531B contains amicetose (2,3,6-trideoxy-D-erythro-hexose) and TM-531C the 3-hydroxy analogue, 2,6-dideoxy 4-O-methyl-D-arabino-hexose, not previously found in nature.[121]

Synthesis of fragments of antibiotics from sugars is covered in Chapter 23.

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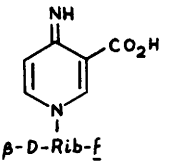
19

Nucleosides

1 General

Clitidine (1), a toadstool toxin, has been characterized by degradation of NAD-analogues prepared enzymatically.[1]



(1)

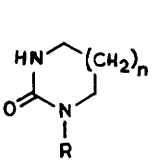
Reviews have appeared on the chemical transformations of sugars in nucleosides,[2] the chemistry of naturally-occuring pyrimidine nucleosides and their analogues,[3] carbohydrate derivatives of purine and pyrimidine,[4] the synthesis and reactions of didehydronucleosides,[5] and the structural elucidation of modified nucleosides from ^{t}RNA by high resolution m.s.[6] In addition, symposium lecture reports have discussed the functionalization of nucleosides, especially 5'-O-sulphonylation[7] and the use of new phosphorylating reagents, and improvements in phosphorylation and tritylation procedures in nucleoside chemistry as applied to the synthesis of minigenes.[8]

2 Synthesis

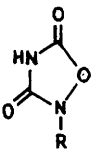
Nucleoside synthesis[9,10] and the Hilbert-Johnson reaction in nucleoside synthesis[11] have been reviewed. Vorbrüggen's group has described the use of trimethylsilyl trifluoromethanesulphonate, perfluorobutanesulphonate, and perchlorate as selective and efficient catalysts in the Hilbert-Johnson condensation of silylated bases and peracyl sugars,[12] and have reported an abbreviated procedure using this approach in a "one-pot" recipe, giving high yields of uridine and adenosine in sample syntheses.[13] The same group has investigated the mechanism of the Hilbert-Johnson reaction, and concludes that initial formation of the glycosyl carbocation is followed by complex formation between base and catalyst,

with consequent glycosidation of the complex.[14]

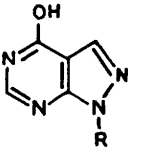
As usual, there have been many reports of new nucleoside analogues prepared using standard glycosyl halide or peracetyl sugar procedures with appropriate bases. These have included N-(β-D-ribofuranosyl) derivatives of cyclic ureas (2),[15] oxadiazole (3),[16]



(2) n = 2-5

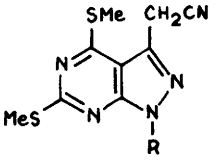


(3)

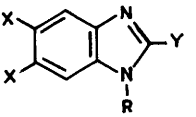


(4) R = β-D-Rib-f

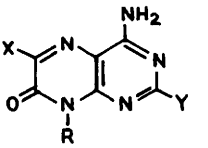
allopurinol (4),[17] pyrazolopyrimidines, e.g., (5) and its N-8 glycosylated isomer,[18] benzimidazoles (6),[19] pteridine (7), (compounds which are photolytically cleaved at the glycosidic linkage),[20]



(5)



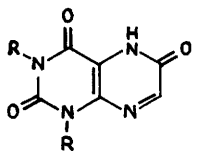
(6) X = H, F, or I
Y = H, Me, or Pr^i



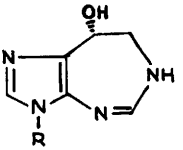
(7) X, Y = H, Ph

R = β-D-Rib-f

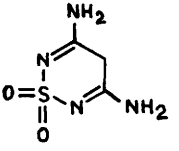
3-deazauracil,[21] and the heterocyclic bases leading to analogues of coformycin (8) and its 2'-deoxy derivative pentostatin.[22] Reaction of 5,6- dihydro-6-oxolumazine (9, R=H) in a peracylsugar-boron trifluoride-catalysed procedure gave the bisribosyl derivative (9).[23] An improved synthesis of nicotinamide ribonucleoside results from using liquid sulphur dioxide as the solvent.[24] Reaction of the 1,2,6-thiadiazine derivative (10) with peracylsugars or corresponding glycosyl bromides gave various glycosyl derivatives linked through C, O, or N, depending on the conditions used.[25]



(9)



(8) R = β-D-Rib-f



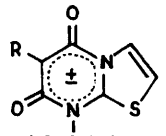
(10)

The synthesis of D-arabino-nucleosides has been reviewed.[26] An enzymic route to D-arabino-purine nucleosides has been described,

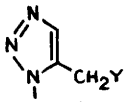
in which 2,2'-anhydro-1-β-D-arabinofuranosyl cytosine was hydrolysed to Ara-C, which was then sequentially converted to Ara-U, D-arabinofuranosyl 1-phosphate and purine D-arabinonucleosides with appropriate enzymes from E. coli, giving overall yields of 60-80%.[27]

A series of hexopyranosyl pyrimidine β-nucleosides have been prepared from D-glucose and D-galactose derivatives, including disaccharide analogues, using the Niedballa-Vorbrüggen procedure. Their ^{13}C n.m.r. spectra were analysed, and the results applied to the disaccharide nucleoside antibiotic, anthelmycin, (see Vol. 11, p. 166) to show that it prefers an anti-conformation.[28] Other papers report the synthesis of β-D-glucopyranosyl derivatives of nitroimidazo-pyridines[29] and 1,2,4-triazines,[30] and L-rhamnopyranosyl derivatives of 2-methoxyadenine[31] and 3-deazaguanine.[32]

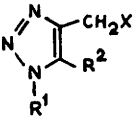
Further examples of nucleosides prepared from glycosyl-nitrogen derivatives have also been reported. Ribosylamine has been used to prepare N-nucleoside analogues of showdomycin, i.e., N-ribosyl derivatives of maleimide, by condensation with substituted maleic anhydrides; the products lacked any in vivo anti-tumour activity.[33] Ribosylhydrazine was converted to the 3-formyl-1,2,4-triazole nucleoside by sequential condensation with a glyoxylic acid iminoester and triethyl orthoformate.[34] Ribose with 2-amino-2,3-dihydrothiazole gave the corresponding glycosylamine which with malonic esters gave mesoionic xanthine nucleosides (11).[35] Benzoylated ribofuranosylazide leads to 1,2,3-triazole nucleosides (12) by cycloaddition with appropriate Wittig reagents ($Ph_3P{=}CHCOCH_2Y$)[36] and analogous products (12a) have been obtained from corresponding D-galactopyranosyl- and D-mannopyranosyl-azides by cycloaddition with alkynyl derivatives.[37] The ribosylenamine (13) has been used



(11) R = H or Et



(12)



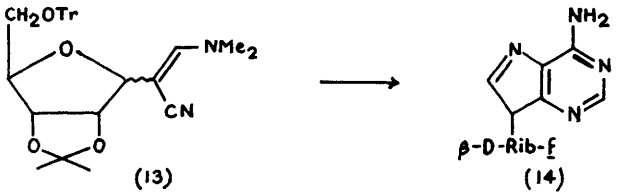
(12a)

R^1 = β-D-Gal-p or β-D-Man-p
R^2 = H or CH_2Cl
X = Cl or Br

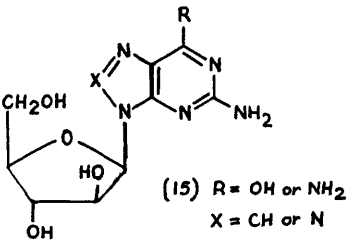
to prepare 9-deaza-adenosine (14) and its α-anomer.[38]

Gylcosyl isothiocyanates have been employed to prepare glycosyl derivatives of 1,2,3-thiadiazole, imidazolidine, and thiazolidine (from D-glucose, D-arabinose, and D-ribose),[39] and 5-thiono-1,2,4-triazolines of D-glucose.[40] Carbocyclic analogues (15) of

arabinosylpurine nucleosides have been prepared from the corresponding (±)-(aminodihydroxycyclopentyl)methanol; some of these

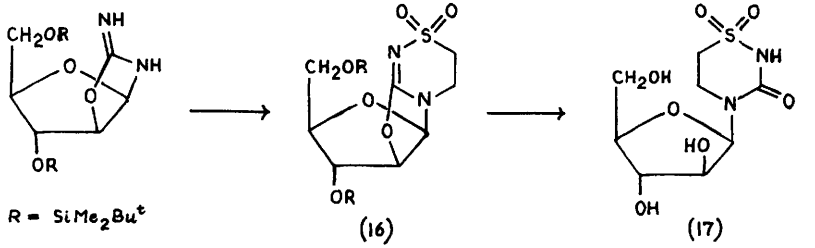


compounds showed cytotoxic or antiviral activity in vitro.[41]



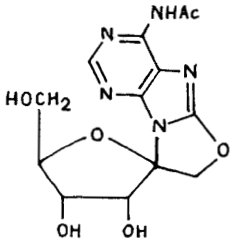
3 Anhydro and Bridged Nucleosides

Treatment of 6-amino-8-chloro-9-(β-D-arabinofuranosyl)-adenine with base gave 2,8-anhydro-adenosine.[42] Another synthesis of 1,2,6-thiadiazine nucleoside analogues mentioned above utilized the anhydro intermediate (16) which was obtained from an imino-oxazoline derived from D-arabinose (See Vol. 12, p. 167) by cyclization with 2-chloroethanesulphonyl chloride; cleavage of the anhydro ring gave the corresponding arabinosyl-uridine analogue (17) (Scheme 1).[43]

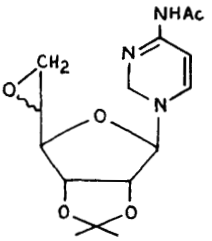


Scheme 1

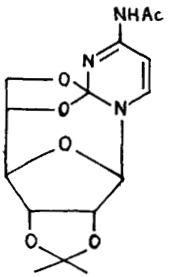
A novel anhydro-adenosine analogue (18) has been prepared from 6-amino-8-bromo-9-(β-D-psicofuranosyl) adenine, in which the base is locked in the syn conformation; the analogous anhydrocytosine derivative was also prepared.[44]



(18)



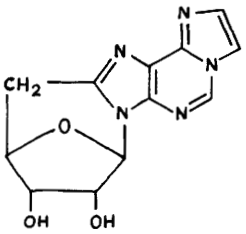
(19)



(20)

Treatment of the isomeric epoxide mixture (19) with boron trifluoride etherate led to the unusual nucleoside (20) containing an intramolecular acetal bridge between the base and the sugar.[45]

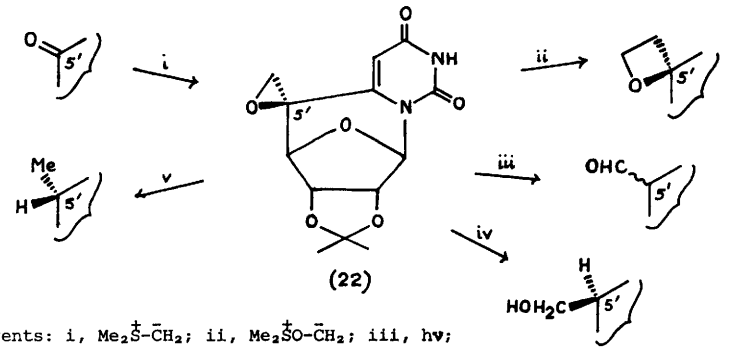
1,N^6-Etheno-5'-deoxy-5'-adenosylcarbalamin formed the corresponding 5',8-bridged derivative (21) with concomitant displacement



(21)

of the cobalamin upon aerobic photolysis.[46] Similarly, formation of a free radical at the 8-position of 5'-deoxyadenosine by standard procedures gave 5',8-cycloadenosine derivatives in high yield; the same products form from 5'-radical attack at the 8-position of the adenine ring.[47]

2',3-O-Isopropylidine-5'-oxo-5',6-cyclouridine has been converted to the spiro-oxiran (22) using a sulphonium ylid, which was used to prepare further derivatives illustrated in Scheme 2.[48]

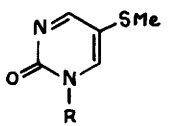


Reagents: i, $Me_2\overset{+}{S}-\bar{C}H_2$; ii, $Me_2\overset{+}{S}O-\bar{C}H_2$; iii, hν; iv, H_2-Pt; v, $LiEt_3BH$

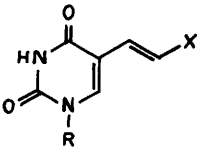
Scheme 2

4 Deoxy Nucleosides

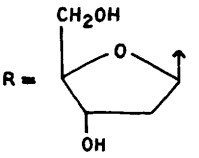
Standard methods have been used to synthesize 2'-deoxy-3-deaza-adenosine and its α-anomer,[49] the anti-viral thiomethyl analogue (23) of uridine,[50] and the haloalkene derivatives (24) of 2'-deoxyuridine.[51] The influence of O-3 and O-5 substituents of 2'-deoxy-D-erythro-pentofuranosyl chlorides on the anomeric ratio



(23)

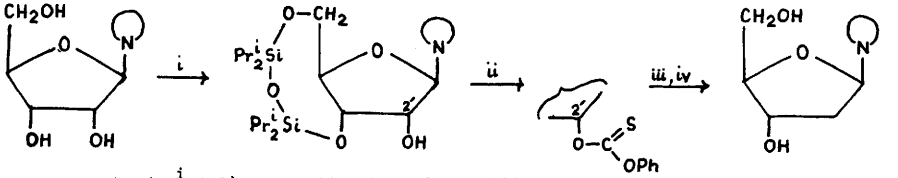


(24) X = Cl, Br, or I



of products in the $SnCl_4$-catalysed condensation with silylated bases has been studied; participation by 3- and 5- ester groups appeared to be of most importance, although steric effects of non-participating groups could also be significant.[52]

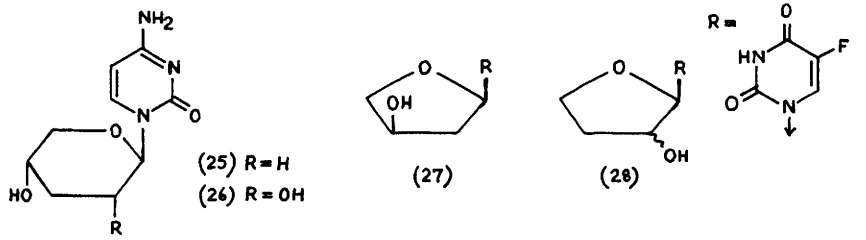
A specific 2'-deoxygenation procedure for ribonucleosides utilizes the new bis(di-isopropylsilyl)oxy group to block the 3',5'-positions, with deoxygenation at C-2' achieved by tributyl-stannane reduction of the 2'-phenoxythiocarbonyl ester derivative; in this way good yields of 2'-deoxyadenosine and 2'-deoxyuridine were obtained from the ribonucleoside (Scheme 3).[53] A related procedure involved similar reduction of a ribonucleoside 2'-thiono-benzoate otherwise substituted with benzoate groups.[54]



