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Carbohydrate Chemistry

VOLUME 17

Part I

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

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Carbohydrate Chemistry

Volume 17
Part I

A Specialist Periodical Report

Carbohydrate Chemistry

Volume 17
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Mono-, Di-, and Tri-saccharides and Their Derivatives

A Review of the Literature Published during 1983

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Preface

This report covers the literature for 1983 available to us by February 1984.

I regret that it has not yet proved possible to capitalize on the faster publication rate that the camera-ready format makes possible; several factors have contributed to this unfortunate situation, the most serious being a postal error between authors which should not be repeated. We are well aware of the need to hasten the process.

We are also aware that the publication is being made against a background of declining sales and profitability for the general series of Specialist Periodical Reports, although at the present time this particular title is still viable. We depend on our readers, and especially purchasers, to keep it so. I refer in the introduction to the value of readers' comments, and would like to encourage further constructive suggestions. It is evident that the camera-ready format, and perhaps even more the home-spun 'amateurish' diagrams, do not meet with universal approval, but there is no longer any realistic alternative to the former, and more elegant structures would undoubtedly cost more in time and money to produce. I hope that I am right in assuming that most readers are prepared to concur with my decision in this matter.

As usual, I wish to thank my colleagues for all their hard work in helping to produce this volume, and we are again indebted to Mrs. A.Beattie, Ms. W.F.James, and Ms. S.J.Wharton for producing the typescript. I would also like to thank Dr. P.Gardam and Mrs. H.Pape at the Royal Society of Chemistry, who have been instrumental in producing the improved author index, which now supplies chapter-reference rather than simple page indicators.

May 1985 Neil R. Williams

REPRINTS

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

Contents

Abbreviations

The following abbreviations have been used:

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

1
Introduction

We have abstracted over 1400 references in carbohydrate chemistry for 1983. The areas of interest reflected in these references have confirmed the trends apparent in recent years. Besides the well-established fields of glycoside, nucleoside, and antibiotic chemistry, there has been a rapid increase in papers reporting the synthesis of chiral natural products from carbohydrate precursors, and a separate chapter on oligosaccharides has clearly justified its inclusion. Incidentally, these last two chapters have both resulted from suggestions made to us by interested readers, and we would like to encourage further participation of this kind. The emphasis in these areas should not obscure the fact that many other aspects of monosaccharide and oligosaccharide chemistry continue to attract much interest, as is demonstrated by the fact that only six of the twenty-four chapters in this volume contain fewer than thirty references.

An appreciation of the life and work of J.K.N.Jones has been published.[1]

Reviews covering general aspects of carbohydrate chemistry have included a survey of nucleophilic substitution reactions in carbohydrate derivatives,[2] discussions of the role of lone-pair interactions in the selective functionalization of hexopyranosides in esterification and etherification reactions,[3,4] and a review of some studies in asymmetric synthesis, Diels-Alder reactions, and stereospecific sugar synthesis.[5]

References

1 W.A.Szarek,M.Stacey, and G.W.Hay, Adv. Carbohydr. Chem. Biochem., 1983, 41,1.

2 Z.Smiatacz and A.Moczulska, Wiad. Chem., 1982, 36, 595 (Chem. Abstr., 1983, 99, 105 588).

3 V.G.S.Box, Heterocycles, 1983, 20, 677.

4 V.G.S.Box, Heterocycles, 1983, 20, 1641.

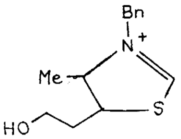
5 T.Mukaiyama, Pure Appl. Chem., 1982, 54, 2455.

2
Free Sugars

A review of the structures and nomenclature of the sugars of honey has appeared.[1]

1 Synthesis

Two reviews on the synthesis and utilization of sugars produced by the formose reaction have appeared.[2,3] The use of chemical ionization - m.s. to characterize the products of the formose reaction has been described.[4] A report of a study on the catalytic activity of rare earth element hydroxides, M(OH)$_3$, where M is Er, Pr, Sm, Ho or Ce, together with calcium hydroxide on the formose reaction, includes measurements of the ratios of three- and four-carbon products to those containing five- and seven-carbon atoms, when glucose was used as co-catalyst.[5] The factors affecting formation of 2,4-bis(hydroxymethyl)-3-pentulose in the formose reaction when carried out in methanol or water in the presence of various alkaline earth salts and potassium hydroxide have been investigated: the optimum yields were obtained with strontium salts in methanol.[6] In the formose reaction catalyzed by N,N-diethylethanolamine, it was shown that addition of monosaccharides and of organic bases such as quinuclidine and 3-quinuclidinol increased the amount of conversion, whereas a decrease in pH caused a decrease in conversion. It was suggested that the bases inhibited the competing Cannizzaro reaction.[7] In the related formoin reaction, in which the autocondensation of formaldehyde catalyzed by the thiazolium salt (1) and a tertiary amine in an aprotic solvent such as DMF occurs, the effect on the yields of the resultant glucose, galactose, xylose, and arabinose of varying the conditions has been studied.[8]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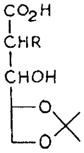
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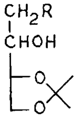
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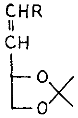
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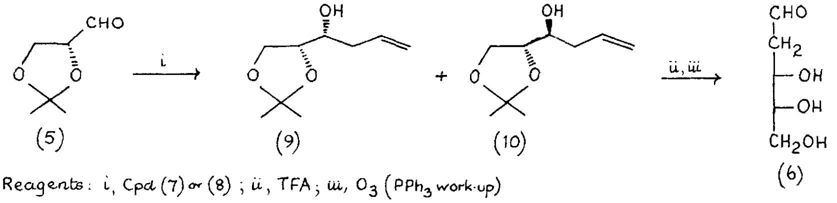
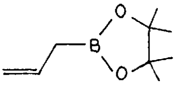
Reaction of 2,3-O-isopropylidene-D-glyceraldehyde with carboxyl-containing active methylene compounds gave products of type (2), which were decarboxylated to triols (3) and then dehydrated to yield the unsaturated derivatives (4). Dihydroxylation of the appropriate derivatives of (4) was carried out to give 1-deoxy-D-sorbose and -fructose.[9] 2,3-O-Isopropylidene-D-glyceraldehyde (5) has been converted into 2-deoxy-D-erythro-pentose (6) using the route shown in Scheme 1. When reagent (7) was used the ratio of (9) to (10) was 1:4, whereas when chiral reagent (8) was employed this ratio increased to 1:24. Chain extension using the cis and trans-2-buten-1-yl reagents (11) and (12) corresponding to the allyl reagent (8) gave the diastereomeric products, (13) and (14), (15) and (16) in the ratios shown in Scheme 2.[10]



Reagents: i, Cpd (7) or (8); ii, TFA; iii, O_3 (PPh_3 work-up)

Scheme 1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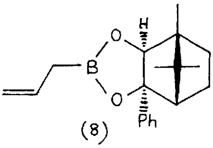
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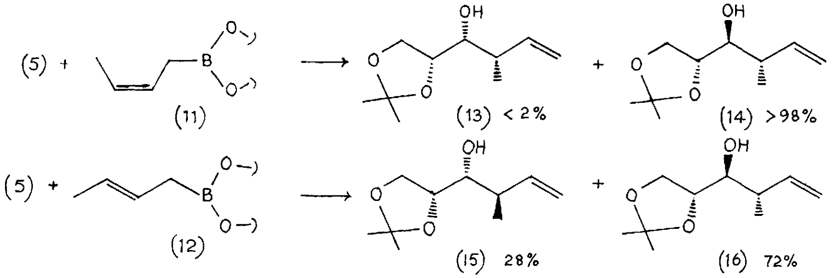
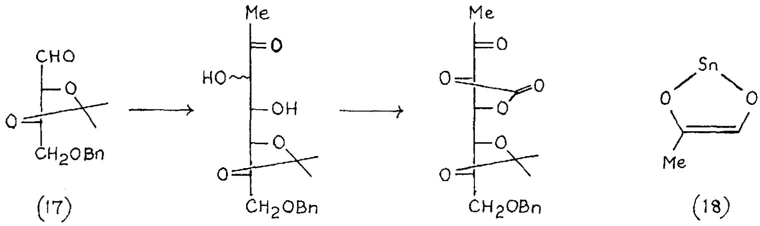


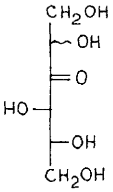
Scheme 2

Aldol-type condensation of 4-O-benzyl-2,3-O-isopropylidene-L-threose (17) with the tin(II) enediolate (18), derived from methylglyoxal, gave the C-3 epimers (19) in high yield. Both of these epimers, upon reaction with N,N-carbonyldiimidazole gave the same cyclic carbonate (20), probably due to imidazole-catalyzed isomerization at the α-position (Scheme 3). The carbonate (20) is a new precursor for L-sugar synthesis.[11] Base-catalyzed condensation of formaldehyde with D-threo-pentulose gave rise to the epimeric 3-uloses (21) which were converted as a mixture to the di-*O*-isopropylidene derivatives (22) and (23). Separation by column chromatography allowed examination of the products by mass spectrometry and i.r. spectroscopy.[12] Condensation of ethyl acetoacetate with either D-ribose or D-arabinose has been shown to yield the erythro-triol (24), while the epimeric threo-product (25) was obtained from D-xylose.[13]



(17) (19) (20) (18)

Scheme 3



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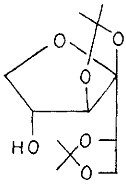

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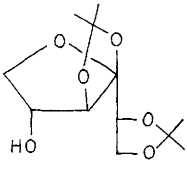

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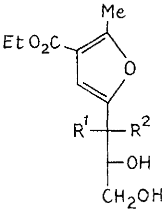
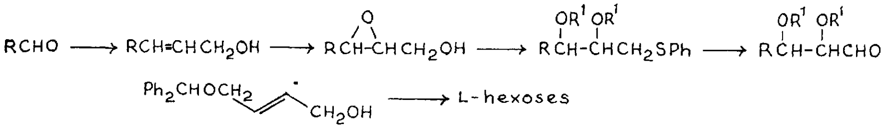


(24) R^1=H, R^2=OH
(25) R^1=OH, R^2=H

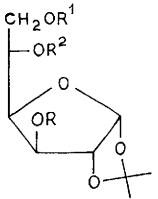
A procedure for the synthesis of L-hexoses by a reiterative two-carbon extension cycle of four steps has been described, traced in Scheme 4. The products were enantiomerically pure. The cycle can be repeated, leading to higher sugars.[14]



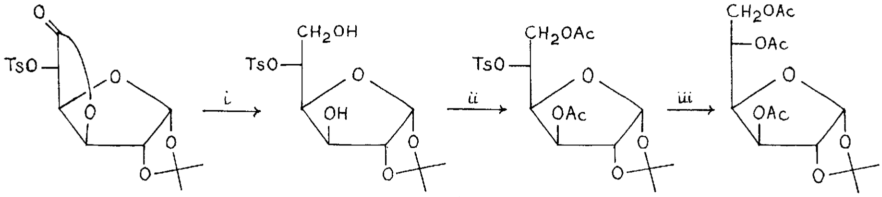
Scheme 4

Indirect electrochemical oxidation of D-glucono-(1→5)-lactone to yield D-arabinose with 65% yield has been achieved at low temperature and low current densities by using cerium sulphate as mediator in aqueous sulphuric acid and platinum electrodes.[15]