Reagents: i, $(Pr^i_2SiCl)_2O$-Py; ii, PhOCSCl-Py; iii, Bu_3SnH; iv, Bu_4NF

Scheme 3

3'-Deoxy and 2',3'-dideoxy derivatives of cytosine have been prepared from corresponding deoxy-pentose derivatives, including pentopyranine B (25) and D (26).[55] The pyrimidine nucleoside analogues (27) and (28) have been prepared by chlorination of



(25) R = H
(26) R = OH

(27)

(28)

3-benzyloxy-tetrahydrofuran and condensation with silylated 5-fluoro-uracil, the products being 3'- and 4'-hydroxy analogues of fluorofur.[56] 5-Fluoro-2'-deoxyuridine [6-^{3}H], which is potently cytotoxic, has been detected as an impurity in a commercial sample of the antitumour agent 5-fluoro-uracil [6-^{3}H].[57] A ribofuranosyl-imidazole derivative has been converted to 5'-deoxy, N-methyliso-guanosine, deoxygenation being achieved conventionally via a 5'-iodo intermediate.[58]

Ionizing radiation degraded 2'-deoxythymidine to 2-deoxy-N-formyl-D-erythro-pentofuranosylamine, which has been studied in detail.[59]

5 Halogenosugar Nucleosides

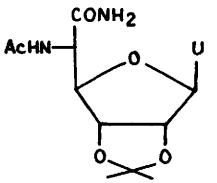
2'-Deoxy-2'-halogeno-guanosines have been prepared by 2'-trifluoro-methanesulphonyl ester displacement sequences on appropriately substituted arabinosyl-guanosine precursors.[60] Treatment of 2,2'-anhydrouridine with labelled sodium iodide yielded 2'-iodo-2'-deoxyuridine [2'-^{123}I].[61] A reinvestigation of the reaction of thionyl chloride with thymidine has shown that the erythro-3',5'-

dichloro derivative is also formed as a minor component besides the threo-isomer previously claimed to be stereochemically pure.[62]

The radiolysis of some halogeno-sugar nucleosides has been studied; solvated electrons both add to the base and eliminate halogen (Br,I) ions from the sugar; the base radical anion formed either induces halogen loss by electron transfer, or undergoes protonation; 2'-Bromo-2'-deoxyuridine gave erythrose (in low yield) on radiolysis in aerated water.[63]

6 Amino-sugar Nucleosides

A bacterial transferase from Erwinia herbicola has been used to convert 2'-amino-2'-deoxyuridine with hypoxanthine or 2-chloro-hypoxanthine to the corresponding 2'-amino-2'-deoxy-inosine derivative and hence to 2'-amino-2'-deoxy-guanosine or -adenosine.[64] 3-Amino-3-deoxy-1,2;5,6-di-O-isopropylidene-α-D-allofuranose has been conventionally degraded to a 3-amino-3-deoxy-ribofuranosyl acetate derivative which was then used to prepare 3'-amino-3'-deoxy-5-fluorocytidine by Niedballa-Vorbrüggen coupling.[65] 3-Azido- and 3-amino-3,4-dideoxy-DL-threo-pentopyranoses have been converted to corresponding adenine nucleoside analogues; the resulting amino-sugar nucleosides only showed weak antiviral activity, however.[66] The Ugi reaction has been used to prepare a derivative (29) of the nucleoside core of the polyoxins.[67] 5-chloropuromycin and hence



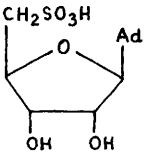
(29)

5'-deoxy puromycin have been synthesized by initial modification of the nucleoside (3-amino-3-deoxy-β-D-ribofuranosyl)-6-N,N-dimethyl-aminopurine, which was then coupled to the amino-acid side-chain through the sugar-amino group conventionally.[68] Trimethyl ammonio derivatives of adenosine have been prepared by methylation of the corresponding 3'- and/or 5'- amino-sugar nucleoside by formaldehyde-borohydride dimethylation and trimethylphosphate quaternization. The presence of the quaternary ion at C-3' rendered an adjacent 2'-O-acetyl particularly labile, being hydrolysed in 12 h at pH 7.5

and 37°C.[69] 5'-Amino-5'-deoxy-inosine and a homologue, (6-amino-2,5,6-trideoxy-β-D-erythro-hexofuranosyl)-thymine, have been converted to a range of amide derivatives at the sugar amino group, giving N-nitrosoureido, bromoacetamido, carbamoyl and phenylsulphonyl compounds; some of these showed some cytotoxic activity.[70]

7 Thio-sugar Nucleosides

A new method for synthesizing analogues of 5'-(methylthio)adenosine involves treating N-methyladenosine with homo-cysteine in the presence of S-adenosylhomocysteine hydrolase; S-methylation of the product followed by acid decomposition gave 5'-(methylthio)-N-methyl adenosine. 5'-(methylthio) formycin was prepared similarly.[71] Conventional halogen displacement of 5'-halo-nucleoside derivatives with sulphur nucleophiles has led to the synthesis of S-adenosyl-1,8-diamino-3-thio-octane[72] and S-(3-deaza-adenosyl)-L-homocysteine.[73] Likewise treatment of halo-sugar nucleosides with sodium sulphite yields the corresponding sugar sulphonic acid derivatives of the nucleosides, e.g., (30).[74] Treatment of 2,6-diamino-8-bromo-9(2-O-tosyl-β-D-ribofuranosyl)



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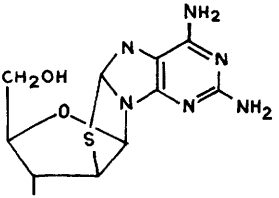
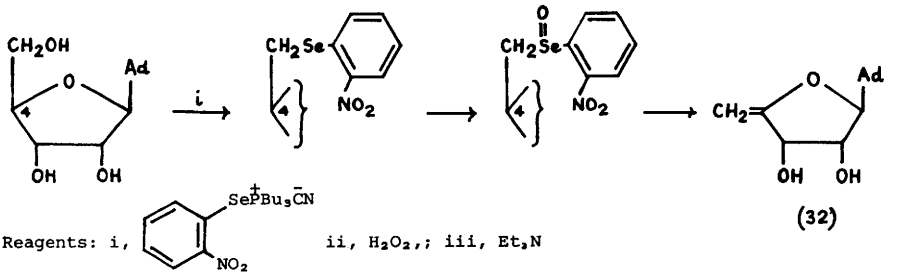


(31)

purine with sodium hydrosulphide in DMF yields the 8,2'-anhydro-thio-nucleoside (31), which can be desulphurized over Raney nickel to give the corresponding 2'-deoxy-2,6-diaminopurine nucleoside.[75]

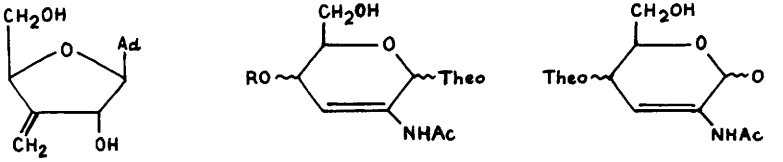
8 Unsaturated-sugar Nucleosides

Adenosine has been converted to the corresponding pent-4-eno-furanosyl nucleoside (32) by a procedure involving selenium intermediates as outlined in Scheme 4.[76] The C-methylene branched-chain nucleoside (33) has been prepared together with its α-anomer from the 1,2-O-isopropylidene derivative of the parent unsaturated sugar by an acyl-sugar, chloromercuriadenine coupling procedure.[77]



Scheme 4

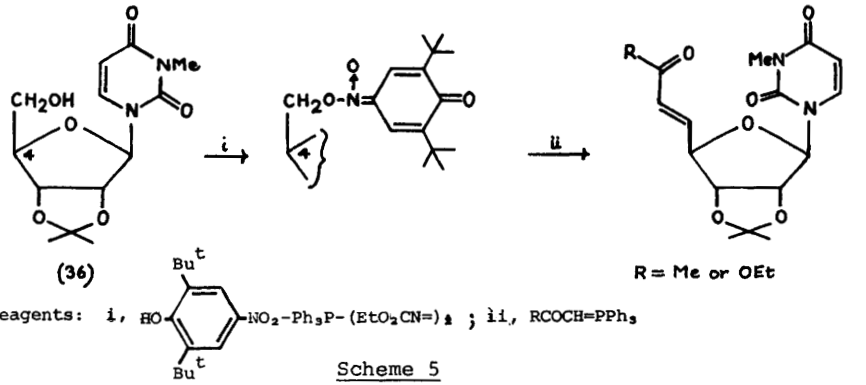
Fusion of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-D-glucal with theophylline in the presence of boron trifluoride etherate, followed by an alcoholic work-up procedure, yielded a mixture of the theophylline nucleoside analogues (34) together with the isomeric 4-theophyllinyl substituted sugars (35);[78] it was subsequently shown that (34) rearranges to (35) in boiling methanol in the presence of boron trifluoride, and a mechanism involving intermediate allylic carbocations with 4→1 intramolecular acetate



migration and subsequent methanolysis was proposed.[79]

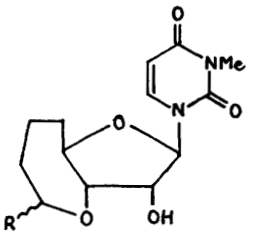
9 Keto-Sugar and Uronic Acid Nucleosides

Glycenosulose nucleosides have been prepared from the N-3-methyluridine derivative (36) (or the O-2 methyl isomer) by reaction of its unstable 5'-acinitroester with a Wittig reagent as outlined in Scheme 5; a high yield of the enone nucleoside was obtained in a one-pot procedure.[80] A similar approach using Wittig condensations has been used for the synthesis of the 3',7'-anhydro-octose nucleosides (37), and a derived octuronic acid nucleoside (38) related to ezomycins and octosyl acids, starting from the dialdose analogue of (36).[81] Esters analogously prepared have been used to prepare diazomethyl ketone nucleosides (39).[82] The enone nucleos-

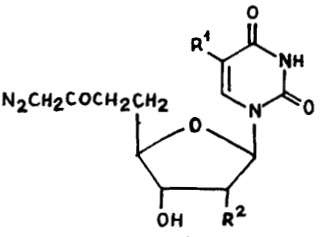


Scheme 5

ides (40) have been synthesized, and shown to have similar anti-leukemic activity to 3-en-2-one analogues previously tested.[83]

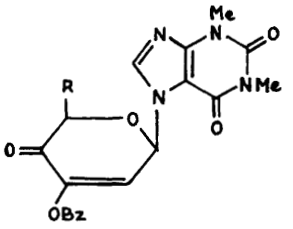


(37) R = Me
(38) R = CO_2H

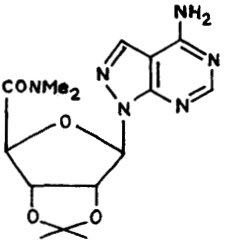


(39) R^1 = H or Me
R^2 = H or OH

Uridine 5'-aldehyde has been coupled to hydrazido-glutaryl or adipinyl-modified sepharose to give sepharose-anchored uridine



(40) R = Me or CH_2OH



(41)

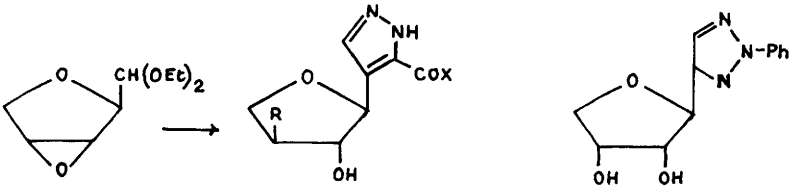
derivatives which are effective as adsorbents.[84]

A conventional coupling sequence has been used to convert D-lyxuronic acid to D-lyxuronamide purine nucleosides,[85] and also to

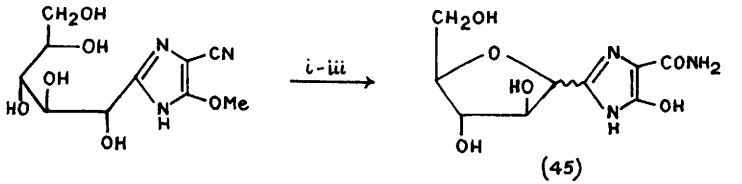
prepare 5-halouracil glucuronic acid nucleosides from corresponding base and acid precursors.[86] Pyrazole and pyrazolo [3,4-d] pyrimidine nucleosides, e.g., (41), have been prepared from the glycosylhydrazone of N,N-dimethyl-D-riburonamide using standard sequences to construct the heterocyclic bases on the hydrazine residue.[87]

10 C-Nucleosides

The synthesis of C-nucleosides has been reviewed (in Japanese).[88-90] 3-(β-D-ribofuranosyl)-6-nitro-indole has been prepared by arylation of a ribofuranosyl bromide derivative.[91] D-Xylose has been used to prepare the branched-chain C-nucleosides (42) via the 2,5-anhydro-sugar oxiran (43), using standard reactions.[92]



Several syntheses utilize cyclization of polyhydroxyalkyl heterocycles. Dehydration of phenylosazones derived from standard hexoses in methanolic sulphuric acid gave the 3,6-anhydro-osazone analogue, which could be converted to the triazole (44).[93] The glycosylamine obtained from D-glucose with diaminomaleonitrile gives a pentahydroxypentylimidazole on DDQ oxidation, which was cyclized to the D-arabinose C-nucleoside (45) as indicated in Scheme 6.[94] Buchanan's group has reported the synthesis of 3-α-



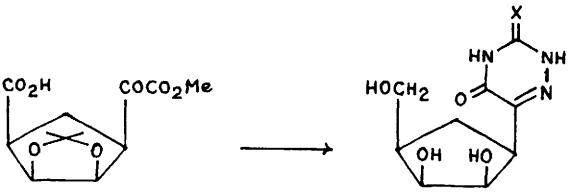
Reagents: i, $HOAc\text{-}EtOCH_2CH_2OH\text{-}150^{o}$; ii, $KOH\text{-}Bu^{t}OH$; iii, Me_3SiCl

Scheme 6

and 3-β-(D-xylopyranosyl)pyrazoles in a multistep sequence from D-gulonolactone, generating 3-(D-gulo-pentahydroxy-pentyl)pyrazole

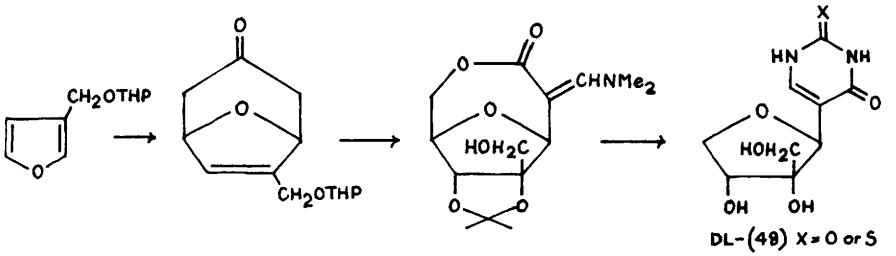
by sequential reaction with lithium acetylide and hydrazine, followed by cyclization utilizing 2-O-mesyl derivatives.[95]

The classical cyclopentadiene-maleic anhydride Diels-Alder adduct has been used to prepare the cyclopentane dicarboxylic acid derivative (46) by standard conversions, which was then elaborated to give the 1,2,4-triazine nucleoside analogues (47).[96] Further



DL-(46) DL-(47)

application of the cyclo-coupling reaction of 1,1,3,3-tetrabromopropanone with furan derivatives (see Vol. 13, p. 186) has yielded the pseudo-uridine analogues (48) derived from the branched-chain sugar hamamelose by the route outlined in Scheme 7.[97]



DL-(48) X = O or S

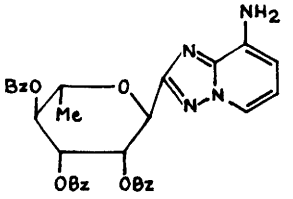
Scheme 7

The conversion of thio-imino-esters derived from glycosyl cyanides to heterocycles has been employed to prepare a series of 1,2,4-triazolo [1,5-a] pyridine C-nucleosides from L-rhamnose, e.g., (49),[98] and S-triazolo [4,3-b] pyridazine C-nucleosides (50).[99]

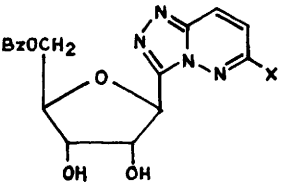
Aldoses condense with β-aminovinylcarbonyl compounds such as 2,6-diamino-4-pyrimidone or 6-aminouracil to give moderate yields of C-glycosides, e.g. (51).[100]

Oxazinomycin has been converted to its 2'- and 5'-deoxy analogues (52) by standard deoxygenation procedures.[16] Likewise ψ-uridine has been converted to 2'-deoxy-ψ-isocytidine and 2'-deoxy-1-methyl-ψ-uridine.[101]

Alkaline hydrolysis of the ψ-thymine analogue (53) yielded the

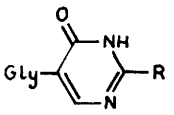


(49)

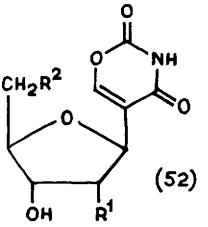


(50)

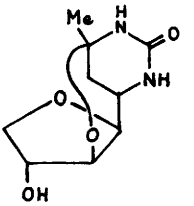
cyclic anhydro derivative (54).[102]



(51) R = OH or NH_2



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



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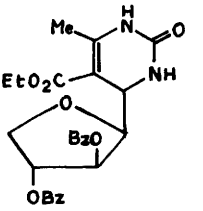
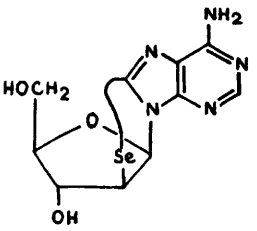


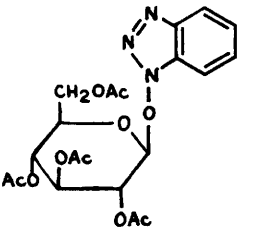
(53)

11 Miscellaneous Nucleoside Analogues

Treatment of 8-seleno-adenosine with 2-acetoxyisobutyryl chloride



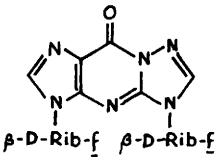
(55)



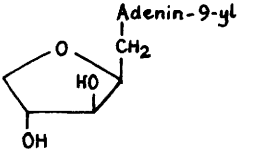
(56)

in acetonitrile yielded the cyclonucleoside (55).[103]

Reaction of N-hydroxy compounds with glycosyl bromides or related glycosyl reagents yielded O-glycoside nucleoside analogues, e.g., (56).[104] The double-nucleoside (57) was obtained from the parent nucleoside by stannic chloride-catalysed reaction with peracetylated ribofuranose.[105]



(57)



(58)

Reaction of standard nucleoside bases with 5-chloro-5-deoxy-1,4-anhydro-DL-xylitol yields corresponding homo-nucleoside analogues, e.g., (58).[106]

12 Nucleoside Phosphates

As usual, routine synthesis of nucleotides is not covered.

Selective O-5' phosphorylation of thymidine can be achieved using bis(2,2,2-trichloro-1,1-dimethyl-ethyl)phosphorochloridate, the blocking ester groups being cleaved efficiently using a cobalt-phthalocyanine complex.[107] New methods for phosphorylating suitably blocked nucleosides include the use of p-chlorophenyl, (2-cyanoethyl)phosphorochloridate,[108] methyl N,N,-dimethyl-phosphoramidochloridite,[109] arylphosphorodichloridates in the presence of 1-hydroxybenzotriazole,[110] and 4-nitrophenyl, 4-morpholinyl phosphorochloridate,[111] each of which give esters readily converted to simple phosphates or intermediates for dinucleotide synthesis.

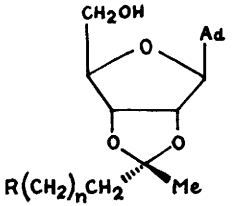
13 Acetal and Ester Derivatives

Treatment of nucleosides with o-nitrophenyldiazomethane in the presence of stannic chloride resulted in 1:1 mixtures of photo-labile 2'- and 3'-O-(o-nitrobenzyl) ether derivatives, the primary 5'-position being unsubstituted.[112] Methylation of nucleosides using trimethyl phosphate or dimethyl sulphate in the presence of boric acid led to base-substituted derivatives, the boric acid inhibiting ribose O-methylation.[113] Methylation using methanolic diazomethane in the presence of stannous chloride proceeds via a

2-stanna-1,3-dioxolan complex, which leads to a mixture of 2'- and 3'-O-methyl derivatives.[114] The tritylation of nucleoside 3'-phosphates is referred to in Chapter 4.

Conditions have been described for the selective 3'-silylation of 5'-substituted nucleosides using tert-butyldimethylsilyl chloride.[115] Isomerization occurs between 2'- and 3'-O-tert-butyldimethylsilyl ethers in protic solvents, and the kinetics and equilibria have been studied under a variety of conditions.[116] The rearrangement of 3',5'-tetraisopropyldisiloxane derivatives of nucleosides to 3'-mono-silyl ethers is mentioned in Chapter 4 (ref. 27).

2',3'-O-Alkylidene acetals prepared from adenosine and unsymmetrical ketones have been separated into R- and S- forms, the former predominating, and then used as stereochemical probes for the active site of adenosine deaminase; the R-isomers, e.g., (59), were much more strongly bound than the S-forms.[117] 2',3'-O-[1-(2-



(59) R = Me, CO_2H, or CO_2Et
n = 1-3

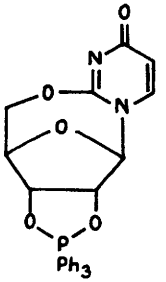
carboxyethyl)ethylidene]xanthosine, prepared from xanthosine and ethyl 4-oxovalerate, has been coupled through its carboxylic acid group to 6-aminohexylagarose to give a polymer useful for affinity chromatography of guanine aminohydrolase.[118]

5'-O-Glucopyranosyl-inosine has been prepared conventionally from the corresponding disaccharide and heterocyclic base,[119] and 5'-O-glucuronides of the anti-cancer nucleosides 5-fluorouridine and 5-fluorocytidine have also been synthesized by several alternative standard methods, giving products showing only weak activity against leukaemia cells.[120]

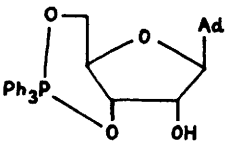
14 Reactions

The reactions of nucleosides with diethyl azodicarboxylate and triphenylphosphine have been studied. Uridine gave the triphenylphosphoranediyl anhydronucleoside (60), whereas adenosine gave the 3',5',-cyclic phosphorane (61); differences in products were attributed to different acidities of the bases.[121] The formation

of epoxides using this reagent mixture is mentioned in Chapter 4.



(60)



(61)

N-Acyl groups in acylated nucleoside derivatives can be selectively removed with zinc bromide in the presence of alcohols to give O-protected nucleosides.[122]

An interesting study of the effects of sugar structure on the rates of acid-catalysed hydrolysis of adenine nucleosides has been reported; the A-1 mechanism was indicated, and rates were found to be dependent on steric interactions, the inductive effects of hydroxy groups, and the reverse anomeric effect.[123] Protolysis constants for adenine, adenosine, AMP, ADP and ATP in aqueous sodium perchlorate have been determined, and related thermodynamic parameters were calculated.[124]

Adenosine undergoes homolytic cleavage of the glycosyl bond on treatment with benzene diazonium ion.[125]

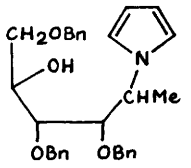
The greater ease of electrochemical reduction of uridine than uracil in DMSO has been attributed to the electron-withdrawing effect, and possible steric hindrance, of the ribose ring, which markedly effects the reaction sequence following initial one-electron reduction to the base radical anion.[126]

The reaction of O-benzylated ribonucleosides of pyrrole and adenine with Grignard reagents has been studied, following an earlier report of 1,2-trans ⟶ 1,2-cis-furanosides by this procedure; whereas tert-butyl magnesium bromide caused anomerization (β:α,2:1 ratio) with the pyrrole nucleoside, methyl magnesium iodide gave the ring-opened product (62), and the adenine analogue underwent 2-O-debenzylation with both reagents to give (63).[127]

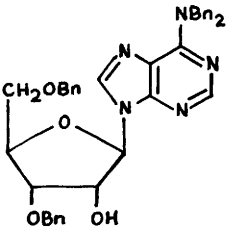
15 Conformational, Spectral and Theoretical Aspects

The conformational properties of nucleosides and nucleotides have

been reviewed.[128] The pseudo-rotation of furanoses has been examined in terms of a three-state conformational equilibrium, involving n(C3'-endo), s(C2'-endo) and e(O1'-endo) forms, and the model was used to estimate puckering populations of nucleic acid analogues in conjunction with n.m.r. J values; the e domain becomes important in certain derivatives which contain bulky substituents on the base, leading to syn-glycosyl arrangements.[129]



(62)



(63)

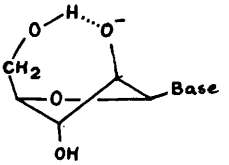
High resolution (270 MHz) ^{1}H n.m.r. measurements have been made on tetrahydrofuranylmethanol, methyl β-D-ribofuranoside and its 2-deoxy analogue and on their 5-phosphates, as models for nucleosides and nucleotides. The models preferred the C-3 endo form to the C-2 endo form found in nucleosides and nucleotides, and also adopt different rotamer states about the C-4/C-5 bond, but the phosphates show similar rotamer states about the C-5/O-5 bond to those found in nucleotides.[130] The conformational equilibrium of the ribose ring in nucleosides has been studied by signal broadening in the ^{13}C n.m.r. of C-1' and C-4' in their complexes with Mn(II).[131]

The formation of an intramolecular hydrogen bond between O-2 and the 2'-hydroxy group in pyrimidine nucleosides, which stabilizes the 3'-endo conformation, has been confirmed from an analysis of coupling constant data.[132] Another study examined the rotational isomerism about the glycosidic bond of pyrimidine nucleosides from chemical shift and coupling constant measurements, which suggested a dependance of rotamer population on the electronegativity of substituents in the carbohydrate ring;[133] a further paper deduces syn conformations for a uracil-3-yl nucleoside analogue and a related imidazolidione derivative.[134]

A study of syn and anti conformations in ribo- and 2'-deoxyribo-nucleosides and nucleotides from ^{1}H n.m.r. relaxation measurements indicate a preference for the anti-state in 5'-

nucleotides, and also in pyrimidine nucleosides and 3'-nucleotides, while for purine nucleosides the populations of the two states are almost the same.[135]

A ^{13}C-n.m.r. study of uridine and cytidine in the sequence of solvents DMSO, D_2O, DMF, $(MeO)_3PO$, methanol and pyridine revealed a steady shift away from the 3'-endo (anti) conformation in the above order, the population being greatest in DMSO and least in pyridine.[136] Changes in the conformations of 1-β-D-arabinofuranosyl cytosine and its O'-methyl derivatives induced by hydroxy group ionization in strong alkali have been probed by ^{13}C n.m.r. The data confirmed earlier ^{1}H n.m.r. evidence suggesting that enhanced hydrogen bonding from the 5'-hydroxy group to an ionized 2'-oxygen caused the shift in the C-2'-endo⇌C-3'-endo equilibrium in favour of the former, as indicated in (64).[137] α-L-Arabinofuranosyl nucleo-



(64)

sides have also been studied in the same laboratory; the equilibrium between ^{2}E⇌^{3}E states was dependent upon the aglycone and type of hydroxy protecting group, giving ^{3}E populations in a 16-89% range; this conformer was also associated with a high gauche-gauche rotamer about the C-4'/C-5' bond.[138]

The ^{13}C n.m.r. spectra of various 2'-substituted 2'-deoxyadenosines have been fully assigned, and the ring carbon chemical shifts discussed.[139] The ^{15}N n.m.r. data for 5-azacytidine have been reported,[140] and the ^{1}H n.m.r. spectra of S-adenosyl-L-methionine and S-adenosyl-L-homocysteine recorded at 360 MHz.[141]

High-pressure, high-resolution n.m.r. has been used to derive the activation volume for the syn⇌anti rotation in 6,7-diphenyl-1-β-D-ribofuranosyl-lumazine.[142] Other n.m.r. studies on nucleosides are mentioned in Chapter 20.