Conventional means have been employed to synthesize some L-idose derivatives (26) from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose via the 5,6-epoxide.[16] Several routes leading to 3,5,6-tri-O-acetyl-1,2-O-isopropylidene-β-L-idofuranose required on 100g scale, have been evaluated. A successful synthesis is shown in Scheme 5.[17]



(26) R = Bn; $R^1, R^2 = H$;
R = $MeSO_2$; R^1, R^2 = H or Ac

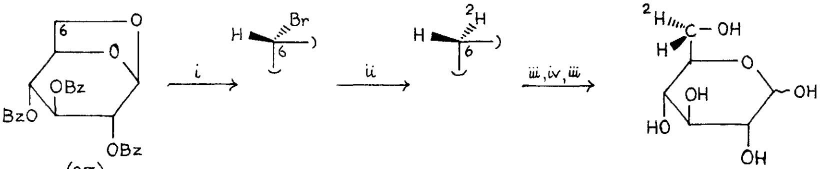


Reagents: i, $NaBH_4$; ii, Ac_2O-Py; iii, Resin(OAc^-)-Ac_2O

Scheme 5

D-Fructose has been produced in over 90% selectivity by catalytic hydrogenation of D-glucosone using 5% Pd/C. In conjunction with enzymic oxidation of D-glucose to D-glucosone this represents a patented conversion of D-glucose to D-fructose.[18] A procedure for raising the efficiency of enzymic conversion of lactose into glucose and galactose has been described. The overall conversion was raised to 80-90% by separating unreacted lactose by crystallization after passage over the β-galactosidase used; since galactose inhibits this enzyme the conversion is limited per pass so that re-passage is required. The solubilities of lactose, glucose and galactose were determined at various temperatures and sugar ratios, as were the effects of rates of cooling, thus leading to convenient and simple processes for the isolation of lactose from the hydrolysis products.[19] The reduction of methyl (methyl-3-deoxy-2-aldulosid)-onates with sodium borohydride to yield methyl 3-deoxy-2-ketosides, followed by resin-H^+ catalyzed hydrolysis of the glycoside, has been used to synthesize free 3-deoxy-2-ketoses.[20]

Sugars enriched with carbon isotopes have been prepared by reaction of aldoses with labelled potassium cyanide, the epimeric aldononitriles being hydrogenated over palladium-barium sulphate to yield the epimeric alditolylimines. The latter spontaneously hydrolyse to yield the requisite labelled aldose with one more carbon atom. The epimers were separated on Dowex 50(Ba^{2+} or Ca^{2+}) columns.[21] By using deuterium gas in the hydrogenation step these same authors prepared doubly labelled sugars. Carrying out the Kiliani-Fischer reaction in $H_2^{18}O$ led to the oxygen labelled products. Using these methods variously labelled D-erythrose and D-threose were prepared from D-glyceraldehyde and D-[2-^{18}O]arabinose and D-[2-^{18}O]ribose were prepared from D-erythrose.[22] A remote semiautomated synthesis for routine production of 1-[^{11}C]-2-deoxy-D-glucose by reaction of $H^{11}CN$ with 1-O-triflyl-2,3:4,5-di-O-isopropylidene-D-arabinitol has been described. The purity was better than 98% and the yield 24 - 30%.[23] A stereospecific synthesis of (6S)-D-glucose-6-^{2}H *via* Ferrier photobromination of 1,6-anhydro-2,3,4-tri-O-benzoyl-β-D-glucopyranose has been reported (Scheme 6).



(27)

Reagents: i, Br_2-CCl_4-hν ; ii, $Bu_3^nSn^2H$; iii, NaOMe ; iv, Ac_2O-AcOH

Scheme 6

A similar sequence was used to prepare the (6R) isomer by starting with the [6,6-$^2H_2$]isomer of (27) and carrying out the reduction with unlabelled tri-n-butyltin hydride.[24]

Reference to conversion of 2-methoxyethyl glycosides of benzyl-protected sugars to free sugars by means of titanium tetrachloride will be found in chapter 3.

2 Physical measurements

Calorimetric methods have been used to determine the integral enthalpies, partial molal heat capacities, and apparent molal volumes of sugars and polyols in water at low concentrations.[25] The structure-forming abilities of sugars, as evidenced by their activity coefficients, viscosities, and apparent molal volumes have been determined, and shown to be in the order glucose > mannose ~ galactose,[26] and maltobiose > maltose > glucose.[27] The data obtained from measurements of excess enthalpies of aqueous solutions of monosaccharides at 298.15 K suggest that the behaviour is governed primarily by solute-solvent interactions.[28] The solubilities of several mono- and disaccharides in 2-methoxyethanol has been shown to be greatly enhanced in the presence of 5 - 20% w/w of lithium chloride.[29] The dissociation of ammonium hydroxide in water was increased by the presence of amylose, D-glucose, and poly(ethylene glycol).[30] A near i.r. differential spectrophotometric method of determining hydration numbers of solutes in aqueous solution has been applied to eight different sugars; the effect of concentration and temperature were examined.[31]

Kinetic parameters have been determined for the mutarotation of D-xylose between pH 1.2 and 1.7 and 3.6 - 4.4 at 25^{o}, 160^{o} or 180^{o} C. It was shown that increasing the pH decreased the rate at 25^{o} but increased it at 180^{o}C.[32] A detailed further study of mutarotation of 2,3,4,6-tetra-O-methyl-D-glucose in benzene catalyzed by 2-pyridinone has been carried out using O-^{2}H, N-^{2}H, and $C_{(1)}$-^{2}H labelled compounds. A mechanism involving hydrogen bonding of the sugar hydroxy group to the carbonyl of the catalyst with the O-5 forming a hydrogen bond with the NH and simultaneous transfer of the two hydrogens was envisaged.[33] The effects of pressure on the mutarotation of α- and β-D-glucopyranose have been studied; rate constants and activation volumes were determined for the uncatalyzed reaction and for the reaction catalyzed by copper perchlorate. The mechanism was discussed.[34] Hydroxide ion-catalyzed mutarotation of a series of glucopyranoses in water has been studied by stopped-flow polarimetry. Glucose was shown to differ remarkably from its substituted analogues, probably due to dissociation of two hydroxy groups as the hydroxide ion concentration was increased. The data suggested coupled proton transfer in water alone, whereas for the hydroxide ion a stepwise mechanism, involving formation of a sugar anion (or dianion for glucose), was more likely. The kinetic data were best explained by assuming a second dissociation constant of glucose to be no larger than $10^{-14.6}$ and those for the substituted compounds to be considerably smaller.[35]

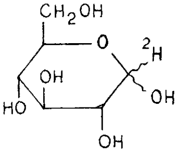
A study of the vacuum thermal dehydration of sucrose and cellobiose between 150° C and 250° C showed that water is the major decomposition product together with small amounts of one- and two-carbon fragments. The so-called melting with decomposition of sugars is in reality a high temperature dissolution in the water or alcohol produced.[36] Values for Arrhenius activation energies, ln A and orders of reaction for the thermal decomposition of D-xylose have been obtained.[37] The thermal stabilities of D-xylose, D-glucose, D-galactose and D-fructose in the presence of zinc chloride, with which they form unstable complexes, was shown to be decreased: the temperatures for the onset of decomposition and for the maximum gas evolution were decreased.[38]

A study of X-irradiated single crystals of L-rhamnose has shown that an electron is trapped in an interstitial site formed by two hydroxy groups of the sugar and one hydroxy group of the water molecule. The trapped electron decays by cleavage of an oxygen - hydrogen bond to yield a hydrogen atom, which in turn abstracts a hydrogen atom from carbon to which the hydroxy group was attached; this produces a hydroxyalkyl radical. The electron trap pre-exists in the crystal and no dipole reorientation is necessary to stabilize the electron.[39] Radicals induced in polycrystalline α-D-glucose by γ-rays were trapped in aqueous ethanol solution of 2-nitroso-2-methylpropane. By means of specific labelling of the D-glucose and by e.s.r., five long-lived nitroxide spin-adducts were tentatively assigned.[40] E.s.r. measurements in the free radicals generated by irradiation of lactose confirmed a lyoluminescent reaction of singlet oxygen, involving a ring-cleaved intermediate and the formation of a carboxyl group with a localized electron. The luminescence occurs at λ_{max} 630 nm.[41] Reaction of D-xylose and D-ribose with hydroxy radicals gave radicals which were examined by e.s.r.; the spectra were interpreted in terms of non-selective hydrogen abstraction from the ring carbon atoms. A range of other carbohydrates including sucrose were also examined, and it was concluded that hydrogen abstraction from positions adjacent to the ring oxygen were facilitated in furanose derivatives.[42]

The fluorescence observed in 0.1 M glucose at pH 10 and 70° has been ascribed to fluorescent substances derived from the sugars themselves, whether or not air or asparagine are present.[43] A further paper from the same authors reports the separation of the fluorescent compounds and their u.v. and fluorescence spectra, but structures were not assigned.[44]

3 Isomerization

Lactulose has been prepared in 25 - 30% yield by isomerization of lactose with alkaline sodium sulphite.[45] Maltulose and cellobiulose have been prepared in about 90% yield by the alkaline isomerization of maltose or cellobiose in the presence of an equivalent of boric acid. Using aqueous sodium hydroxide, high concentrations, up to 40% w/v, of disaccharides could be efficiently transformed. The high yields result from the specific complexation of the products while only weak complexation occurs with the starting materials, whose reducing moieties cannot exist in furanose forms due to the 4-*O*-substituent. The product mixtures were analyzed by h.p.l.c. on primary amine-bound silica columns using amine modifier in the eluant; semi-preparative h.p.l.c. on Ca^{2+} resin columns were used for isolation of the pure ketodisaccharides.[46] Epimerizations of aldoses at C-2 and C-3 catalyzed by molybdic acid have been reviewed.[47] D-Mannose has been prepared by molybdate-catalyzed epimerization of D-glucose; after crystallization of the excess D-glucose, the D-mannose was isolated as either *N*-phenyl-D-mannosylamine or as methyl α-D-mannopyranoside. Although the yield from one cycle is only 10%, the glucose recovered materials may be recycled.[48] In a study of D-glucose isomerase which produces D-fructose from D-glucose, it has been shown that 3-, 5-, and 6-deoxy-D-glucose and 3-*O*-methyl- and 6-*O*-methyl-D-glucose are also substrates, whereas 4-*O*-methyl and 4-deoxy-D-glucose are not. Specifically deuterated D-glucoses (28) and (29) on treatment with D-glucose isomerase gave the [1-^{2}H]fructoses (30) and (31) respectively.[49]



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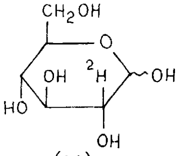

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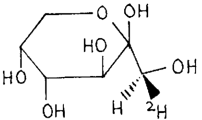

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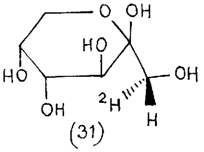

(31)

The results of an optical rotation study of the complexation of D-glucose and D-fructose with germanate ion have been used to predict suitable conditions for improving the yield of D-fructose from D-glucose by means of D-glucose isomerase.[50] The autohydrolysis of 1,2-*O*-isopropylidene-α-D-glucofuranose 5-(hydrogen sulphate) led not to the expected D-glucofuranose 5-sulphate, but to D-fructopyranose 5-sulphate in high yields.[51]

4 Oxidation

In the oxidation of maltose by cupric ions in ammoniacal solution in which the tetra-ammine copper(II) ion is formed, the rate was found to be independent of the concentration of copper(II) ion, to be proportional to that of maltose and to have a dependence on the square root of the concentration of ammonia. A common ion effect was observed by retardation of rate on addition of ammonium chloride. The mechanism proposed included the rate determining formation of an intermediate enediol.[52] A similar conclusion on the mechanism of oxidation of D-glucose by hexacyanoferrate(III) in the presence of ethylenadiamine was supported by a zero order dependence on the transition metal ion concentration and measurements showed that the rate of enolization to yield the intermediate enediolate ion was the rate of oxidation.[53] The kinetic parameters for the pseudo-first order oxidation of pentoses and hexoses using Cu^{2+} have been reported; Arrhenius energies fell in the range 136 - 143 kJ mol^{-1}.[54] The kinetics and mechanism of the oxidation of D-galactose by manganese(III) sulphate have been reported.[55] A further investigation of the oxidation of D-glucose to D-gluconic acid by hexachloroiridate(IV) and by tetrachloroaurate(III) has led to the proposal that the rate determining step is the reaction of -D-glucopyranose with oxidant to produce a free radical and an Ir(III) or Au(II) species. This free radical then rapidly reacts with a further molecule of oxidant to give the products.[56] For the oxidation of L-sorbose by cerium(IV) in aqueous perchloric acid, in which the reactive species is the hydrated cerium(IV) ion, the reaction is first order in the oxidant and in the sugar but the pseudo-first order constants decrease with an increase in the initial concentration of cerium(IV) ion. The enthalpy and entropy of activation were determined and a mechanism, involving no complexation between cerium(IV) and the sugar, was proposed.[57] The conversion of D-gluconic acid, or its lactone into D-arabinose by electrochemical oxidation in aqueous sulphuric acid in the presence of ceric sulphate has been described.[58]

D-Fructose has been oxidatively degraded to D-erythrose, which comprised more than 80% of the total products, by photolysis in the presence of iron(III) chloride in aqueous solution in presence or absence of air. An iron(III)-D-fructose complex was implicated as being the photoreactive species.[59]

A new type of reactor for gas-liquid two-phase enzyme reactions has been described and applied to the oxidation of D-glucose to D-gluconic acid. The membrane reactor consisted of a solution of glucose oxidase and catalase enclosed in a semi-permeable membrane surrounded by a compartment which was fed D-glucose and oxygen.[60] The kinetics were determined,[61] and the system was adapted for continuous flow using a trickle-bed reactor.[62]

The kinetics for the alkali-catalyzed oxidation of D-glucose with sodium 2-anthraquinone sulphonate in water and aqueous ethanol have been investigated. At high quinone concentrations, enolization of D-glucose was the rate determining step for oxidation, D-glucosone being the only primary oxidation product.[63] The oxidation of hexoses by bromamine-T follows zero order kinetics in the oxidant and is first order with respect to sugar and hydroxide ion concentrations. The reaction is independent of ionic strength. A mechanism has been suggested.[64]

Aldohexoses have been prepared by the manganese(III) pyrophosphate oxidation of the hexitols.[65]

5 Other aspects

The 3 to 6-fold increase in free D-galactose, but not other sugars or myo-inositol, in ripening tomato fruit has been confirmed by capillary g.l.c. of the aldononitrile acetate derivatives.[66]

A study of the acid-catalyzed reversion of the aldopentoses has identified 17 pentosyl-pentoses in the product mixture using g.l.c., m.s. and polarimetry.[67] The oligomerization of D-glucose by treatment with hydrogen chloride in DMF for between 7 and 48 hours gave, among other products, 1,6-anhydroglucopyranose, 1,6-anhydroglucofuranose, 6-*O*-α- and -β-D-glucopyranosyl, 1,2-anhydro-α-D-glucopyranose, kojibiose, sophorose, isomaltose, and gentiobiose.[68] Similar acid-catalyzed oligomerization of methyl α-D-glucopyranoside lead to the methyl glycosides of isomaltose, gentiobiose, cellobiose, and maltose.[69]

The hydrothermal degradation of D-[U-^{14}C]glucose and D-[U-^{14}C] fructose gave glyceraldehyde, dihydroxyacetone, methyl glyoxal, glycolaldehyde, 5-hydroxymethylfurfural, and furfural, identified by t.l.c.[70] Repetitive laser irradiation of sugars induces thermal degradation effects within the sample layer to yield higher oligosaccharides. The generated species are well suited for use as a probe for thermal effects with desorption techniques.[71]

The enzymic conversion of L-arabinose to L-arabinono-1,4-lactone using β-D-galactose dehydrogenase from *Pseudomonas fluorescens* has been used as an assay for this monosaccharide.[72] A new monosaccharide, 1-deoxy-D-*altro*-heptulose phosphate, has been synthesized enzymatically from DL-acetoin and D-ribose 5-phosphate using a transketolase mutant of *B. penicillus*.[73] A pyranose-2-oxidase from *Polyporus obtusus*, purified and immobilized, has been used to prepare D-*arabino*-hexos-2-ulose from D-glucose.[74]

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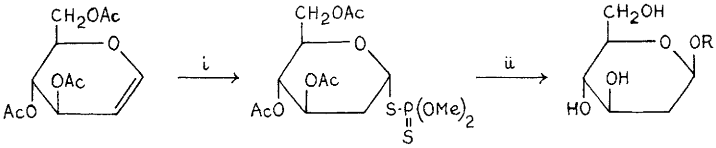
3
Glycosides and Disaccharides

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.- A review with 168 references has appeared (in Japanese) of recent developments in the synthesis of O-glycosides.[1] The acid-catalyzed formation of D-fructosides and 2-thio-D-fructosides in DMSO is believed to proceed by way of the cyclic carbonium ions, and furanoside-pyranoside isomerization by way of the bicyclic 2,6-anhydro-β-D-fructofuranose (which is also 2,5-anhydro-α-D-fructopyranose). Sucrose can be selectively converted into fructosides and 2-thiofructosides.[2] Kinetic methanolysis of arabinose to give the furanosides has been used to obtain the furanosyl acetates which were subsequently produced by acetolysis reactions. It was claimed that in the initial reaction substantial proportions of hemiacetals were produced; this is not in accord with previous observations, and the conclusion may have followed from an irregularity in the analytical procedures used.[3] Acid resin-catalysed reaction of D-glucose with benzyl alcohol was used to give the mixed furanosides and pyranosides which were separated (3 g/24 h) by means of an analytical h.p.l.c. unit adapted for automated preparative use.[4]

1-Thioglycosides have received further attention as precursors of O-glycosides. Phenyl 1-thioglycosides, activated by use of NBS (in the presence of molecular sieve to remove water) and treated with alcohols, yield glycosides in a mild procedure which is applicable with complex alcohols. Yields were in the 60-80% range and anomeric ratios varied from 1:1 to 9:1.[5] In parallel work, phenylmercury triflate was used as activating agent with benzylated or acylated phenyl 1-thio-β-D-gluco- or galactopyranosides; acylated precursors gave β-glycosides exclusively, while α-products predominated when the benzyl ethers were used.[6] In Scheme 1 the use of the phosphorodithioate group as leaving group in 2-deoxy-glycoside synthesis is illustrated,[7] and glycals have also been used to prepare 2-deoxy-glycosides of 2-hydroxycyclohexanone for

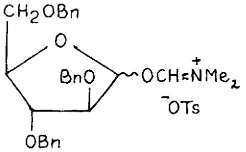


Reagents: i, $(MeO)_2P(S)SH$; ii, ROH-RONa

Scheme 1

C.D. study.[8]

Further work has been reported on the use of glycosyl fluorides as glycosylating agents. 2,3,5-Tri-O-benzyl-β-D-ribofuranosyl and α-D-arabinofuranosyl fluoride were prepared from the corresponding free sugars by use of 2-fluoro-1-methylpyridinium tosylate and, on treatment with alcohols, including sugar derivatives, in the presence of tin(II) chloride and trityl perchlorate, gave good yields of the pentofuranosides with 1,2-*cis*:1,2-*trans* ratios of 4-7:1.[9] The same two pentose triethers have also been used as their iminium tosylates, *e.g.* (1), produced by treatment first with DMF-phosgene complex to give the halides and then with silver tosylate; on reactions with alcohols, α,β-glycoside mixtures were produced in 60-90% yields.[10]



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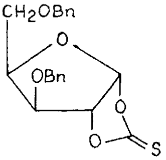

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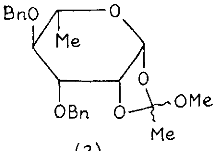

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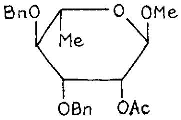

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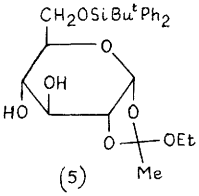

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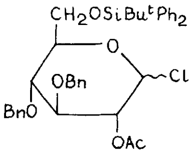
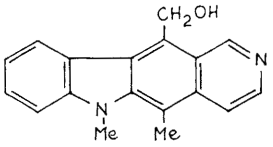


(6)

An interesting procedure which gave β-D-xylofuranosides almost specifically involves treatment of the 1,2-thiocarbonate (2) with alcohols (including carbohydrate derivatives) in the presence of methyl fluorosulphonate as activating agent (S-methylation) and caesium fluoride as acid captor and nucleophile activator.[11] This is somewhat like the well known 1,2-orthoester method which has received further study: thus rearrangement of compounds (3) to the α-glycoside (4), which occurs in the presence of catalytic 1,1,3,3-tetramethylurea-triflic acid, has been shown to be a first order and intramolecular process,[12] and the silylated orthoester (5) has been converted into the glycosyl chlorides (6) for use in oligosaccharide synthesis.[13] The competitive formation of 1,2-orthoacetate derivatives during the Koenigs Knorr glycosidation of various alcohols with 2,3,4-tri-O-acetyl-β-L-arabinopyranosyl bromide has been studied,[14] and the orthoester-based β-glucoside procedure has been employed in efficient syntheses of 2-hydroxy-3-alkyl-1,4-naphthoquinone glucosides.[15]

Glycosyl acetates continue as useful glycosylating agents and alkyl and 1-thioglycosides of 2-deoxy-2-phthalimido-D-glucose were produced in high yields, with the β-isomers predominating, by use of the peracetate and boron trifluoride as catalyst.[16] In analogous fashion thirteen peracetylated 1,2-trans-related 2-bromoethyl glycosides have been prepared[17] as well as a β-D-ribofuranoside of carbazole derivative (7).[18]



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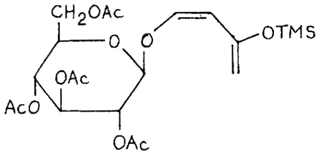
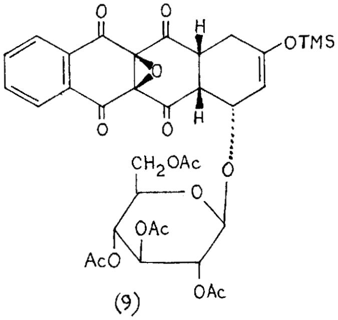