Data from crystal structures of 127 nucleosides and nucleotides have been compared with results of a circular correlation analysis. It was concluded that conformational changes of nucleosides and nucleotides are concerted.[143]

Laser Raman spectra of nucleic acid components, including nucleosides, have been recorded, using a surface enhanced technique with

the compounds absorbed at a silver electrode. Frequencies were correlated with normal solution spectra, but intensities were enhanced.[144]

C.d. and magnetic c.d. spectra of cytidine and uridine derivatives have been measured, their spectroscopic parameters calculated, and spectral assignments made; the tautomerism of these compounds was discussed from the results.[145]

Cytosine, adenine and the corresponding nucleosides have been examined by pulsed laser and fission fragment-induced desorption m.s.; no striking differences were observed between the two types of spectra.[146] Secondary ion m.s. of pyrimidines, purines and their nucleosides have also been recorded; intense peaks derived from molecular ions were observed, but only a few fragment ions appeared, resulting from simple bond cleavages.[147] The m.s. of deuteriated monosibyl derivatives of 2'-deoxyribonucleosides have been measured in order to study the stereochemistry of water elimination; a 6-membered cyclic transition state was proposed, involving a sugar hydroxy group and a proton in the nucleobase.[148] Other papers report m.s. of trialkylsilyl and acyl derivatives of 2'-deoxynucleosides, which give detailed information on isomeric substitution patterns,[149] and C.i. desorption m.s. of a series of glucopyranosyl and ribofuranosyl pyridinium salts.[150]

A molecular orbital study of 3'-deoxyadenosine (cordycepin) and 3'-amino-3'-deoxyadenosine has been carried out; the results suggest that these nucleosides have very similar conformational preferences, and differ considerably from those of adenosine, especially in aqueous solution, which may have important biological significance.[151]

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20
N.m.r. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

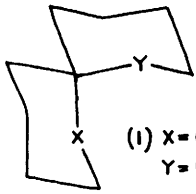
The provisional recommendations of the IUPAC convention for the conformational nomenclature of five- and six-membered ring forms of monosaccharides and their derivatives have been published.[1]

Reviews have been published on the following topics: rules and exceptions for nucleotide conformations;[2] the conformational properties of nucleosides and nucleotides;[3] ^{13}C-n.m.r. of isotopically enriched carbohydrates;[4] ^{13}C-n.m.r. of aminoglycoside antibiotics;[5] and the application of 500 MHz ^{1}H-n.m.r. to the structure determination of carbohydrates derived from glycoproteins.[6]

The room temperature distribution of hydrogen bond geometries has been predicted by a Monte Carlo calculation using an empirical potential energy function. The results are compared with those from crystal structure determinations. The lengths of the hydrogen bonds were predicted with an r.m.s. deviation of 0.06Å and the O-H---O bond angles with an r.m.s. deviation of 9°. The analysis showed that the shorter the hydrogen bond the closer to 180° the bond angle became.[7]

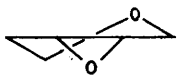
Ab initio RHF/4-31G molecular orbital calculations on 1-methoxyethanol as a model for the anomeric effect showed that the negative synclinal orientation of a β-OH anomer is favoured over the positive synclinal conformation by 4.2 kJ mol^{-1}, a result consistent with the exo-anomeric effect and practical results from X-ray crystal structure determinations. A value for the anomeric effect of 8.4 kJ mol^{-1} was obtained. Application of the same method to 1-methoxyethanediol as a model for the Δ2 effect gave anomeric differences in energy of 5 - 8.4 kJ mol^{-1}. In all cases bond length predictions accorded well with observed values.[8] The anomeric and exo-anomeric effects have been studied using a quantum-chemical PCILO method applied to 2-methoxytetrahydrofuran. Values of 3 kJ mol^{-1} for the former, and 6 kJ mol^{-1} for the latter (axial conformer) or 7 kJ mol^{-1} (equatorial conformer) were predicted.[9] Changes in the position of oxygen signals in ^{17}O-n.m.r. spectra due to anomeric effects have been examined by means of 2-alkoxytetrahydropyrans. The axial anomers gave upfield signals for both ring and glycosidic oxygen atoms.[10] The conformations of spiro-

heterocyclics of type (1) have been rationalized by consideration of the anomeric and exo-anomeric effects.[11]

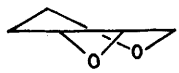


(1) X = O or S, Y = O or S

An analytical approach for the description of the ring puckerings using endocyclic ring torsion angles of a five-membered saturated ring, independent of any reference conformation, has been suggested, together with a revised notation system for such torsion angles.[12] The pseudorotation of furanose derivatives has been considered in terms of a three-state conformational equilibrium. The states used were those describing C-3'-endo, and C-2'-endo, together with the more unusual O-1'-endo conformations, the latter being important in the description of nucleic acids with large substituents in the heterocyclic base, i.e., those giving synclinal arrangements. The model was used to predict the puckering populations of nucleic acid analogues.[13] Some important improvements in the relationship between J_{vic} and the pseudorotational properties of the sugar ring in nucleosides and nucleotides have been claimed by authors who have included orientation and electronegativity effects in a new generalized Karplus equation. Accurate correlation with parameters governing conformation obtained by 178 crystal structure determinations was obtained.[14] Computer fitting employing the LEQUOR variation of the LAOCOON/III program , for ^{1}H-n.m.r., of the conformational equilibria of 3,4-epoxytetrahydrofuran and its 2,2,6,6-tetradeuterio-derivative, using cis- and trans-2-tert-butyl-4,5-epoxytetrahydropyran as models, has shown that the two half-chairs (2) and (3) differ by 34.3 kJ mol^{-1}, with (2) predominating.[15]



(2)



(3)

The pD dependence of the mutarotation of N-acetyl-D-neuraminic acid has been studied by n.m.r. It has a minimum at pD 5.4, and below pD 1.3 or above pD 11.7 it is too fast to measure.[16]

Gadolinium(III) trinitrate-inositol in molar equivalence is an effective paramagnetic relaxation reagent in highly polar media. The reagent has been assessed for spin-lattice relaxation, N.o.e., and line/width values in DMF.[17] Double Fourier transform n.m.r. methods have been applied to D-glucose, D-galactose, D-fructose, sucrose, melibiose, and raffinose to obtain otherwise inaccessible ^{1}H- and ^{13}C-chemical shifts, which may be thus obtained simultaneously.[18] Zero-quantum transition two-dimensional n.m.r. spectroscopy (ZQT-2D) has been used on tetra-O-(trideuterioacetyl)-α-D-glucpyranoside to show that it gives a better description of spin systems than its single quantum transition counterpart.[19] The relative orientations and electronegativities of substituents have been used to predict $^{3}J_{(aa)}$, $^{3}J_{(ae)}$, and $^{3}J_{(ee)}$, coupling constants and hence to derive a simple additivity rule for anti and gauche vicinal ^{1}H-^{1}H coupling constants in pyranose rings.[20]

2 Acyclic Systems

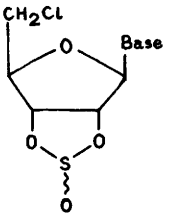
Correlation of ^{13}C-n.m.r. and ^{1}H-n.m.r. data of some di-O-benzylidene derivatives of L-iditol has enabled determination of the configuration and conformation of these compounds.[21] Esterification shifts in ^{13}C-n.m.r. spectra for C-1 and C-6 of 3,4-di-O-tosyl-D-mannitol were found to be unusually high, e.g., a deshielding of 13.5 p.p.m. upon full acetylation, and 12.7 p.p.m. upon full benzoylation was noted.[22]

3 Furanose Systems

A comparison of the conformation of ethyl 2-S-ethyl-1,2-dithio-α-D-mannofuranoside as determined by ^{1}H-n.m.r. and by X-ray crystal structure showed a poor correlation and attempts to fit a Karplus equation to the crystal structure were unsuccessful. The differences were ascribed to the differing strengths of hydrogen bonds in solid and solution states.[23] Comparisons of published ^{13}C-n.m.r. chemical shifts for all unsubstituted carbons of α- and β-D-glucosides and -galactosides have shown that they may be used to determine both anomeric configurations and ring-sizes.[24]

Examination of the 270 MHz ^{1}H-n.m.r. spectra of tetrahydrofuranylmethanol, methyl β-D-ribofuranoside, and methyl 2-deoxy-β-D-erythro-pentofuranoside and their 5-phosphates as models for nucleosides and nucleotides, has shown that C-3' rather than C-2'

prefers the exo-planar conformation, that the models are not good analogues for prediction of the rotameric state about C-4 and C-5 of nucleosides and nucleotides, but that they are useful in predictions of the C-5,O-5 rotamer populations.[25] Constants for the equilibrium between the syn and anti conformations of ribo- and 2-deoxy-ribo-nucleosides and -nucleotides in solution have been determined from a ^{1}H-n.m.r. relaxation study. It was concluded that the anti-state predominated in 3'- and 5'-nucleotides and in pyrimidine nucleosides, while for purine nucleosides the equilibrium constant was close to unity.[26] Solvent shifts for DMSO, D_2O, DMF, trimethylphosphate, methanol, and pyridine showed that there was progressive conformational change in uridine and cytidine away from 3'-endo(N)(anti) in the solvent order given, i.e., more of this conformer was present in DMSO, less in pyridine.[27] The ^{13}C- and ^{1}H-n.m.r. spectra of three anomeric pairs of 2',3'-O-isopropylidene-imidazole and -uracil nucleosides, analysed as an overlapping ABX system, have shown that the method may be used to identify α- and β-anomers.[28] Signal broadening in ^{13}C-n.m.r. of C-1' and C-4' of the ribose ring of nucleosides caused by complexation with manganese(II) ions has been used to study the conformational equilibria.[29] A significant downfield shift for the appended carbon atom results upon glycosylation of a hydroxy group of a ribose nucleoside. Together with the smaller upfield shifts of the adjacent carbon atoms, this provides a means of determining the position of glycosylation and differentiation of the type of linkage involved. The method was used to show that the products of enzymic galactosylation of uridine, inosine, and adenosine were all 1→3 linked.[30] Epimeric 2',3'-cyclo-sulphites of nucleosides (4) have a barrier to inversion about the sulphur atom of 180 kJ mol^{-1}. The epimer with the (S)-configuration had a positive optical rotation while that of tht (R)-configuration was negative.[31] An analysis by ^{1}H-n.m.r. of α-L-arabinofuranosyl nucleosides, together



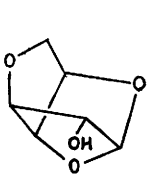
(4)

with some theoretical studies, shows that a conformational equilibrium exists between $^{2}\underline{E}$ and $^{3}\underline{E}$ states. The populations of each depend upon the aglycone, the hydroxy protecting groups, and the solvent. The $^{3}\underline{E}$-state was associated with a preponderance of the gauche-gauche rotamer, which was very minor in the $^{2}\underline{E}$-conformer.[32]

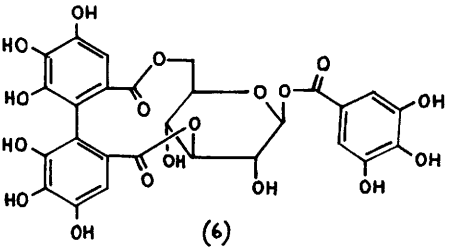
Adenylyl-(3',5')-adenosine has been studied in aqueous solution, and by means of model compounds, using c.d. Some influences important in determining conformation were discussed.[33]

4 Pyranose Systems

Application of the INDOR n.m.r. method to some monosaccharides has shown that β-L-arabinopyranose, α-D-xylopyranose, α-D- and β-D-mannopyranose all exist in the $^{4}\underline{C}_{1}$ conformation, whereas α-L-rhamnopyranose adopts the $^{1}\underline{C}_{4}$ conformation.[34] A $^{4}\underline{C}_{1}$ conformation is present in the crystal state of 2-deoxy-β-D-arabino-hexopyranose at -150°,[35] and in the solution state of both anomers of methyl (methyl D-galactopyranosid)uronates and their acetates.[36] The X-ray crystal structure and ^{1}H- and ^{13}C-n.m.r. spectra of 1,4:3,6-dianhydro-α-D-glucopyranose (5) (obtained by pyrolysis of cellulose) show that the pyranose ring is in a much strained $\underline{B}_{4,1}$ (D) conformation. Although the conformation is necessarily rigid, and hence very similar in both solution and solid states, the Karplus equation gives a poor fit with the experimental data.[37]



(5)



(6)

All carbon signals in the ^{13}C-n.m.r. spectrum of corilagin (6) and some of its methylated derivatives have been assigned and the analysis extended to geraniin.[38]

^{13}C-N.m.r. data on 5-thioaldopyranoses, 1-thiopyranosides, and their peracetylated derivatives have been collected. Both anomers of the 5-thioaldopyranosides have comparable $^{1}J_{(C-1,H-1)}$ values to those in normal β-glycosides, while those in α-glycosides are characteristically about 10 Hz larger. A "γ-anti-effect", was

demonstrated, in which an oxygen atom, but not a hydrogen, chlorine, sulphur, or hydroxymethyl substituent, situated antiperiplanar to a γ-carbon atom promotes increased shielding of that carbon atom, and the effect was shown to be larger for C-5 than C-3 when the atom concerned is the glycosidic oxygen.[39] Anomeric distortions in methyl 4,6-O-benzylidene-hexopyranosides have been examined by i.r. methods.[40] Certain methyl 4,6-O-benzylidenated glycosides with a cis-arrangement of potential donor groups chelate lanthanide shift reagents well. The induced ^{1}H-n.m.r. shifts were calculated using an approximate model which was then used to predict the rotamer populations of the glycosidic methoxyl group.[41] The assignments of the 2-, 3-, and 4-O-acetyl methyl proton signals in the ^{1}H-n.m.r. spectra of some acetylated methyl D-glucosides have been made by utilizing the crossover phenomenon induced by lanthanide shift reagents.[42]

5 Oligosaccharides and Other Macromolecules

A review of the n.m.r. of natural macromolecules including oligo- and poly-saccharides and oligo- and polynucleotides has appeared.[43]

^{13}C-N.m.r. data for all possible α- and β-(1→2)-, (1→3)-, and (1→4)-xylobioses, together with many model compounds has been published.[44] ^{1}H- and ^{13}C-N.m.r. data for the six hexa-O-acetyl reducing disaccharides composed of D-xylopyranose units have been obtained. The effect of the removal of one acetyl group and of its replacement by monochloroacetyl group on chemical shifts was determined and discussed.[45] Measurements of line-widths and chemical shifts of water in aqueous solutions of sucrose under various conditions of temperature and concentration have confirmed that the former increases with concentration of sucrose while the latter shifts downfield, thus showing the existence of multiple hydrogen bonds.[46] Temperature and solvent induced chemical shifts in ^{13}C-n.m.r. spectra of cello- and malto-oligosaccharides in water have been collected.[47] The effects of tritylation at C-6 or 6' on the conformation of interglycosidic linkages in methyl β-maltosides[48] and cellobiose[49] have been examined. Reference to the use of the methyl glycosides of galactomannans as models for ^{13}C-n.m.r. of the polysaccharides obtained from Trypanosoma cruzi protozoa will be found in Chapter 3. The ^{13}C-n.m.r. spectra of the 6-aminohexyl glycosides of β-D-glucopyranose, O-β-D-galactopyranosyl-(1→3)-, and -(1→6)-N-acetylglucosamine, and O-β-D-galactopyranosyl-(1→4)-