(8)

Glycosyl halides remain the most used glycosylating reagents, and amongst new reports are those on the application of 2-azido-3,4,6-tri-O-benzyl-2-deoxy-β-D-galactopyranosyl chloride in the synthesis of 2-amino-2-deoxy-α-D-glycopyranosides and of appropriate glycosyl bromide derivatives in the preparation of mono- and disaccharide glycosides of benzyl and 2-phenylethyl alcohols,[19] and of the diene derivative (8), which was converted into the anthra-



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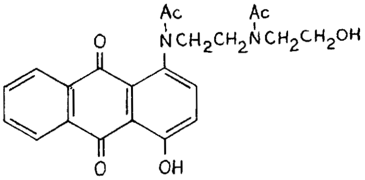
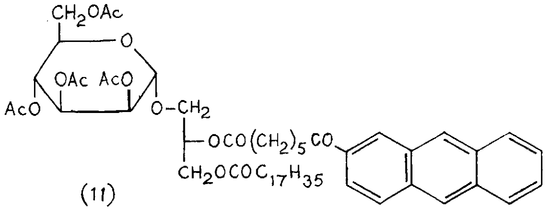


(10)

cycline analogue (9).[20] Seven 1-O-glycosides of the anthraquinone (10) have been tested as possible antineoplastic agents.[21]

Interest in glycosides of glycerol and related compounds has remained high: 1,2-di-O-alkyl-3-O-glycosyl-sn-glycerols have been made from the peracetates of D-glucose and maltose,[22] and closely related β-glucosides and α-mannosides have been prepared from racemic 1,2-di-O-benzyl- and 1-O-benzyl-2-O-stearyl-glycerol. Resulting diastereoisomers were separated[23] and the fluorescent mannosyl diglyceride (11) has also been reported by the same Russian group.[24] For use in affinity chromatography work, allyl 2-acetamido-3,4,6-tri-O-benzoyl-2-deoxy-α-D-galactopyranoside has been converted into the corresponding 3-amino-2-hydroxy- and the 2-hydroxy-3-mercapto-glycosides.[25] Several aliphatic polyamines and polyamine alcohols show antibacterial activity in the form of their α-D-glucosides and 2-amino-2-deoxy-α-D-glucosides.[26]



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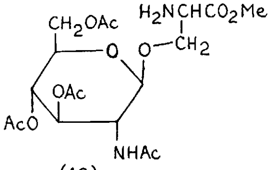


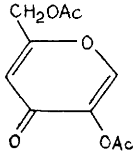
(12)

Several papers have dealt with amino acid glycosides: these refer to the serine glycoside (12) and its conversion into the corresponding asparagine-leucine-serine compound,[27] and corresponding O-glycopeptides built from O-D-galactopyranosyl-L-threonine,[28] -D-threonine, -L-allothreonine and -D-allothreonine. These last compounds were studied by ^{13}C spectroscopy which affords means of determining the enantiomeric nature of the glycopeptides and of assaying the racemization of amino acids.[29] The bindings of Gd^{3+} and Mn^{2+} to peptide units of glycopeptides have also been examined by use of this technique.[30,31] As well as producing glycosylated peptides by chain extensions from the amino ends, it is possible to extend from the carboxylic acid end if the 2-bromoethyl ester protecting group is used.[32] A new way of glycosylating serine, threonine and hydroxyproline involves the use of alkyl glycosides and triflic anhydride as catalyst.[33]

Steroidal glycosides continue to attract attention; the following have been reported: a 2,6-dideoxy-β-D-ribo-hexopyranosyl-digitoxigenin,[34] a 3-β-O-α-L-arabinofuranosyldigitoxigenin,[35] a β-D-glucopyranoside of fucosterol,[36] and several L-rhamnosyl-D-glucosylpennogenins.[37]

Pivaloyl protecting groups allow improved syntheses of β-D-glucopyranosiduronic acid derivatives;[38] more traditional methods have been used for the following glucuronides: 17β-linked derivatives of ethynyl estradiol,[39] 3- and 21-derivatives of tetrahydro-11-deoxycortisol[40] and *O*-substituted derivatives of (R) and (S) propanolol.[41]

In the area of aryl glycosides, phenyl α- and β-, D- and L-arabinopyranosides[42] and phenyl α-L-arabinofuranoside[43] have been reported, and 9 glycosides of some flavanones and dihydrochalones have been examined for their sweetness; some were 400 times sweeter than sucrose.[44] A synthesis of *p*-nitrophenyl β-D-mannopyranoside was based on oxidation of the 3,4,6-triacetate of the β-D-*gluco*-isomer followed by reduction. Oxidation of the alcohol with DMSO-phosphorus pentaoxide in DMF was successful; use of DMSO in acetic anhydride led to the pyrone (13).[45]



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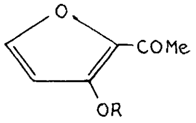


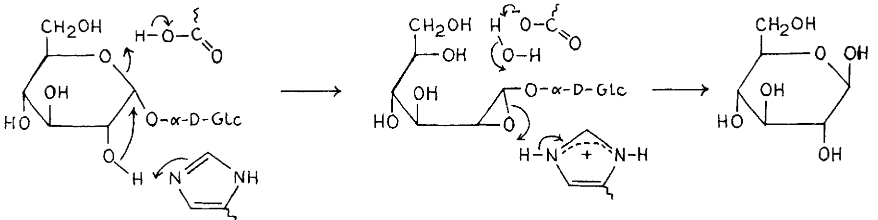
(14) R = β-D-Glucopyranosyl
(15) R = β-D-Galactopyranosyl
(16) R = H

Heating maltose or lactose with secondary amino acids in ethanolic triethylamine gave the furan glycosides (14) and (15). Dry distillation of the former gave isomaltol (16) which may account for the production of this compound during bread making.[46]

1.2 Synthesis of Disaccharides and Their Derivatives.- Several syntheses of disaccharide derivatives have been described in papers noted in the previous section - particularly in those which refer to new methods of glycoside bond formation; other related work appears in papers covered in Chapter 4. In the following section compounds are dealt with according to the natures of their non-reducing portions.

Reviews have appeared on the chemistry of sucrose and its conversion into a range of selectively substituted derivatives[47] and on the relative reactivity of the hydroxy groups of lactose.[48]

Self condensation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-trimethylsilyl-α,β-D-glucose with trimethylsilyl triflate as catalyst gave a mixture of perbenzylated α,α- and α,β-trehalose in high yield. Analogous reaction of the D-galacto- and D-manno-isomers gave only α,α-linked products.[49] α-D-Mannopyranosyl α-D-mannopyranoside has also been prepared from α,α-trehalose by way of the 4,6-, 4',6'-di-O-benzylidene acetal 2,2'-ditriflate.[49A] (1,1-^{13}C)α,α-Trehalose has been obtained in 37% yield from tetra-O-benzyl-D-(1-^{13}C)glucopyranose and was used in the investigation of mode of action of an insect trehalase. It was proposed that the enzyme activated the hydroxy group at C-2 and this oxygen atom nucleophilically opened the pyranose ring with the assistance of an acid group which caused protonation of the ring oxygen (Scheme 2).[50] Sucrose can be easily converted into α-D-glucopyranosyl 3,4-anhydro-β-D-tagatofuranoside (stereochemical inversion at C-4) by reaction of partially substituted isopropylidene or benzoate derivatives with the DEAD-TPP reagent. In the course of the work the new 1',4'-anhydride of sucrose was encountered.[51]



Scheme 2

Five disaccharides and two trisaccharides were isolated following treatment of methyl 4,6-O-benzylidene-α-D-glucoside with tetra-O-acetyl-α-D-glucopyranosyl bromide; the main products were 2- and 3-linked compounds but some reaction involved substitution at O-6.[52] Reaction of D-glucose in DMF containing hydrogen chloride gave several disaccharides as well as 1,6-anhydro-β-D-glucofuranose and -pyranose and 1,2-anhydro-6-O-α- and -β-D-glucopyranosyl-α-D-glucopyranose.[53] Similar treatment of methyl α-D-glucopyranoside gave several disaccharide glycosides.[54] Besides expected monosaccharide acetals, 1,3-, 1,4- and 1,6-linked disaccharide acetals have been isolated from the products of treatment of D-glucose and D-mannose with acetone-sulphuric acid.[55]

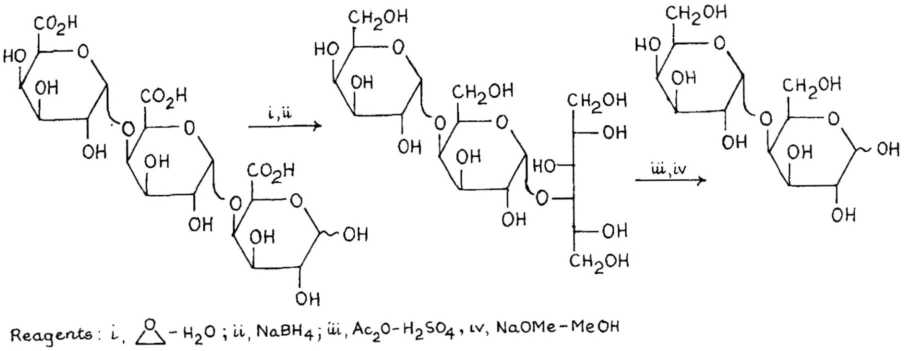
Hydrothermolysis of cellobiose between 180 and 250°C is independent of pH in the range 3-7; the disaccharide is destroyed 8 times faster than is D-glucose, therefore the latter sugar is the main reaction product.[56] The phytotoxic compound rhynchosporoside is the 1-*O*-α-cellobioside of propane-1,2-diol and not the 2-linked compound as previously proposed. Both compounds were made by displacements from the corresponding benzylated β-phenyl 1-thioglycoside.[57] A full 2D-n.m.r. investigation of cellobionitrile octa-acetate has been reported.[58] Several specific reactions have been carried out on methyl 2-*O*-glucopyranosyl-β-D-glucopyranoside, including its conversion to the corresponding glucosyl-β-D-allopyranoside. A range of 6,6'-disubstituted and 6- and 6'-monosubstituted compounds were described.[59]

Among disaccharides having D-glucose bonded to another hexose derivative, 2-acetamido-2-deoxy-3- and 6-*O*-β-D-glucopyranosyl-D-glucose,[60] 4-*O*- and 6-*O*-α-D-glucopyranosyl-α-D-galactose [as *p*-(trifluoroacetamido)phenyl glycosides],[61] 6-*O*-β-D-glucopyranosyl-D-galactose,[62] 4-*O*-α-D-glucopyranosyl-α-L-rhamnose [as the *p*-(trifluoroacetamido)phenyl glycoside][63] and 2,3-di-*O*-methyl-4-*O*-(3,6-di-*O*-methyl-β-D-glucopyranosyl)-L-rhamnose[64] have been prepared - mostly for biological studies. Various 1,2-glucopyranosylidene disaccharide analogues are referred to in Chapter 16.