D-glucosamine have been determined.[50]

The trisaccharide structures of two O-β-D-glucopyranosyl-(1→3)-O-4-O-acetyl-α-L-rhamnopyranosyl-(1→6)-O-β-D-galactopyranosyl flavanols have been obtained by means of ^{1}H- and ^{13}C-n.m.r. spectroscopy, the relatively large T_1 values of the glucoside moiety being used to locate it as the terminal residue.[51] The ^{13}C- and ^{1}H-n.m.r. signals of α-, β-, and γ-cyclodextrins in DMSO have been assigned.[52]

Complete assignments of ^{13}C-n.m.r. spectra for streptomycin and dehydrostreptomycin in 30% aqueous solutions at pH's between 1.0 and 7.0,[53] and for neomycin B and its 3'-phosphate, monomycin A and kanamycin A in 25 - 28% solutions at pH's from 1.0 to 10.0 have been made.[54] ^{13}C-Glycosidation shifts were used to assign the L-configuration to the sugar unit in the triterpenoid arabinosides obtained from Lycopodium inundatum.[55] All but four of the 66 carbon atoms in vancomycin have been assigned in the ^{13}C-n.m.r. spectrum.[56] A detailed assignment of the ^{13}C-n.m.r. signals of ristocetins A and B and several derivatives has enabled definition of hitherto doubtful configurations at anomeric carbon atoms, and has paved the way for ^{13}C biosynthetic studies.[57] Selective deuteration has assisted signal assignment in the ^{13}C-n.m.r. spectra of dammarane-saponins of Panax notoginseng.[58] A number of cardenolide glycosides, including digitoxigenin analogues have been examined by ^{13}C-n.m.r.[59]

6 Glycopeptides

Natural abundance ^{13}C-n.m.r. spectroscopy has been applied to D-galactopyranosyl and 2-acetamido-2-deoxy-D-galactopyranosyl glycopeptides,[60] α-D-mannopyranosyl and α-L-arabinofuranosyl glycopeptides,[61] and D-glucopyranosyl glycopeptides.[62]

7 Other Nuclei

The ^{15}N-n.m.r. of 5-azacytidine has been reported.[63]

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21

Other Physical Methods

1 I.r. Spectroscopy

Further infrared studies of methyl 4,6-O-benzylidenehexopyranosides have considered molecular conformations,[1] and low frequency (20-400 cm^{-1}) Raman examinations of aqueous solutions of uridine, cytidine, guanosine and adenosine have led to assignments of bands below 100 cm^{-1}.[2]

2 Mass Spectrometry

A comprehensive review with 341 references has appeared,[3] and other reviews on middle mass molecules (10^3-10^4 Daltons)[4] and applications of the Field Ionization technique (in Italian)[5] have also been published.

Two studies[6,7] of the application of combined h.p.l.c.-mass spectrometry to mono- and di-saccharides have been described, the former including work on nucleosides.

Secondary ions produced from glucose, fructose, sucrose, lactose and raffinose by different methods have been compared,[8] and electron impact studies on 1,6-anhydro-dideoxy-β-D-hexopyranoses with deuterated samples have allowed structural characterization and also stereochemical assignments at C-3.[9]

Permethylated compounds have been examined as follows: differently linked L-rhamnose di- and tri-saccharides,[10] various di-, tri- and tetra-saccharides (to establish methods for determining linkages present)[11] and permethylated saccharides as sources of the ion with m/e = 101 $(C_5H_9O_2)^+$.[12] Stereoisomeric permethylated disaccharides can be characterized from their chemical ionization spectra using both ammonia and trimethylamine as reagent gases.[13]

The mass spectra derived from sucrose by laser-desorption, electron impact and flash desorption have been compared.[14] A useful method of extending the available mass range for the

examination of oligosaccharides by the field desorption method involves generation of $(M + Ba)^{2+}$ ions.[15]

Field desorption studies on phenyl, phenyl-1-thio, and nitrophenyl hexopyranosides showed that good molecular ions could be produced without derivatization and that simple fragmentation at the anomeric centre occurred. α- And β-isomers can be distinguished - especially with the p-nitrophenyl compounds.[16] Similar examinations of oligoglycosidic saponins by proton-induced fragmentations showed that cleavages were similar to those induced by acidic hydrolysis.[17]

The e.i. spectrum of methyl 3,4-di-O-acetyl-2-O-(methyl 2,3,4-tri-O-acetyl-α-D-galactopyranuronate)-β-L-rhamnopyranoside has been discussed,[18] as have the negative ion desorption chemical ionization spectra of some underivatized steroidal glucuronosides. With hydroxide as reactant ion, $[M-H]^-$ and $[steroid-O]^-$ ions were produced abundantly.[19]

Significant differences in the intensities of corresponding ions were found in the chemical ionization mass spectra of isomeric dimethylacetals and diethyldithioacetals of aldo-pentoses and -hexoses.[20]

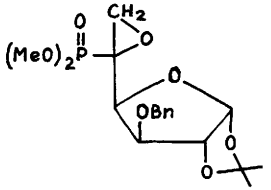
The mass spectra of 2-thiouridines show prominent $[base + 41]^+$ ions following capture of formaldehyde.[21] Other aspects of the mass spectrometry of nucleosides are described in additional papers.[22-25] Spectra of di-N-acetyl-tri-O-methyl-2-deoxystreptamine, tetra-N-acetyl-tetra-O-methylneamine and tetra-N-acetyl-hexa-O-methylribostamycin[26] and of adenomycin (a nucleoside-containing aminoglycoside antibiotic) (see Chapter 18) have also been examined.

3 X-Ray and Neutron Diffraction Crystallography

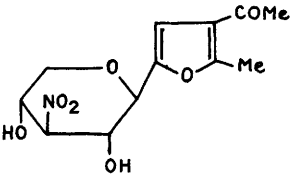
Specific crystal structures have been reported as follows, neutron diffraction studies being identified by the letters 'n.d.' (It should be noted that several of the compounds listed could have been listed under more than one heading):

Free Sugars and Simple Derivatives Thereof.- 2-Deoxy-β-D-*erythro*-pentopyranose,[27] 2-deoxy-β-D-*arabino*-hexopyranose,[28] 6-deoxy-α-L-sorbofuranose (5% of β-anomer present),[29] tetra-O-acetyl-β-D-ribofuranose,[30] penta-O-acetyl-α-D-talopyranose,[31] 1,2-O-ethylene-β-D-glucopyranose (at 120 K),[32] 1-O-benzoyl-4,6-O-benzylidene-2-deoxy-

3-O-methyl-α-D-arabino-hexopyranose,[33] 2,3:4,6-di-O-isopropylidene-5-thio-α-D-glucopyranose,[34] 1,5:2,3-bis-O-(N-diethylamidothiono-phosphate)-β-D-ribofuranose,[35] and the phosphonate (1).[36]

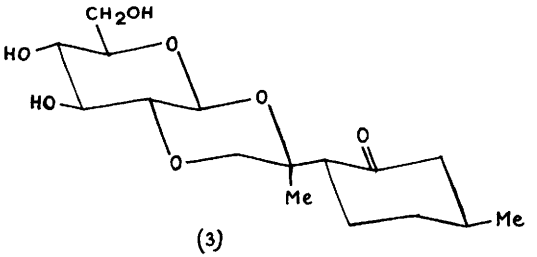


(1)



(2)

Glycosides and Derivatives Thereof.- Methyl 3,4-anhydro-1,6-bis-O-(toluene-p-sulphonyl)-β-D-tagatofuranoside,[37] (methyl-O,N,N-azoxy)-methyl β-D-glucopyranoside,[38] methyl 2,3,4-tri-O-acetyl-β-D-lyxopyranoside,[39] methyl 3,4-di-O-acetyl-2,6-anhydro-α-D-altro-pyranoside,[40] S-methyl 1-thio-β-D-galactopyranoside (at 123 K),[41] methyl 5-thio-β-D-ribopyranoside S-oxide (both diastereoisomers),[42] the furan C-glycoside (2)[43] and gilvocarcin M (a C-linked α-L-fucofuranosyl antibiotic),[44] methyl 4,6-O-benzylidene-2-chloro-2-deoxy-α-D-idopyranoside,[45] bis(methyl 4,6-O-benzylidene-α-D-gluco-pyranoside)-18-crown-6 (glucose units in the "head-to-tail"



(3)

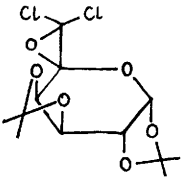
arrangement),[46] and schizonepetoside B (3)[47] (a monoterpene gluco-side from Schizonepeta tenuifolia).

Methyl 3,6-epimino-4-C-nitromethyl-N-tosyl-2,3,6-trideoxy-α-D-arabino-hexopyranoside,[48] methyl 2-acetamido-3-O-acetyl-2-deoxy-5,6-O-isopropylidene-α-D-glucofuranoside,[49] and methyl 2-acetamido-2-deoxy-5,6-O-isopropylidene-3-O-methyl-α-D-mannofuranoside and its β-anomer.[49]

Disaccharides and Derivatives Thereof.- N-Acetyl-lactosamine,[50] 6'-O-trityl-α-cellobiose hepta-acetate,[51] 4-O-(β-D-galactopyranosyl)-α-D-galactopyranose octa-acetate,[52] potassium sucrose octa-sulphate,[53] 6-O-acetyl-2-azido-3,4-di-O-benzyl-2-deoxy-α-D-gluco-pyranosyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside,[54] and

avermectin B_{1a}[55] (an α-L-oleandrosyl-α-L-oleandrosyl macrocycle).

Halogen- and Nitrogen-containing Compounds.- 2,5-Anhydro-1-chloro-1-deoxy-L-ribitol 3,4-cyclic sulphate,[56] the geminal dichloroepoxide (4),[57] 1,6-anhydro-2,4-diazido-2,4-dideoxy-β-D-glucopyranose,[58] the 1,2-cyanoethylidene acetals (5) and (6) (both stereoisomers of each)[59] and 1-(3"-chloro-2"-oxo-5"-cyanopyrrolidin-1-yl)methylene-2-oxo-β-D-arabinofurano[1',2':4,5]oxazoline.[60]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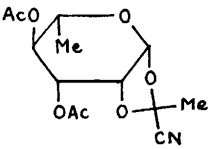
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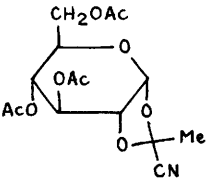
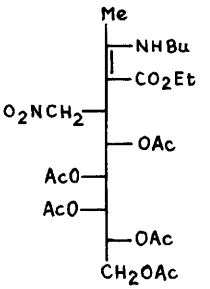
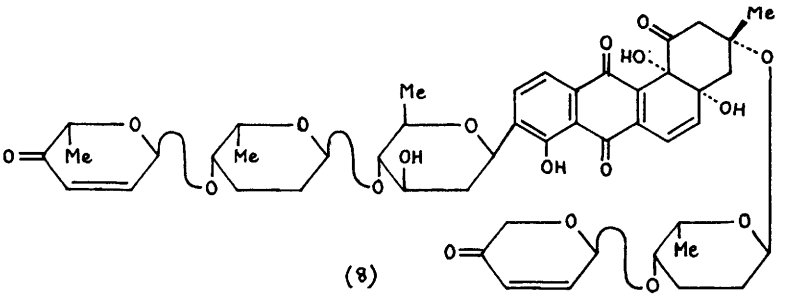

(6)

Unsaturated Compounds.- Tri-O-acetyl-D-glucal and ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside,[61] 1,5-anhydro-4-deoxy-D-glycero-hex-1-en-3-ulose,[62] and the nonenitol derivative (7),[63] the disaccharide derivative 4-O-β-D-glucopyranosyl-2,3,6-trideoxy-L-threo-hex-2-en-ono-1,5-lactone (angiopteroside)[64] and compound (8) which is a collagen proline hydroxylase inhibitor isolated from a streptomyces culture broth.[65]


(7)

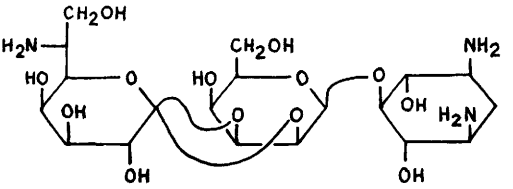
Anhydro-compounds.- 1,6-Anhydro-β-D-allopyranose,[66] 1,4:3,6-dianhydro-α-D-glucopyranose,[67] 1,6'-anhydro-(6-O-β-D-glucopyranosyl)-



(8)

β-D-glucopyranose,[68] and bis(3-O-acetyl-5-deoxy-α-D-xylofuranose)-1,2':2,1'-dianhydride.[69]

Acid Derivatives.- Ammonium D-gluconate,[70] D-ribono-1,4-lactone (123 K),[71] methyl(methyl 4,5,7,8-tetra-O-acetyl-3-deoxy-α-D-manno-2-octulopyranosid)onate[72] and destomycin A (9) which is an aldono-lactone acetal.[73]



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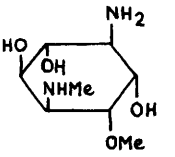


(10)

Alditol and Inositol Derivatives.- Erythritol (n.d. at 22.6 K),[74] 1-O-α-D-glucopyranosyl-D-mannitol[75] and a bisdianhydro-D-mannitolo-30-crown-10-(S)-α-aminoethylbenzene perchlorate complex.[76]

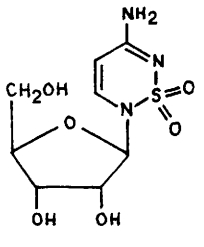
Sodium scyllo-inositol diborate,[77] fortamine (10) (as sulphate)[78] and 1-O-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-myo-inositol [as N-(5-bromo-2,4-dinitrophenyl)derivative].[79]

Nucleosides, Nucleotides, Derivatives and Related Compounds.- Data from crystallographic studies on 127 nucleosides and nucleotides and a circular correlation analysis have led to the conclusion that conformational changes are concerted.[80] The following individual studies have been reported: 2',3'-O-isopropylideneuridine,[81] 2,'3'-O-isopropylidene-5'-deoxy-6(R),5'-cyclo-5,6-dihydrouridine,[82] 5'acetamido-3'-O-acetyl-5'-deoxythymidine,[83] 5-iodo-2'-deoxy-cytidine,[84] cytidine 5'-diphosphoethanolamine,[85] 3',5'-O-(tetra-

isopropyl-1,3-disiloxanediyl)cytidine[86] and 1-α-D-xylofuranosylcytosine.[87]

Adenosine 5'-diphosphate potassium salt,[88,89] S-adenosyl-L-homocysteine,[90] guanosine 5'-phosphate disodium salt,[91] guanosine 2'-phosphate copper(II) complex (polymeric),[92] inosine 5'-phosphate strontium salt,[93] and calcium salt[94] and 3'-amino-3'-deoxyinosine.[95]

1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) $CuCl_2$ complex,[96] 5-hydroxy-2-(β-D-ribofuranosyl)-3(2H)-pyridazonine,[97] the sulphone (11),[98] the dinucleotide derivative (12),[99] amicetin {1-[4-O-(4,6-dideoxy-4-dimethylamino-α-D-glucopyranosyl)-2,3,6-trideoxy-β-D-erythro-hexopyranosyl]-N^4-[4-(2-methyl-L-serylamino)benzoyl]cytosine}[100] and nucleoside antibiotic oxanosine (see Chapter 18).