Several β-linked D-mannopyranosyl disaccharides have been produced using a benzylated α-D-mannopyranosyl bromide and a silver zeolite. Good yields were afforded with primary alcohols and α:β ratios were *ca.* 1:6; with secondary alcohols yields were more moderate and the ratios were not so favourable.[65] 3-*O*-(α-D-Mannopyranosyl)-D-mannose has been synthesized by way of a substituted α-D-mannopyranosyl tosylate which was more effective than the corresponding halides and gave a yield of 87% in the condensation step. The disaccharide was conjugated to bovine serum albumin for immunological work.[66]

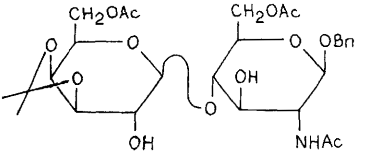
Glycosylation of benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside afforded access to 2- and 3-*O*-β-D-galactopyranosyl-D-galactose[67] and the 4-*O*-α-linked disaccharide has been made from "polygalacturonic acid" which is a commercially available, enzymically deesterified pectin. Pectinase gave di- and trimers, the former giving the required product directly, while the latter was treated as indicated in Scheme 3.[68] The peracetylated 2-bromoethyl 4-*O*-α- and β-D-galactopyranosyl-β-D-galactopyranosides and the corresponding 2-deoxy-4-*O*-β-D-galactopyranosyl-2-phthalimido-β-D-glucopyranoside ester have been treated with various difunctional compounds such as hexane-1,6-dithiol to give products containing suitable 'spacer arms' for coupling to proteins.[69]

Three papers have reported on galactosyl-substituted 2-amino-2-



Scheme 3

deoxy-D-glucose derivatives: the acetates of the α- and β-1,4 linked compounds have been made from 2-acetamido-1,6-anhydro-3-O-benzyl-2-deoxy-β-D-glucopyranose,[70] and N-acetyl-lactosamine, obtained from the commercially available 3-O-β-D-galactopyranosyl-D-arabinose, has been used to prepare compound (17) which is a potential intermediate for the synthesis of a blood group substance



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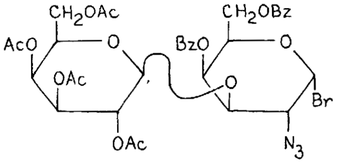
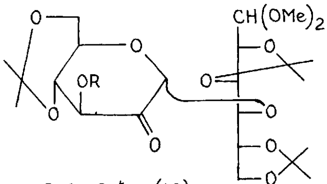


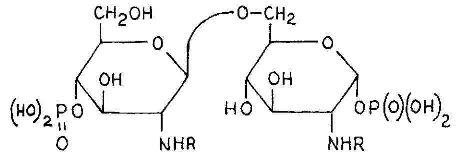
(18)

tetrasaccharide.[71] Peptides bearing 2-acetamido-2-deoxy-3-O-β-D-galactopyranosyl-α-D-glucose units have been prepared by amide condensation procedures.[72] For related work the α-glycosylating agent (18) has been developed.[73] Degradation of keratan sulphate afforded access to 2,5-anhydro-4-O-β-D-galactopyranosyl-[1-^3H] mannitol 6-sulphate and 6,6'-disulphate, which were required for use as β-D-galactosidase and 6-O-sulphogalactose sulphatase substrates.[74]

Many disaccharides with amino-sugars as non-reducing moieties have been reported. 2-O- And 3-O-(2-deoxy-2-phthalimido-β-D-glucopyranosyl)-D-galactose[75] the β-p-nitrophenyl glycoside of the N-acetyl analogue of the latter[76] have been made by conventional methods, and maltose has been used to prepare 2-acetamido-2-deoxy-α-D-glucosyl and α-D-mannosyl disaccharide derivatives by way of the unusual carbonyl derivative (19) and the derived oxime. Related L-idose compounds were also described in this study, which was



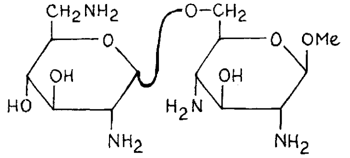
R = SiPh$_2$Bu^t (19)



(20) R = (R)-3-hydroxytetradecanoyl

aimed at the preparation of heparin model compounds.[77] Several of the disaccharides which have been synthesized have amino-sugars in both components, notably the β-1,6-linked D-glucosamine dimer. The 6'-phosphate was prepared using a 6-phosphonylated oxazoline derivative,[78] and the 1,4' diphosphate (20), which is a lipophilic part of bacterial cell surface lipopolysaccharides (lipid "A"), has been made,[79] as has the 4'-monophosphate.[80,81] 2-Acetamido-3-O- and -6-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-α-D-galactose have been synthesized as benzyl glycosides by standard procedures.[82]

The tetra-amino compound (21), which is active against Gram-negative bacteria, has been made by the "azido procedure",[83] and compound (22) has been prepared from maltose as a potential inhibitor of α-glucosidases.[84]



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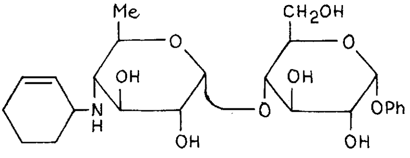
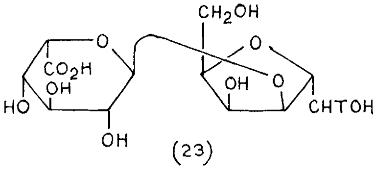


(22)

Various specifically labelled uronic acid derivatives of 2,5-anhydro-D-mannitol sulphates, e.g.,(23) and (24), were made from dermatan sulphate as substrates for α-L-iduronidase, β-D-glucuronidase and



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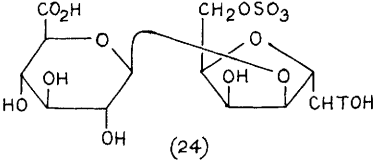
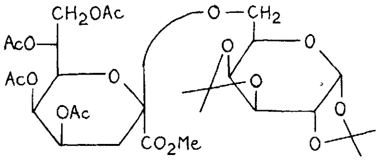


(24)

sulphoiduronate sulphatase,[85] and in related work the methyl ester of 4-O-(α-L-idopyranosyluronic acid)-β-D-glucose was made from cellobiose by way of 6'-deoxy-5'-enose derivative. Hydroboration gave a mixture of the D-gluco- and L-ido-disaccharides, the latter being oxidized to the required uronic acid.[86] The glycosyl bromide procedure was used to prepare the D-*manno*-2-octulopyranosylonic acid disaccharide (25) derivative in high yield. With secondary alcohols elimination occurred, but with mercury(II) catalysts it was still possible to obtain reasonable (60%) yields of disaccharide derivatives.[87]

In the study of the acid-catalysed reversion of aldopentoses, 17 disaccharides have been identified.[88] 2-*O*-α-L-Lyxopyranosyl-D-galactose has been made and coupled to naringenin. Since the product was less bitter than the natural L-rhamnose analogue it was concluded that the taste of the latter was related to the presence of the methyl group at C-5'.[89] Various xylopyranosyl disaccharides have been made by use of the 3,4-di-*O*-acetyl-1,2-*O*-(1-cyanoethylidene) derivative.[90]



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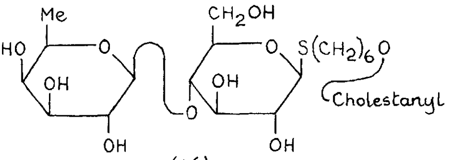
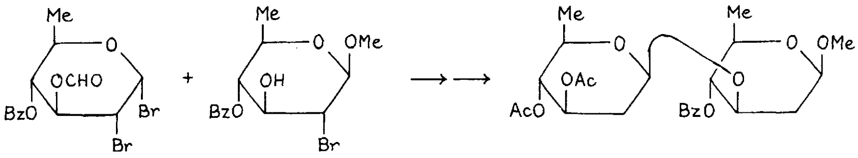


(26)

L-Rhamnose-containing disaccharides continue to attract interest: the 1,2-*O*-cyanoethylidene procedure has been used to link the sugar to *O*-3[91,92] and *O*-4[92] of D-glucose, *O*-2[93] and *O*-3[91] of D-galactose, *O*-2 of D-mannose[93] and *O*-6 of 2-amino-2-deoxy-D-glucose.[94]

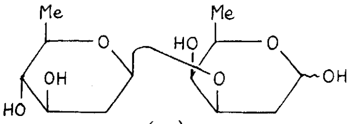
Disaccharides comprising L-rhamnose attached to O-3 and O-4 of D-glucuronic acid derivatives have also been reported[95] as have 6-deoxy-2-*O*-(α-L-rhamnopyranosyl)-L-talose,[96] *p*-aminophenyl 2-*O*-acetyl-3-*O*-α-L-rhamnopyranosyl-α-L-rhamnoside[97] and 2-*O*-(α-L-rhamnopyranosyl)-D-xylose and -6-deoxy-L-glucose.[98] *p*-Nitrophenyl 2-*O*-α- and β-L-fucopyranosyl-β-D-fucopyranoside were prepared as fucosidase substrates,[99] and further structure-taste studies have been carried out on flavanones containing D- or L-fucosyl-D-galactose disaccharides.[100] The 6-deoxy-D-galactose disaccharide derivative (26) has also been reported.[101]

Thiem and coworkers have continued their studies of disaccharides of dideoxy-hexoses and have reported on the preparation of the D-C component of aureolic acid (Scheme 4).[102,103] Similarly they have made the B-A unit (27) of mithramycin together with the α-linked isomer and both the 1,4-linked analogues.[104] Compounds (28) and (29) which occur in the trisaccharides of anthracyclinones



Scheme 4

were prepared by a "glycal addition" procedure as indicated in Scheme 5.[105]



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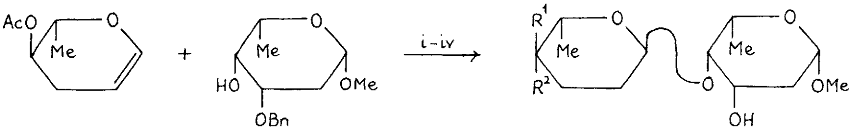


Reagents: i, NIS; ii, H_2-Pd/C; iii, MeONa-MeOH; iv, PDC-CH_2Cl_2. For (28), i-iii,ii; For (29), i-iv, ii

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

(29) $R^1,R^2 = O$

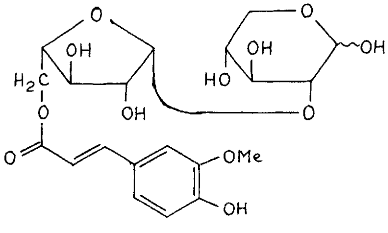
Scheme 5

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

Some further features of the biosynthesis of iridoid glycosides have been elucidated,[106] and epoxide ring opening reactions of epoxyiridoid β-D-glucosides have been investigated.[107]

2- And 3-O-β-D-glucopyranosides of 1-*C*-*p*-hydroxyphenylglycerol and related compounds have been isolated from pine needles; both enantiomers of the aglycones occurred in the plant.[108] Other β-D-glucopyranosides to have been isolated from botanical sources are those of 2-methylpropane-1,2-diol,[109] 3-(hydroxymethyl)furan (structure confirmed by synthesis),[110] and (R)-dihydromaleimide. This last glycoside had plant growth inhibitory properties - apparently, however, only on liberation of the aglycone.[111]

In the area of disaccharide natural products, 2-*O*-[5-*O*-(*trans*-feruloyl)-β-L-arabinofuranosyl]-D-xylose (30) was formed by enzymic hydrolysis of the cell walls of wheat bran and other plants.[112]



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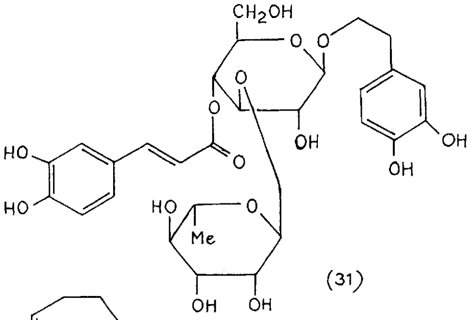

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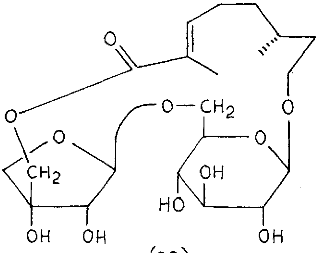
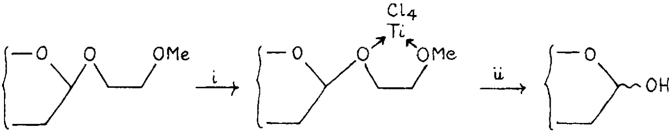


(32)

Cell suspension cultures of <u>Syringa vulgaris</u> accumulate up to 16% of their dry weight as a mixture of hydroxyphenylethyl glycosides of which verbascoside (31) is the major.[113] The interesting cyclic apiosylglucose glycoside (32) is a bitter monoterpene derivative found in a Japanese shrub.[114]

1.4 Hydrolysis and Other Reactions and Features.- The rate limiting step in the acid-catalysed hydrolysis of alkyl α- and β-D-fructofuranosides has been shown to be the unimolecular heterolysis of the C-2—O-2 bond following protonation of the latter atom.[115] A technical report has described the successful use of perfluorinated resin sulphonic acids for the hydrolysis of cellobiose, sucrose or starch in either batch or continuous flow processes.[116]

A new procedure for obtaining 1-hydroxy aldose derivatives containing such acid-labile substituents as allyl or acetyl involves



Reagents: i, $TiCl_4$; ii, H_2O

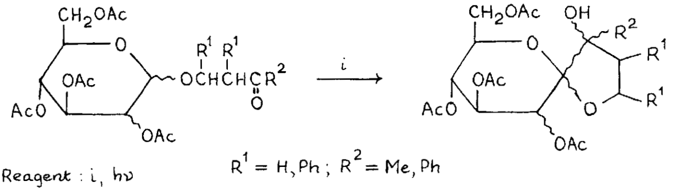
Scheme 6

the use of 2-methoxyethyl glycosides which, with titanium tetrachloride, give complexes which hydrolyse readily with water (Scheme 6).[117] An examination of the rates and mechanisms of the acetolyses of permethylated α- and β-D-glucose, -D-galactose and -D-mannose has indicated that the relative reaction rates differ markedly from the corresponding rates of hydrolysis of glycosides.[118] Trimethylsilyliodide in carbon tetrachloride causes rapid cleavage of the glycosidic bonds of permethylated mono- and di-saccharides. With pertrimethylsilylated analogues 1,6-linkages cleaved fastest and other reactions were slower. Since the iodinolysis products are readily hydrolysed to free sugars, the method constitutes an alternative to acid hydrolysis of glycosidic bonds.[119]

Rates of the acidic hydrolysis of substituted phenyl α- and β-mannopyranosides showed that the α-anomers hydrolysed up to 2.7 times faster than did the β-compounds, and up to 1.7 times faster than did the corresponding α-glucopyranosides. The work was extended to a study of the alkaline hydrolysis of these compounds and, as was to be expected, electron withdrawing groups in the aromatic rings facilitated reactions and α-compounds reacted 100-1000 faster than their anomers - presumably because the C-2 oxyanion can participate in the reactions of the former.[120] A related study of substituted phenyl β-D-glucopyranosides was carried out over the temperature range 40-100°C,[121] and it has been found that the rate of the alkaline hydrolysis of the *o*-nitrophenyl compound is increased 16 times by added phenylboronic acid and hexadecyltrimethylammonium chloride. Apparently hydrophobic boronate esters are formed and are incorporated into a cationic micelle. Strangely, the hydrolysis of the β-D-galactoside analogue is enhanced by a factor of only 2.5.[122] 3'- And 4'-*O*-methylsucrose have been isolated by preparative h.p.l.c. from partially methylated sucrose, and their rates of alkaline degradation were determined in connection with mechanistic studies on the alkaline break-down of sucrose. The former ether was relatively stable, which is consistent with the proposal that the degradation involves ionization at 0-3'.[123]

In acetonitrile, and in the presence of 1,4-dicyanonaphthalene as sensitiser, phenyl α- and β-D-galacto- and D-glucopyranosides on photolysis at 350 nm give radical cations which lose phenoxy radicals to afford the glycosyl carbonium ions. These hydrolyse to give the free hexoses which are then slowly degraded further; in the presence of methanol they are converted into the anomeric methyl glycosides.[124]

Descotes has discussed general aspects of the photoreactivity of 3-oxoalkyl glycosides illustrated in Scheme 7,[125] and with G. Remy

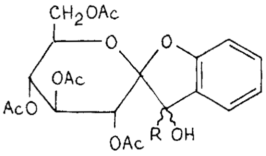


Reagent : i, hν

$R^1 = H, Ph$; $R^2 = Me, Ph$

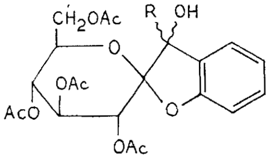
Scheme 7

has specifically reported on the reaction of the 3-oxobutyl L-arabinopyranoside triacetates. 3-Oxobutyl glycosides of 2-deoxy- and 2,3-dideoxy-β-D-glucose were then made from the 2-deoxy-2-mercuri analogue and photocyclised to give mixed *spiro*-products which then afforded the α-anomers predominantly with acid.[125a] As anticipated from earlier work, the α-anomer with an axial H-1 atom reacted faster than did the β-compound.[126] Parallel work on the *O*-formyl- and *O*-acetyl-phenyl β-D-glucopyranoside tetra-acetates gave compounds (33) and (34) which, with acid, readily isomerized into the latter α-forms.[127]



(33)

R = H, Me

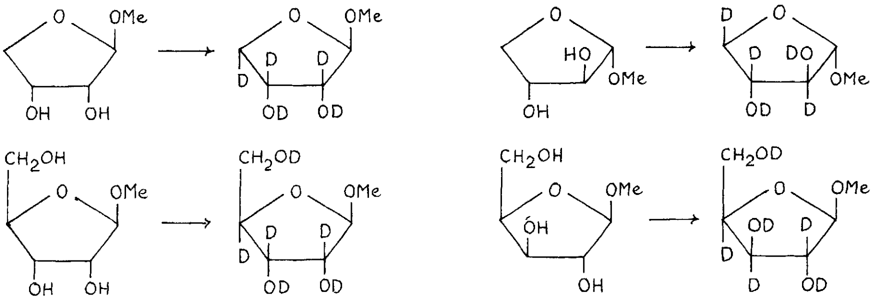


(34)

The equilibrium constants for the ionization of several methyl glycofuranosides in aqueous alkali metal hydroxide solutions were determined and related to the relative retentions of the compounds on anion exchange columns.[128]

A very interesting report has appeared on the deuteration of methyl tetro- and pento-furanosides in the presence of Raney nickel as is illustrated in Scheme 8. Exchange at C-4 did not occur with other pentofuranosides. Several aspects of the reactions were discussed in detail: the synthesis of specifically labelled compounds, the specificities of the reactions and conformational aspects.[129]

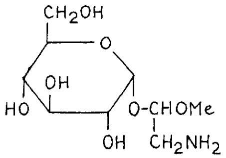
Some long chain alkyl (C_7-C_{10}) glycosides and 1-thioglycosides



Scheme 8

have thermotropic liquid-crystal phases between room temperature and their melting points, and such properties may be expected for glycosides which have heptyl or longer aglycone chains.[130]

Heats of dilution in water of some methyl glycosides have been determined by microcalorimetry, and it has been concluded that no favourable solute-solute interactions relative to solute-solvent interactions occur.[131] The diastereoisomers (35) and (36) are competitive inhibitors of yeast α-glucosidase.[132]



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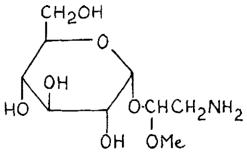
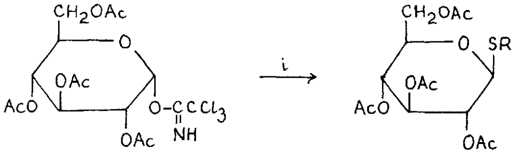


(36)

2 S-Glycosides

The uses of S-glycosides in several syntheses of O-glycosides are noted in the preceding section.

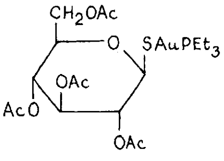
Glycosyl trichloroacetimidate acetates can be used in the pre-



Reagents: i, RSH-BF$_3$

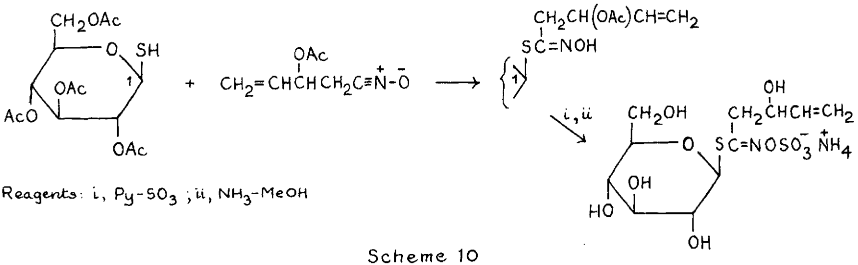
Scheme 9

paration of 1-thio-β-D-glucopyranosides (Scheme 9); the use of the corresponding benzyl ethers gave rise to the α-anomers.[133] More conventional synthesis involves the use of peracetylglycosyl bromides and aromatic thiols in acetonitrile in the presence of triethylamine. In the D-mannose series 1,2-thio-orthoesters were formed together with 1-thio-β-glycosides and attempts to use these procedures with aliphatic thiols led mainly to the elimination product.[134] Long chain alkyl 1-thio-β-D-glucopyranosides were prepared by use of the 1-thio-sugar and alkyl iodides, and it was observed that the cytotoxicity of the products was optimal with the octyl compound.[135] The ^{1}H, ^{13}C and ^{31}P n.m.r. spectra[136] of



(37)

auranofin (37), an antiarthritic drug, as well as syntheses of ^{195}Au-, ^{32}P- and ^{35}S-labelled samples[137] have been described. The synthesis of progoitrin, which is a plant glucosinolate, together with a diastereoisomer is outlined in Scheme 10.[138]



Reagents: i, Py-SO3 ; ii, NH3-MeOH

Scheme 10

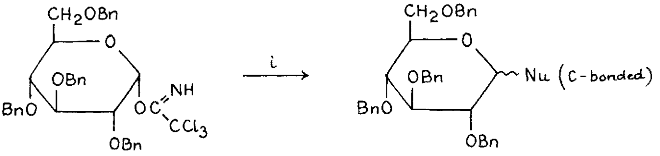
3 C-Glycosides

These compounds are currently attracting extremely wide interest, especially since members of the class are related to many components of other natural products.