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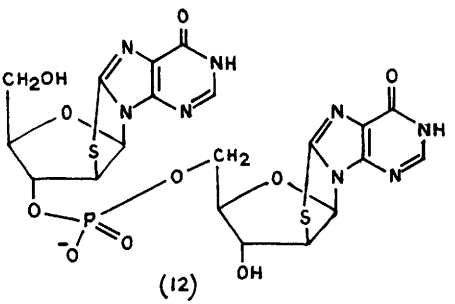


(12)

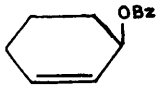
4 E.s.r. Spectroscopy

An e.s.r.-e.n.d.o.r. study of X-irradiated α-D-glucose and methyl α-D-glucopyranoside has been reported. From the former $-\dot{O}_{(2)}$, $-\dot{C}_{(6)}HOH$, $>\dot{C}_{(3)}-OH$ radicals were identified and from the glycoside the following: $-C_{(6)}H_2\dot{O}$, $-\dot{O}_{(2)}$, $-\dot{C}_{(6)}HOH$, $>\dot{C}_{(5)}-O-$. The differences between these were discussed.[101] Radicals were detected in heated (100-170°C) and u.v. irradiated powdered samples of sucrose, lactose, glucose, starch and cellulose.[102] γ-Irradiated single crystals of uridine 5'-phosphate sodium salt gave radicals formed by H· addition of C-5, C-6, O-2 and O-4 and by HO· addition at C-5.[103] Quantitative splittings in the e.s.r. spectrum of irradiated L-rhamnose have been reported (RCHO· radical).[104]

5 Polarimetry and Circular Dichroism

The optical rotations of rigid cyclitols and 1,6-anhydrohexopyranoses and many deoxy derivatives have been examined to assess the interactions between C-O bond dipoles and the contributions from the rings. Effects over two and three carbon atoms were observed and parameters were proposed for the calculation of rotations for each group of compounds.[105] Yamana has contributed in this area again by reporting a study of optical rotations of poly-O-acetates of sugars in relation to their structures. Halogenated derivatives were also examined and consistencies were noted on changing the halogens. New empiricisms were developed, some conflicting with older theories of optical rotation.[106]

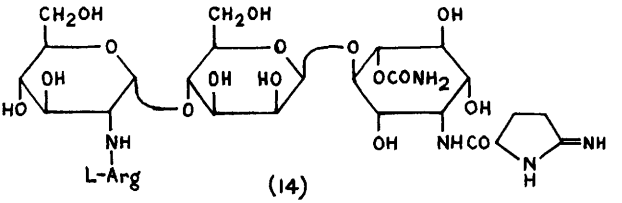
Nakanishi and his collaborators have made several notable new contributions. They propose a method for determining the absolute configurations of allylic alcohols based on the Cotton effect observed at 230 nm for the unit (13).[107] Analysis of the c.d.



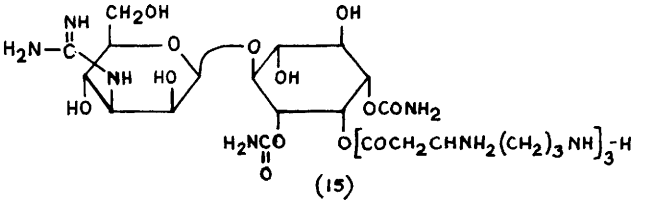
(13)

spectra of 40 pyranose p-bromobenzoates showed them that additivity exists for the differences of $\Delta\varepsilon$ for split extrema resulting from multiple interacting chromophores. Thus values for variously stereochemically related diester units were determined. Calculated and observed values for tri- and tetra-esters were then in good agreement.[108] An ingenious method of determining linkages of oligosaccharides was then developed involving permethylation, methanolysis and p-bromobenzoylation. The u.v. absorbing products (excludes non-reducing terminal units) were then separated by t.l.c. and the numbers of ester groups were determined by mass spectroscopy. Their relationships within sugars were then determinable by the above method.[109] Similar approaches were then applied to glycosylcyclitol derivatives including the antibiotic compounds (14) and (15).[110]

A new method for determining the absolute configuration of aminodeoxy sugars is based on the signs of Cotton effects near 315 and 255 nm for salicylidenimino derivatives,[111] and the anomeric configurations of neuraminic acid derivatives can be determined by c.d. since α- and β-compounds show negative and positive bands,

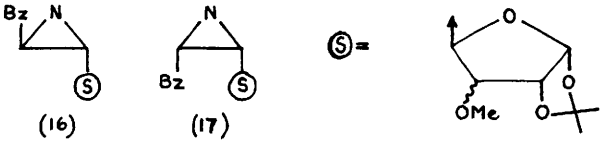


(14)



(15)

,respectively, at 220 nm.[112] The configurations of the aziridines (16) and (17) have been determined by c.d. methods.[113]



(16) (17)

The conformations of uridine derivatives have been examined by c.d. (and i.r. and n.m.r. methods) and are found to be largely dependent on the presence of unsubstituted hydroxy groups at C-5' which can form hydrogen bonds to the base.[114] Magnetic c.d. and c.d. spectra of various nucleosides are referred to in Chapter 19.

6 Nuclear Quadrupole Resonance

The ^{35}Cl n.q.r. frequencies of three anomeric pairs of methyl 2-chloro-2-deoxy-D-glucopyranosides show that α-anomers give values exceeding those of β-anomers by 0.4-1.1 MHz. The same effect was found in the ^{79}Br spectrum of methyl 2-bromo-2-deoxy-α- and -β-D-galactopyranoside. The differences were considered in terms of different orbital populations on the halogens and in terms of the ease of displacement of the chloride by nucleophiles.[115]

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22

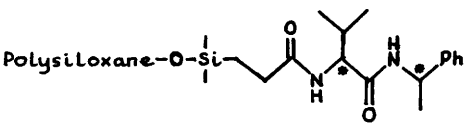
Separatory and Analytical Methods

1 Chromatographic Methods

Gas-Liquid Chromatography.- Alditol acetate derivatives continue to be widely employed for the analysis of monosaccharides, their partially methylated analogues, and 2,5-anhydro-aldoses (derived by 2-aminohexose deamination),[1-3] with data being reported on suitable capillary columns,[4-7] including one with a chiral stationary phase.[8] Sugar alcohols can be determined in the presence of monosaccharides if the latter are converted to O-methyloxime derivatives prior to acetylation.[9] Five inositols occurring in soil hydrolysates were resolved as hexa-acetate derivatives prepared using an acetic acid - trifluoroacetic anhydride reagent.[10] The D.P. of oligosaccharides can be determined as follows: i) borohydride reduction, ii) hydrolysis, iii) separation of alditols from free sugars on basic resin, iv) g.l.c. analysis of fractions as alditol acetates.[11]

Peracetylated aldononitrile derivatives have been prepared using 1-methylimidazole instead of pyridine as solvent and catalyst,[12] and a capillary column with a bonded cyanosilicone rubber stationary phase has been described for their analysis.[13]

Enantiomeric aldoses and methyl glycosides have been separated as trifluoroacetates on a capillary column coated with the chiral stationary phase (1), which is the first application of this approach to carbohydrates.[14,15] 2-Amino-2-deoxy-D-glucose and -galactose were determined as hexosaminitol trifluoroacetates using a nitrogen-specific flame thermionic detector.[16]



(1) * S-configuration

Twenty-two pentoses, hexoses and 6-deoxyhexoses common to cardiac glycosides were investigated as their TMS ethers on both packed[17] and capillary[18] columns, while considerable data on the g.l.c.-m.s. of partially methylated D-glucitol, D-glucose, and methyl glucoside TMS ethers have been reported.[19] The carcinogen methylazomethyl β-D-glucosiduronic acid was determined as its TMS ether.[20]

TMS ethers of alditols are poorly resolved on packed columns, but are sufficiently resolved on an OV-101 capillary column to permit their use as derivatives in the analysis of monosaccharides.[21] D-Glucose, maltose, and maltotriose, and their corresponding alditols, which occur together in "maltitol" syrups used as commercial sweeteners, were analysed as their TMS ethers.[22]

TMS ethers of thirteen partially methylated methyl N-acetyl-β-D-neuraminate methyl glycosides were examined by g.l.c.-m.s. in connection with the analysis of N-acetylneuraminic acid containing polymers.[23] A new combination of standard methods (methanolysis, nitrous acid deamination, and g.l.c.-m.s. of TMS ethers with specific ion monitoring) was employed to determine the monosaccharide composition of hexosamine and sialic acid-containing glycoconjugates, the deamination products being discussed.[24]

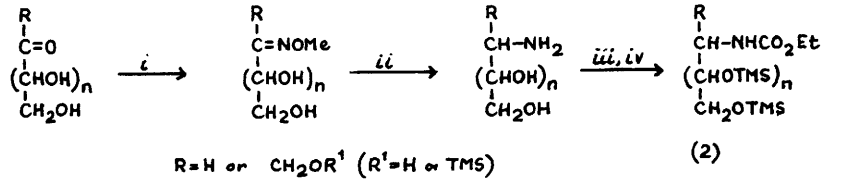
Trimethylsilylated diethyldithioacetal derivatives of partially methylated aldoses were examined by capillary g.l.c.-m.s.[25]

Sucrose hydrolysis was detected under the standard conditions (NH_2OH-py followed by HMDS-CF_3CO_2H) used to prepare TMS-oxime derivatives of sugars in aqueous solution. This problem was overcome by buffering the reagent to pH 5.4-7.4 with dimethylaminoethanol, and the derivatives were examined by capillary g.l.c.[26]

N-Ethoxycarbonylated aminodeoxyalditol TMS ethers (2), prepared as shown in Scheme 1, have been proposed as suitable new derivatives for the g.l.c. analysis of aldoses and ketoses, which form single products and a pair of diastereomers, respectively.[27]

An analysis of amygdalin (D-mandelonitrile β-D-gentiobioside) has been described which involves β-glucosidase hydrolysis and g.l.c. analysis of the liberated benzaldehyde as its O-pentafluorobenzyl oxime.[28]

Column Chromatography.- 2'-Fucosyl-lactose was isolated from human milk by chromatography on cation-exchange resin (K^+-form) and charcoal-celite, other milk sugars in the di- to penta-saccharide range also being usefully separated.[29] Ion-exchange chromatography



Reagents: i, $MeONH_2.HCl$-py; ii, BH_3-THF; iii, $ClCO_2Et$-K_2CO_3; iv, TMSCl-py

Scheme 1

was also employed to separate isomeric sialyloligosaccharides[30] and to determine the relative amounts of the B and C components of neomycin.[31] This latter separation was also achieved by controlled flow column chromatography.[32]

Thin Layer Chromatography.- Good separations of sugars were achieved on silica gel using continuous development.[33] An improved separation of isomeric sialyloligosaccharides was reported,[30] and the purification of monogalactosyldiglyceride suitable for the study of its monolayer properties was achieved by preparative t.l.c.[34] Ligand-exchange chromatography was investigated with a variety of cations. The use of Cu^{2+} gave complexes with the largest stability constants, and provided a simple, inexpensive and rapid resolution of carbohydrate mixtures.[35] A new visualization reagent (Methyl red-EtOH-aq.H_3BO_3-acetone, pH adjusted to give a yellow colour) for carbohydrates was based on pH differences depending upon the extent of complexing with borate.[36]

Aminosugars and their corresponding aminodeoxyalditols were separated as their 2,4-dinitrophenyl derivatives by two-dimensional t.l.c. on polyamide, the inclusion of benzeneboronic acid in the solvent proving particularly effective.[37]

High Pressure Liquid Chromatography.- A useful review of the h.p.l.c. of sugars on silica-based stationary phases has appeared.[38] The novel application of a mass detector for carbohydrate analysis has been described in which column eluent is nebulized into a heated tube to produce finely divided particles of non-volatile solute, which are then assayed by light scattering. It is ca. 10 times more sensitive than r.i.-detection and permits gradient elution.[39] Detection of urinary carbohydrates down to 100 ng was achieved using an optical activity detector.[40] Other reports

describe the application of on-line h.p.l.c.-m.s. for a wide range of carbohydrates using a moving-belt interface[41,42] or a pinhole[43] for direct liquid introduction.

Enantiomeric monosaccharides have been separated on silica gel using their diastereomeric 1-deoxy-1-(N-acetyl-α-methylbenzylamino) alditol acetate derivatives, which were prepared by reductive amination of the D- or L-aldose with chiral α-methylbenzylamine and sodium cyanoborohydride.[44]

Underivatized sugars and alditols have been separated on cation exchange resins (Ca^{2+}-form), with 0.001 M triethylamine in the aqueous eluent to catalyse mutarotation and hence reduce peak widths.[45] Other procedures utilized either radially compressed silica modified by tetraethylenepentamine in the solvent,[46] or amine-bonded silica.[47] Direct analysis of sugars in complex materials such as confectionery and molasses has been achieved using gel filtration and either ion-exchange or amine-bonded silica columns in series.[48]

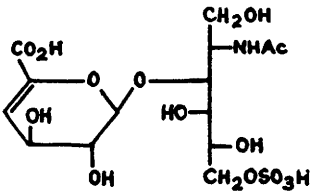
Homologous oligosaccharides, e.g., cello-, malto-, or xylo-oligosaccharides, have been separated either by reversed phase chromatography (up to D.P. 12),[49] or by using amine-bonded silica,[50] or on cation-exchange resin in the Ca^{2+}-form (up to D.P.9),[51] or with better resolution, in the Ag^{+}-form.[52] Complex oligosaccharides derived from glycoproteins,[53] and sialic acid-containing oligosaccharides[54] were separated on amine-bonded silica.

Isomeric methyl[55] and other alkyl and aryl glycosides,[56] and 1-thioglycosides,[57] as well as cardiac glycosides[58] have been separated on reversed phase or amine-bonded silica columns.