3.1 Pyranoid Compounds.

- The main routes to these compounds depend upon nucleophilic attacks at the anomeric centres of a wide range of pyranose derivatives, but, for the first time, reports have appeared on additions of glycosyl radicals to unsaturated compounds as an alternative approach. Also, reactions of glycosyl cyanides can be used to elaborate some members of the class. These approaches will be dealt with in turn.

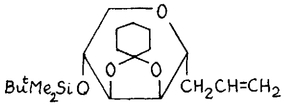
Displacement of the trichloroacetimidate group is illustrated in Scheme 11, the first two nucleophiles listed giving mainly β-linked products, the third a mixture of anomers and the others primarily α-products.[139] Similarly, the corresponding 2'-pyridyl 1-thio-β-D-glucoside derivative, treated with trimethylsilylated enol ethers or with aromatic hydrocarbons, gave α-linked products with C-bonded ketonic (e.g. $PhCOCH_2$-) or aryl substituents.[140] Further work has been reported on C-allyl glycosides produced from glycosyl acetates using allyltrimethylsilane and boron trifluoride; good selectivities were recorded for the production of compounds (38) and (39), the latter being an unexpected observation.[141]



Reagents: i, $Me_3SiNu - BF_3$ or Me_3SiOTf

Nu = ←CN, $EtO_2C\overset{\uparrow}{C}HCH_2CO_2Et$, $←CH_2COR$ (R = Me, Bu^t, Ph), Allyl

Scheme 11



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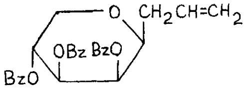
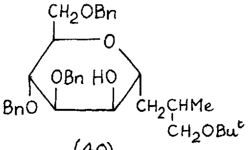


(39)

Anhydro-sugar derivatives can also be used to produce C-glycosides, the corresponding 1,2- and 1,6-anhydrides having been employed together with nucleophilic carbon species to obtain compounds (40)[142] and (41),[143] which were required during synthetic



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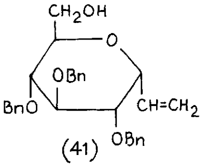

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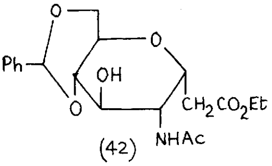
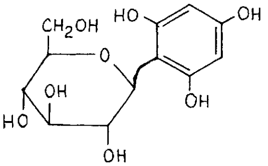


(42)

studies of palytoxin (see also Chapter 24).

Free sugars themselves can undergo nucleophilic attack at the anomeric centre as in the synthesis of the ester (42) from the corresponding free sugar by means of a Wittig reagent,[144] and related procedures must have been involved in the generation of compounds such as (43),[145] (44)[146] and (45)[147] by reactions of



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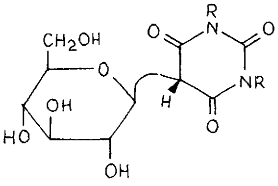
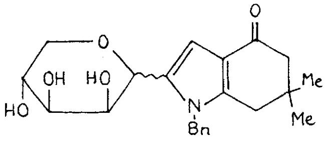


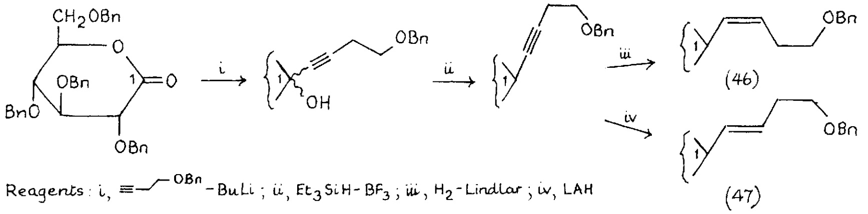
(44) R = H, Me



(45)

appropriate free sugars with polyhydric phenols, barbituric acid or its 1,3-dimethyl derivative and 5,5-dimethyl-1,3-cyclohexanedione, respectively. In each of these cases acyclic products were formed in association with the *C*-glycosides, and in the last case the cyclization had to be induced by a specific acid-catalysed reaction, and while the α- and β-pyranosyl compounds were obtained under thermodynamic control, a furanoid intermediate was involved.

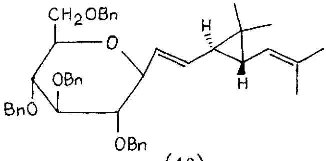
Complex ketose derivatives can be formed by carbanion attack at the carbonyl group of aldonolactones, deoxygenation at the anomeric centre thus giving *C*-glycosidic products. In this way the isomeric alkenes (46) and (47) were made by use of an acetylinic nucleophile



Reagents: i, $\equiv$—OBn -BuLi; ii, Et_3SiH-BF_3; iii, H_2-Lindlar; iv, LAH

Scheme 12

(Scheme 12) and, with 1,1-dibromo-1-alkenes, compounds (48) and (49) were made.[148] The first *C*-linked disaccharide derivative has been



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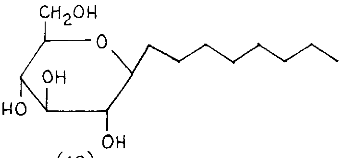
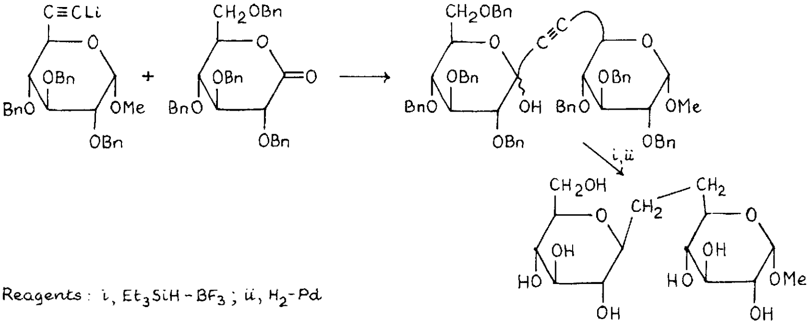


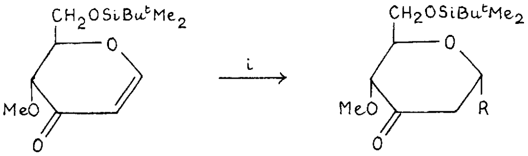
(49)

prepared using this approach, the alkyne anion having been produced from the corresponding 7,7-dibromo-6,7-dideoxyheptose derivative (Scheme 13).[149] Conjugate addition of an organo copper reagent to an enone (Scheme 14) has given α-linked products with high selectivity.[150]



Reagents: i, $Et_3SiH-BF_3$; ii, H_2-Pd

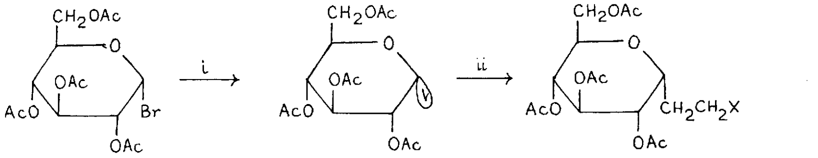
Scheme 13



Reagents: i, R(PhS)CuLi

Scheme 14

Two significant communications have described the generation of glycosyl radicals by treatment of glycosyl bromides or phenyl 1-selenoglycosides with tributyltin hydride, and their trapping with acrylic esters or acrylonitrile. Good α-selectivity was observed with yields of specific adducts of up to 70% (Scheme 15).[151,152]

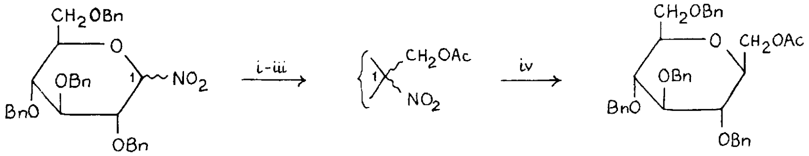


Reagents: i, R_3SnH ; ii, $CH_2=CHX$

X = $\cdot CO_2R$, $\cdot CN$

Scheme 15

To some extent reduction products are formed together with some compounds derived by radical addition to a second acrylic acid derivative. A somewhat related procedure which also depends on the use of trialkyltin hydride involves the use of 1-nitroglycosyl compounds as illustrated in Scheme 16. The procedure was also

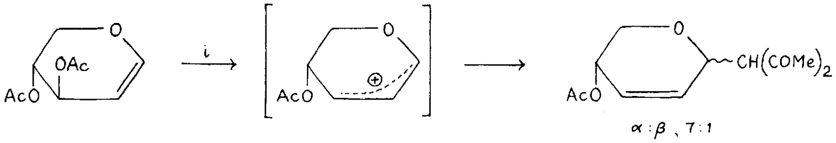


Reagents: i, NaOMe; ii, CH$_2$O; iii, Ac$_2$O-Py; iv, Bu$_3$SnH

Scheme 16

applied in the furanose series.[153]

Additional reports have appeared on the direct derivation of C-glycosides from glycal esters. β-Dicarbonyl compounds, e.g., methyl acetoacetate, in the presence of boron trifluoride or bis(benzonitrile)dichloropalladium, react as illustrated in Scheme 17[154] and, in like fashion, 2,3-unsaturated C-glycosyl-

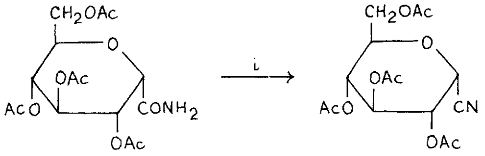


Reagents: i, CH$_2$(COMe)$_2$-BF$_3$ or Pd(PhCN)$_2$Cl$_2$

Scheme 17

cyanides, are formed by reaction of glycal or 2-hydroxyglycal esters with trimethylsilyl cyanide and boron trifluoride (or tin(IV) chloride).[155] A reaction related to these is noted in Chapter 24.

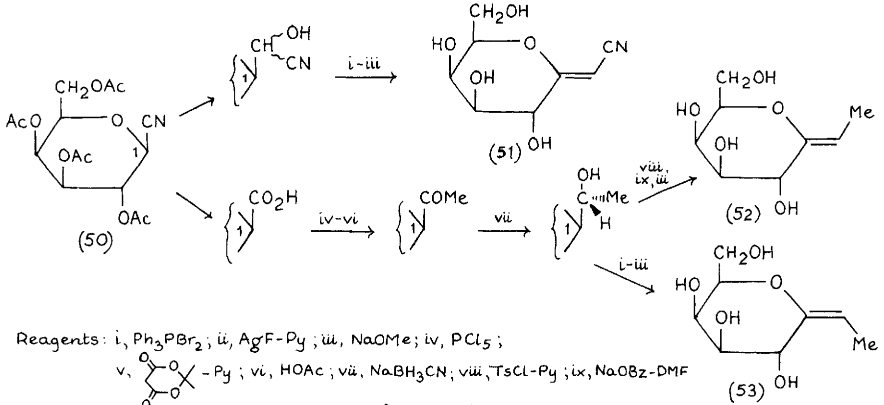
Dehydration of 2,6-anhydro-D-heptonamide peracetates with N-(chloromethylene)-N-methylmethanaminium chloride affords an alternative synthesis of glycosyl cyanides as exemplified in Scheme



Reagents: i, DMF-(COCl)$_2$ (giving $Me_2\overset{+}{N}{=}CHCl\ \overset{-}{Cl}$)

Scheme 18

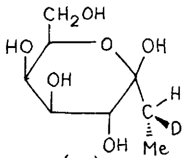
18,[156] and the anomeric configurations of such products have been shown to be assignable from the C≡N stretching frequency in the laser-Raman spectrum, axial nitriles giving absorptions at least 12 cm^{-1} lower than their equatorial anomers. These frequencies were not observable in the i.r. spectra.[157] From the β-D-galacto-cyanide (50), the enolic derivatives (51)-(53) have been prepared



Reagents: i, Ph_3PBr_2; ii, AgF-Py; iii, NaOMe; iv, PCl_5; v, -Py; vi, HOAc; vii, $NaBH_3CN$; viii, TsCl-Py; ix, NaOBz-DMF

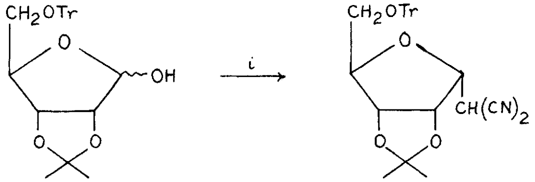
Scheme 19

as shown in Scheme 19, the first two, but not the third, are susceptible to β-galactosidase-catalysed hydration.[158] Such hydration of the deuterated compound (52), C-2(^{2}H), occurred to give the isomer (54).[159] Other references to C-glycosides are made in Chapter 24.