Other procedures convert sugars to derivatives prior to analysis that allow more sensitive u.v.-detection. N-Phenylcarbamate derivatives of sugar alcohols and saccharides in general, and of oligomers from wood hydrolysis in particular, were formed by reaction with phenylisocyanate, which were then analysed in the reversed phase mode.[59] Monosaccharides were determined as their dansyl hydrazones (reversed phase),[60] while the resolution of anomeric per-O-benzylated disaccharides (reversed phase) was used to determine the α- vs. β-stereospecificity of the reactions used in their synthesis.[61] Per-O-acetylated and - benzoylated isomeric glycosides,[56] and per-O-benzoylated oligosaccharides were separated in the reversed phase mode.[62] In the latter case, preliminary reduction was advised to prevent separation of anomers, and quantitation was possible since the absorbance at 230 nm was

strictly proportional to the number of benzoyl groups.

Sulphated, borohydride-reduced, unsaturated disaccharides, such as (3), produced by degradation of glycosaminoglycans, were separated on cyanoamino-bonded silica.[63]



(3)

L-Ascorbic acid, its C-5 epimer D-isoascorbic acid, and related acids have been analysed by both ion-pair[64,65] and weak anion-exchange chromatography.[66]

A semi-preparative, reversed phase separation of Amadori compounds from crude Maillard reaction products has been demonstrated for the isolation of 1-deoxy-1-valino-D-fructose and 1-deoxy-1-prolino-D-maltulose.[67]

The aminoglycoside antibiotics streptomycin and dihydrostreptomycin have been analysed in the presence of process-related by-products by ion-pair chromatography,[68] while similar analyses (reversed phase) of fortimicin A[69] and tobramycin[70] were conducted after derivatization with 2,4-dinitrofluorobenzene, although in the latter case low absolute recoveries were taken to indicate incomplete derivatization. The nucleoside-peptide antibiotic family, the nikkomycins, were assayed in the reversed phase mode.[71]

The h.p.l.c. analysis of nucleosides, nucleotides and bases has been reviewed.[72] Specific separations have been reported using silica gel,[73] reversed phase procedures [74-78] (including 2-fluoro-2-deoxy-arabinofuranosyl pyrimidine nucleosides[79]), ion-pairing with an anionic detergent,[80] and anion- and cation-exchange resins.[78,81,82] Nucleosides were used in testing the performance of open-tubular microcapillary columns with bonded cation-exchange materials.[83] The separation (reversed phase) of benzo[a]pyrene diolepoxide-nucleoside and -deoxynucleoside adducts has been reported.[84] The use of the very hydrophobic 5'-O-(alkoxytrityl) ether derivatives of nucleosides and nucleotides for their reversed phase separation has been demonstrated.[85]

2 Electrophoresis

Adenosine and various adenosine nucleotides were examined under a variety of electrolytic and pH conditions.[86] Isotachophoretic analysis of urinary purine and pyrimidine nucleosides and bases,[87] and of free sialic acid[88] has been described.

3 Other Analytical Methods

Recent advances in the use of periodate oxidation for structure determination have been reveiwed.[89] The potentiometric determination of excess periodate has been described,[90] and the application of periodate oxidation for determining α-glycol groups in aldopentoses reported.[91] Other references to periodate oxidation are given in Chapter 3.

Optimal conditions of pH and ionic strength have been determined for the enzymic assay of glucose using glucose dehydrogenase, this method now appearing to have advantages over the glucose oxidase and hexokinase methods for serum glucose determination.[92]

The use of magnesium oxide as the base in the iodometric determination of aldoses has been recommended, since this reduced iodate formation and thus permitted greater control over the amount of iodine present during the reaction, which in turn minimized over-oxidation of the aldonic acid salts formed in the primary reaction.[93]

Amino-sugars have been determined, both in solution and on paper chromatograms, by reaction with fluorescamine and measurement of the fluorescence intensity.[94]

A colourimetric sugar analysis employing a liquid scintillation counter has been described, in which the quantity of carbohydrate (in the range 60 μg to 3 mg) was correlated with the attenuation of photon intensity from a central sealed $\sim 10^5$ d.p.m. ^{14}C- or ^{3}H-source by a surrounding coloured sample.[95] Manual and automated spectrophotometric methods for the detection and assay of carbohydrates have been reviewed.[96]

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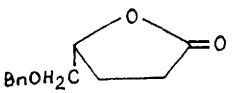
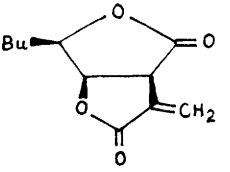
23
Synthesis of Enantiomerically Pure Non-carbohydrate Compounds from Carbohydrates

1 Tetrahydrofuran Compounds

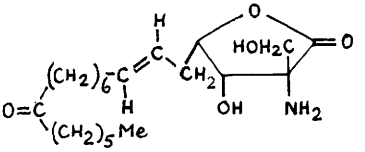
Lactone (1) has been synthesized from 1,2-anhydro-3-O-benzyl-L-glycerol by use of diethyl malonate,[1] and a further preparation of (-)-canadensolide (2) from D-glucose has been reported.[2] The preparation of the lactone (3) from L-arabinose has allowed the configurational assignment of the related, acyclic antifungal agent myriocin.[3]



(1)

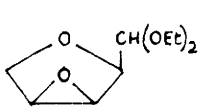


(2)

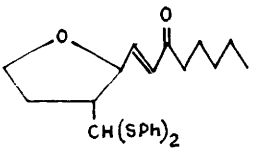


(3)

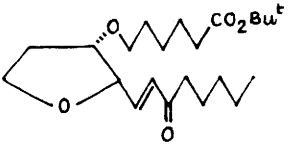
Several compounds having furanoid C-glycosidic character have been reported. Dianhydropentose derivatives, e.g., (4), have been used in the preparation of oxaprostaglandin analogues, e.g., (5) and (6), the epoxide rings being opened by use of the bis(phenylthio)methyl anion to give one- or two-carbon side-chains.[4]



(4)

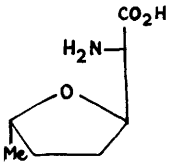


(5)

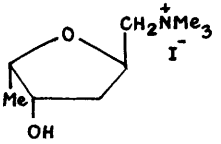


(6)

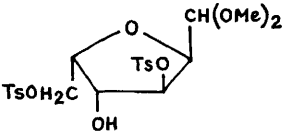
(+)-Furanomycin (7) and some stereoisomers[5] and (2R,4S,5S)-epiallomuscarine (8)[6] have been synthesized from the 2,5-anhydrohexose derivative (9), and (-)-nonactic acid (10) has been made from D-



(7)

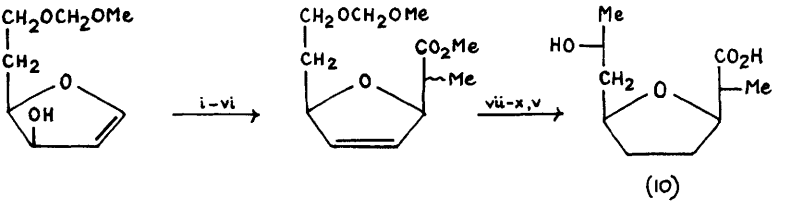


(8)



(9)

mannose as outlined in Scheme 1, the (+)-enantiomer being made similarly from D-gulono-γ-lactone by way of the enantiomeric

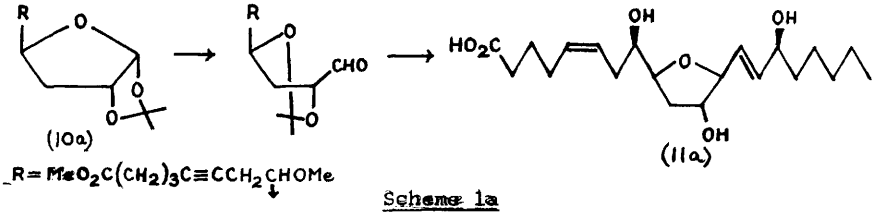


(10)

Reagents: i, BuLi; ii, $MeCH_2COCl$; iii, LDA; iv, Me_3SiCl; v, ^-OH; vi, CH_2N_2; vii, H_2,Rh/C; viii, H^+; ix, DMSO,$(COCl)_2$; x, $LiMe_2Cu$

Scheme 1

glycal.[7] The related tetrahydrofuran (11a), which is an oxidation product of arachidonic acid, was made from the carbohydrate-derived (10a) (Scheme 1a).[7a] The preparation of 5-oxaproline enantiomers is reported in Chapter 9.



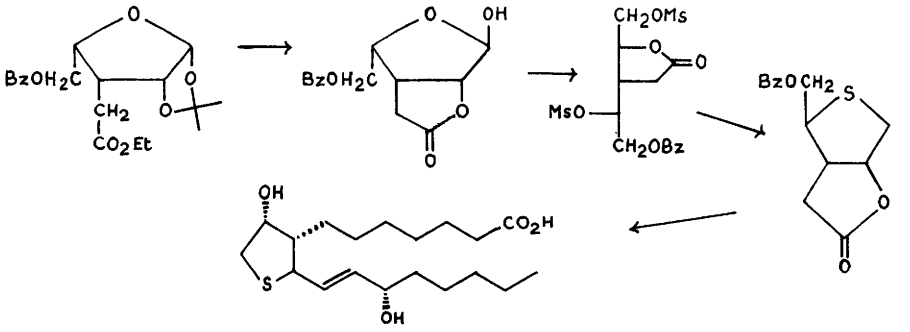
Scheme 1a

2 Tetrahydrothiophen Compounds

In Scheme 2 an outline is given of the synthesis of the enantiomerically pure 11-thioprostaglandin (11).[8]

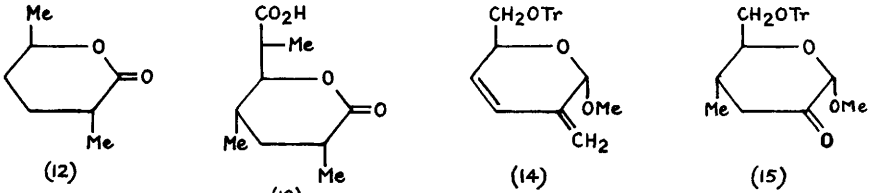
3 Tetrahydropyran Compounds

A detailed account has appeared of Hanessian and Lavallee's synthesis of thromboxane B2[9] (see Vol. 11, p.228), and the same group have described the preparation of the enantiomer (12) of the

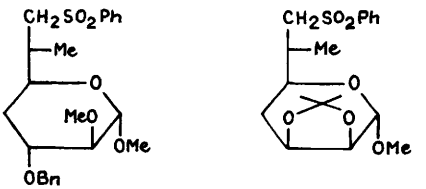


Scheme 2

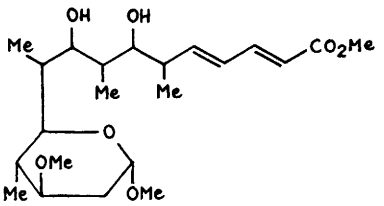
carpenter bee's major sex pheromone by way of a readily made diene (see Chapter 12). In related fashion the Prelog-Djerassi lactone (13) has been produced (together with its C-6 stereoisomer) from the diene (14) or the related ketone (15).[10] In parallel work compound (13) was obtained by an alternative strategy from an appropriate C-glycoside of a hex-5-enopyranoside (see ref. 31).



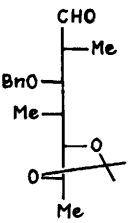
Compounds (16) and (17) were obtained from methyl α-D-manno-



pyranoside as synthetic intermediates for the production of maytansine.[11] The ansa chain compound of rifamycin B (18) has been degraded by ozonolysis and the products were used in Wittig synthetic reactions.[12] The heptose derivative (19) was then synthesized from methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-α-D-altropyranoside as a component of the complex side-chain.[13]



(18)

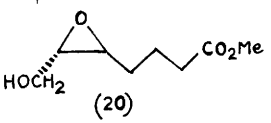


(19)

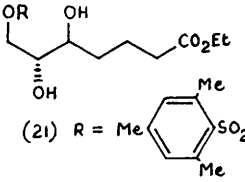
4 Acyclic Compounds

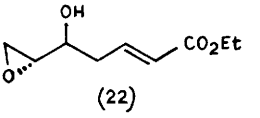
In this section several compounds having cyclic components will be mentioned; these are looked upon as being simple derivatives of acyclic species.

Three interesting communications have reported on the use of 2-deoxy-D-*erythro*-pentose in the syntheses of leukotrienes. Two routes to the key epoxide (20) involved the ester (21), made from the free sugar by a Wittig procedure,[14] and the epoxide (22) which was produced by base treatment of the C-glycosides (23).[15] Collins oxidation of (20) followed by two Wittig reactions gave leukotriene A_4 as its methyl ester (24). An ingenious extension of this

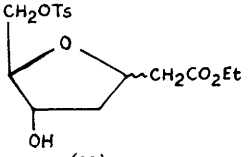


(20)

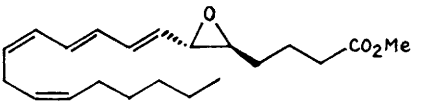




(22)



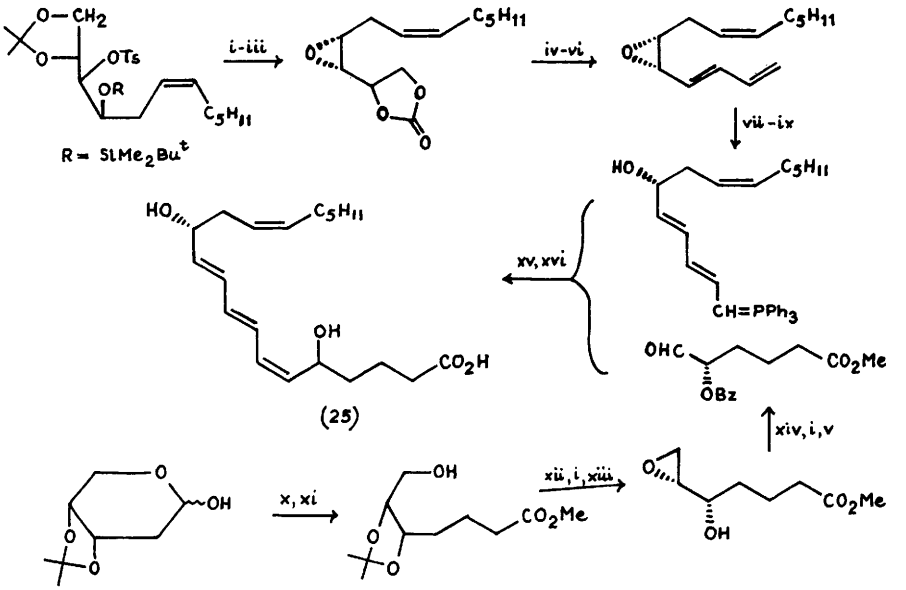
(23)



(24)

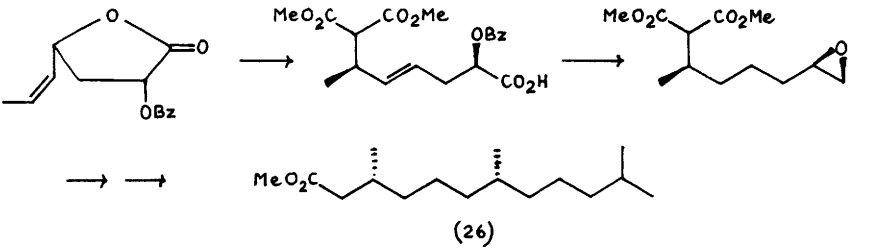
approach used sugars to provide all the required symmetry in leukotriene B (25) (Scheme 3).[16]

A novel ring opening of an unsaturated aldonolactone derivative with dimethyl malonate anion has been used as the basis of the synthesis of the side-chain (26) of vitamin E (outlined in Scheme 4)[17] and the enals (27) and (28), which are readily available from the corresponding acetylated glycals, have been used to make the side-chains (29) and (30) of the trichothecene family of sesquiterpenes.

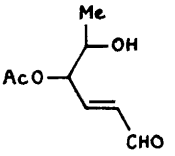


Reagents: i, H^+; ii, $ClCO_2Ph$; iii, DBU; iv, LiOH; v, $Pb(OAc)_4$; vi, $Ph_3P{=}\diagup\!\!\diagdown$ vii, HBr; viii, Ph_3P; ix, BuLi; x, $Ph_3P = \diagup\!\!\diagdown CO_2Me$; xi, H_2,Pd/C; xii, TsCl,py; xiii, K_2CO_3,MeOH; xiv, BzCl,py; xv, condense; xvi, K_2CO_3

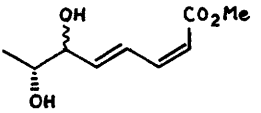
Scheme 3



Scheme 4

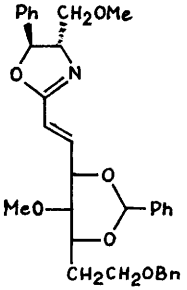


(27) D-Erythro
(28) D-Threo

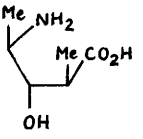


(29) D-Erythro
(30) D-Threo

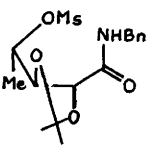
Stereochemical details of the products were determined, and isomeric dienoic acid derivatives with alternative alkene configurations were also prepared.[18] In related fashion, and in connection with syntheses in the carbomycin series, compound (31) was prepared from 5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl-α-D-xylo-hex-5-enofuranose by Wittig procedures.[19] Synthesis of the valeric acid derivative (32) - a component part of bleomycin - was achieved by way of compounds (33) and (34),[20] and 2,3-O-isopropylidene-D-glyceraldehyde has been employed in the preparation of both



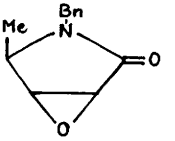
(31)



(32)

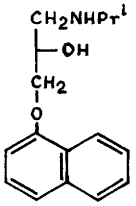


(33)

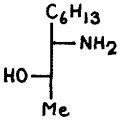


(34)

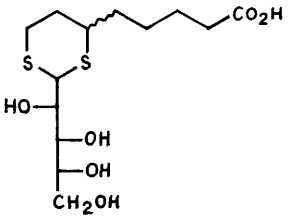
(2R)- and (2S)-1-alkylamino-3-aryloxy-2-propanols [e.g. (35)] which are β-blockers.[21] 4-Amino-2,3,4,6-tetradeoxyhexoses, made from hex-2-enose derivatives, have provided access to the hydroxyamine (36) and its stereoisomers,[22] and the dithianes (37) have been prepared from racemic lipoic acid by reduction to the dithiol and



(35)



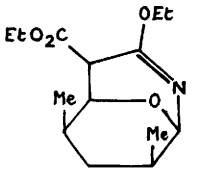
(36)



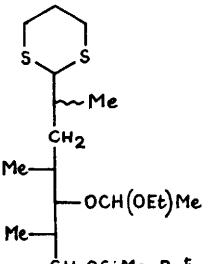
(37)

reaction with D-arabinose. Separation of the resultant diastereoisomers led to the resolution of the acid.[23]

Synthesis of compound (38) and its alkylation at C-6 gave access to the tribranched compound (39) which is a required synthon for a non-macrocyclic polyether antibiotic.[24]



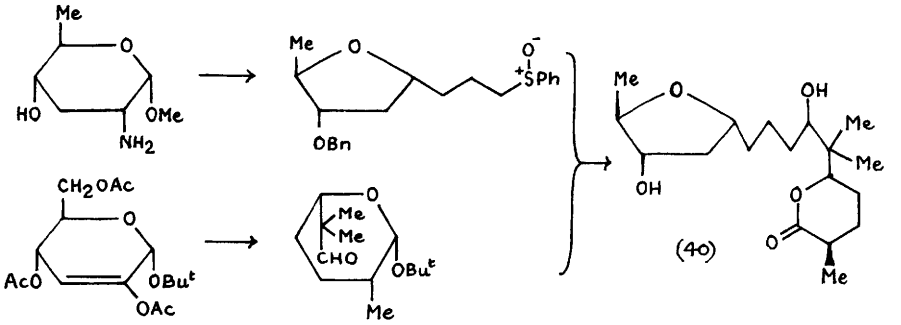
(38)



(39)

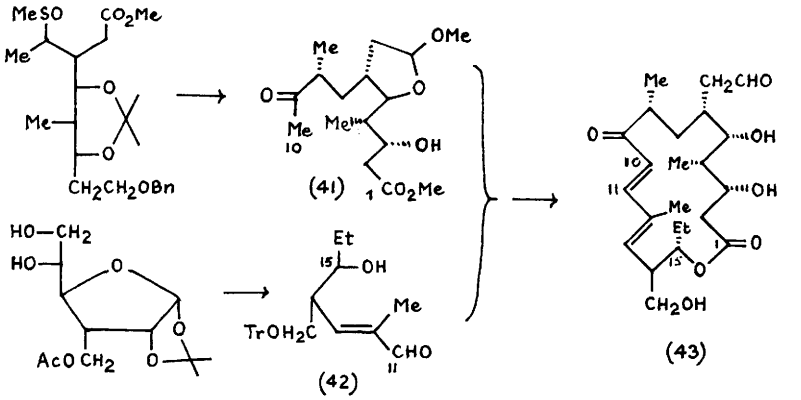
5 Macrocyclic Compounds and Components Thereof

Carbohydrates have been recognized by several groups as suitable starting materials for preparation of the component parts of macrocyclic antibiotics. In Schemes 5-9 the strategies for the syntheses of several of these components from carbohydrate precursors are outlined. Compound (40) (Scheme 5), a major degradation product of boromycin,[25] was prepared from two carbohydrate subunits, each derived from D-glucose (Scheme 5). Components (41) and (42)

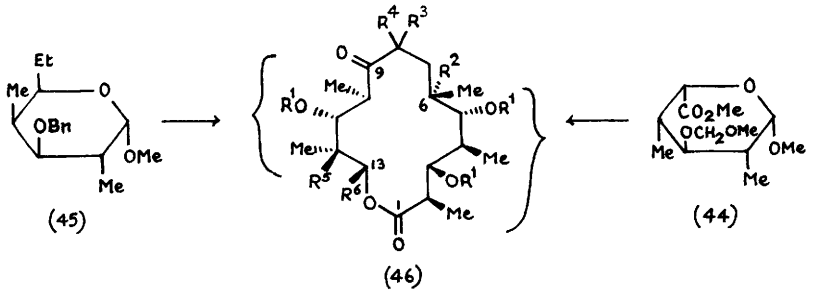


Scheme 5

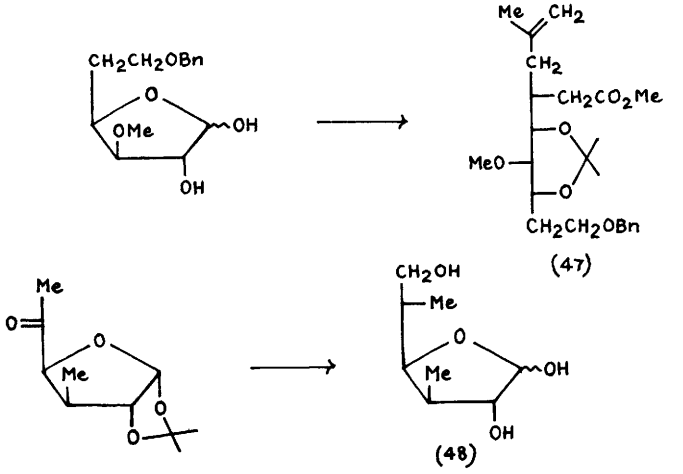
were combined to give the aglycone (43) of tylosine (Scheme 6);[26] compounds (44) and (45) - both synthesized from 1,6-anhydro-β-D-glucose - correspond to the C-1—C-6 and C-9—C-13 segments of several antibiotics of the general structure (46) (Scheme 7).[27,28]



Scheme 6

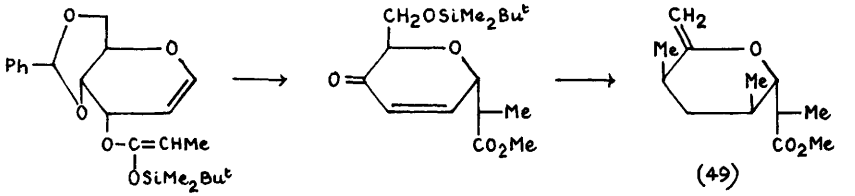


Scheme 7



Scheme 8

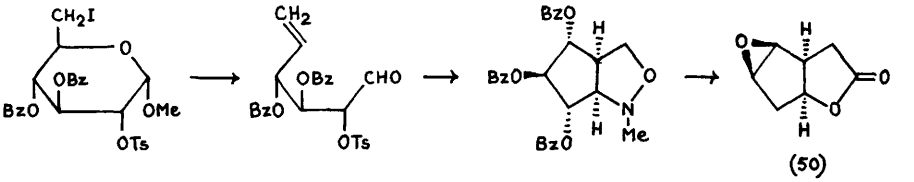
Scheme 8 indicates the origin of the macrolide synthons (47) and (48) in glycofuranose intermediates,[29,30] and the tri-C-methyl alkene (49) was synthesized from a glycal as outlined in Scheme 9, being then converted into the Prelog-Djerassi lactone (13) by ozonolysis.[31]



Scheme 9

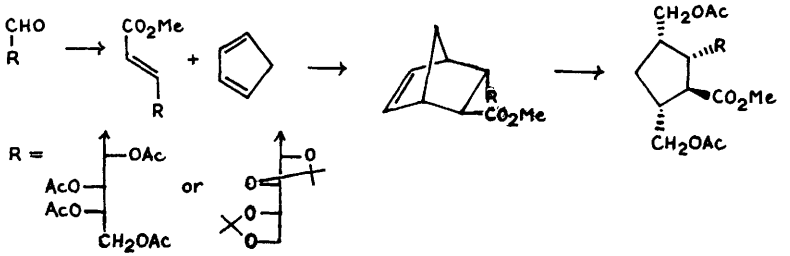
6 Carbocyclic Compounds

The enantiomerically pure prostaglandin intermediate (50) has been synthesized from a glucose precursor as outlined in Scheme 10,[32]



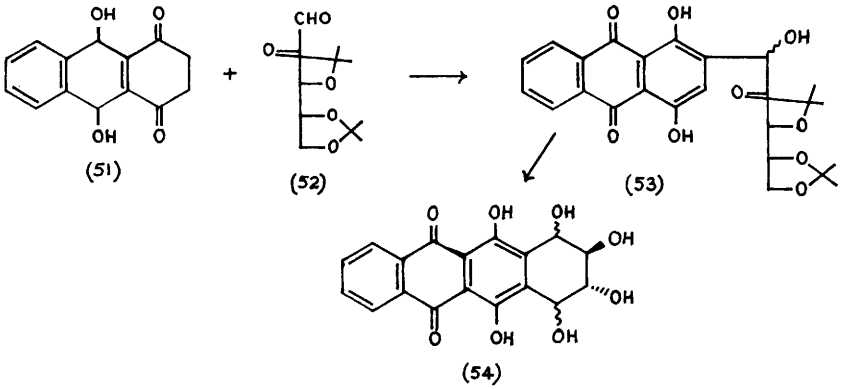
Scheme 10

and in Scheme 11 a different method for obtaining precursors of prostanoid-like compounds from aldehydo-L-arabinose derivatives is illustrated.[33]



Scheme 11

Condensation of leuco-quinizarin (51) with the aldehydo-sugar (52) in base gave access to compounds (53) which, after partial hydrolysis and periodate oxidation, were further transformed into the anthracyclinone derivative (54) (Scheme 12).[34]

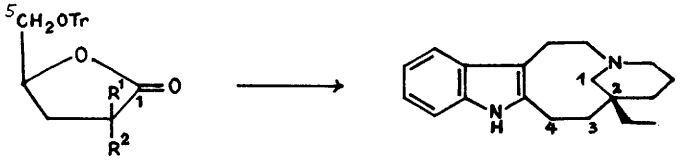


Scheme 12

Schiff bases derived from aminosugars and co-ordinated to copper(II) catalysts have been used in enantioselective syntheses of pyrethroids, the cyclopropane carboxylates being formed by use of diazoacetate addition reactions.[35]

7 Other Compounds

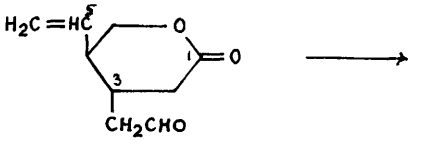
Both enantiomers of quebrachamine (55) have been synthesized from the synthon (56) which is available from D-mannitol,[36] and the unbranched lactone (57), also obtainable from this hexitol, has been used to prepare the branched δ-lactone (58) and hence the indole alkaloid (-)-antirhine (59)[37] by initial condensation with tryptamine in the presence of sodium cyanoborohydride.



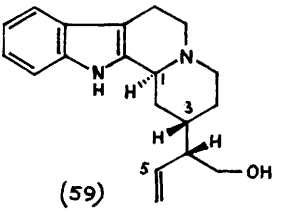
(56) $R^1 = CH_2CH{=}CH_2$, $R^2 = Et$

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

(55)



(58)



(59)

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Author Index