(54)

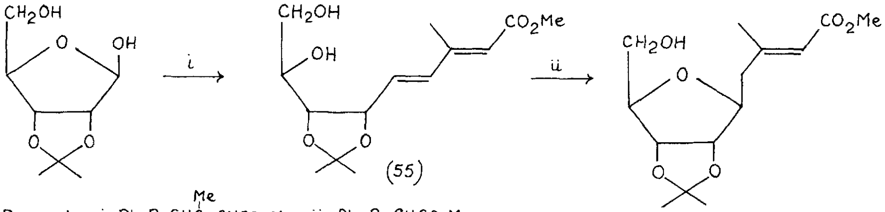
3.2 Furanoid Compounds.- As with the pyranoid compounds several routes to furanoid C-glycosides have been employed. Under phase transfer conditions sodiomalononitrile and related salts give such products from furanoid free sugar derivatives. Intermediate alkenes may be involved, ring closure reactions giving large proportions of thermodynamically less favoured 1,2-cis-related isomers



Reagents: i, $NaCH(CN)_2$

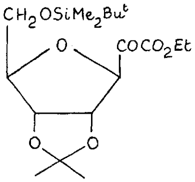
Scheme 20

(*e.g.*, Scheme 20; the illustrated product was isolated in 80% yield).[160] In contrary fashion, 2,3-*O*-isopropylidene-D-ribose gave, under Wittig conditions, the diene (55) which cyclized to the β-anomer (56) exclusively (Scheme 21) and in parallel manner, compound (57) was prepared and from it the *C*-nucleosides (58)-(60).[161] The anomeric phosphonates (61), which are analogues of the glycosyl 1-phosphates, have been made using a Wittig reagent with 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose.[162]



Reagents: i, $Ph_3P{=}CH\overset{Me}{C}{=}CHCO_2Me$; ii, $Ph_3P{=}CHCO_2Me$

Scheme 21



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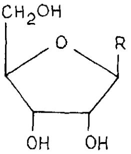

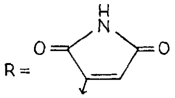

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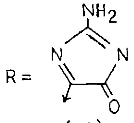

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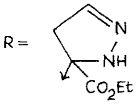

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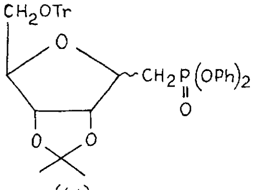

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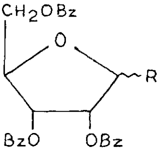
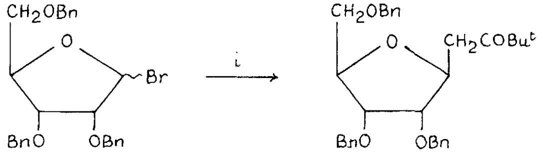


(62) R= $\cdot CH_2CH{=}CH_2$

(63) R= $\cdot CH_2CH{=}CHC_3H_7$

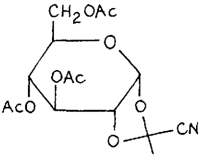
Direct condensation of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and allyltrimethylsilane in the presence of zinc bromide or boron trifluoride gives the anomers (62) in the α:β ratios of 4:1 and 7:1,[141] respectively, and analogous reaction of 1-hexene in the presence of tin(IV) chloride gave not just the *C*-glycosides (63) but also chlorinated adducts. The use of trimethylsilyl triflate avoids this problem, but only 20% yields are obtained. On ozonolysis, the alkenes (63) gave glycosylethanals from which other extended chain compounds were derived.[163]

Silylated enol ethers can be used to prepared functionalized C-glycosides from glycosyl bromides (e.g., Scheme 22) the α:β ratios being ca. 1:9.[164] In related fashion, acetates such as 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose together with trimethylsilyl cyanide and tin(IV) chloride give the corresponding glycosyl cyanides, e.g., 2,3,5-tri-O-acetyl-β-D-ribofuranosyl cyanide;[165] however, an examination of an extensive set of esters indicated that 1-O-acetyl-2,3,5-tri-O-toluyl-β-D-ribose, and hence the 1-bromide which was treated with mercury(II) cyanide, proved to be the best source of the ribofuranosyl cyanide.[166] Treated with trimethylsilyl cyanide and boron trifluoride, tetra-O-acetyl-β-D-ribofuranose gives the β-cyanide by way of the 1,2-O-cyanoethylidene intermediate; under similar conditions penta-O-acetyl-β-D-glucopyranose gave only the corresponding intermediate (64), which resisted further reaction. On the other hand, methyl 2,3,5-tri-O-acetyl-β-D-ribofuranoside underwent reaction with ring opening to give the acyclic product (65).[167]



Reagents: i, $CH_2{=}C(OTMS)(Bu^t)$ - TMS·Br - $ZnBr_2$

Scheme 22



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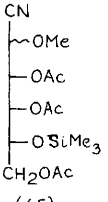

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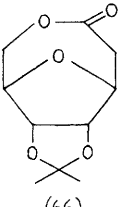

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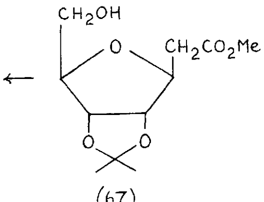
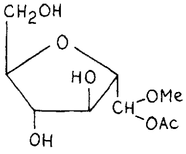


(67)

Several simple anomeric substituents in C-glycosides have been elaborated: e.g., the cyano group, via formyl, to the (R)- and (S)-glycinyl group,[168] chlorocarbonyl to cyanomethylcarbonyl, which can be further transformed into heterocyclic groups for C-nucleoside synthesis,[169] and the $-C{\equiv}CCO_2Et$ group into a pyrazolo[1,5-d]-1,2,4-triazin-4(3H)-on-8yl residue.[170]

Synthesis of 3,6-anhydro-2-deoxy-4,5-O-isopropylidene-D-allo-heptonic acid lactone (66) from D-ribose has been achieved in 31% overall yield via the Wittig-derived intermediate (67).[171]

Whereas methyl 2-amino-2-deoxy-α-D-glucopyranoside with sodium nitrite in anhydrous acetic acid gave mainly the 2,5-anhydro-D-mannose derivative (68), the β-tetra-O-acetate of the same sugar and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamine gave mainly the penta-acetates of D-glucopyranose and D-mannopyranose and of D-glucopyranose, respectively.[172]



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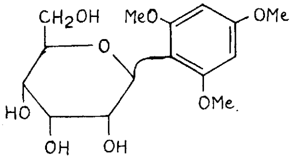

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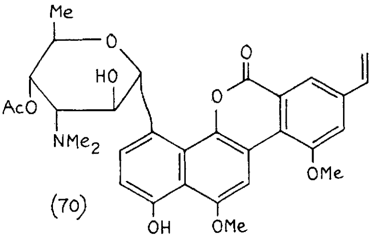

(70)

3.3. Glycosides Isolated from Natural Sources.- The third report of a naturally occurring C-galactoside-8-C-galactopyranosylapigenin the first from a member of the Compositae, has been reported,[173] as has the first example of a C-allosylated compound (2-C-β-D-allo-pyranosyl-1,3,6,7-tetrahydroxyxanthone) from a fern. In association with this work, compound (69) was prepared by zinc oxide-promoted coupling of the acetylglycosyl bromide with tri-O-methyl-phloroglucinol.[174]

Full structural details of ravidomycin (70) have been published[175] and an antibiotic from a Streptomyces has been shown to be the analogous α-L-fucofuranosyl glycoside. On treatment with acid, it isomerized partly into the α-furanoside and β-pyranoside.[176] Various C-bonded glycosides and diglycosides of flavones have been synthesized by use of acetylated glycosyl bromides. Some isomerized substantially in mild acid.[177,178]

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4
Oligosaccharides

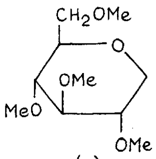
1 General

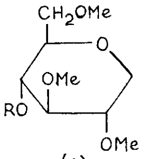
This Chapter deals with specific tri- and higher saccharides; most references relate to their syntheses by specific chemical methods. It does not cover higher, non-specific compounds made by the oligomerisation of monosaccharide derivatives nor does it deal with aspects of the chemistry of the cyclodextrins. Synthetic targets, in the main, are used to classify the compounds covered, but of course in papers dealing with the specific synthesis of, *e.g.*, a pentasaccharide, reference will be made to lower saccharides. The latter are generally not dealt with separately here.

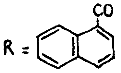
A review has appeared on the synthesis of oligosaccharides which contain 3-deoxy-D-*manno*-2-octulopyranosyl (KDO) residues[1] and another on the syntheses of oligosaccharides which contain an α-D-galactopyranosyl groups.[2]

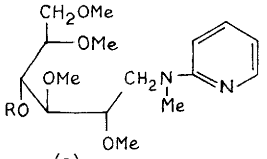
An interesting development has applied enzymic transfer of glycosyl moieties to oligosaccharides bound on polymer supports. Thus, for example, by use of glycosyl transferases or transglycosylases, monosaccharide units have been linked to 4-carboxy-2-nitrobenzyl 4-*O*-β-D-glucopyranosyl-β-D-glucopyranoside which was bonded by an amide link to aminoethyl-substituted polyacylamide gel beads and the resulting trisaccharides were released by photoirradiation.[3]

New methods for sequencing oligosaccharides are based upon i) the total or partial hydrogenolytic cleavage ($Et_3SiH-BF_3$) of the permethylated derivatives, ii) conversion of liberated hydroxy groups into naphthoyl esters and iii) the conversion of reducing moieties into 1-deoxy-1-pyridinylaminoalditol units. The last two steps generate entities which are suitable for fluorescence detection; mass spectrometric methods were used for product analysis. Maltotriose gave compounds (1)-(3) which were separated by h.p.l.c. and analysed directly by chemical ionization mass spectrometry. The rates of hydrogenolysis of inter-unit glycosidic

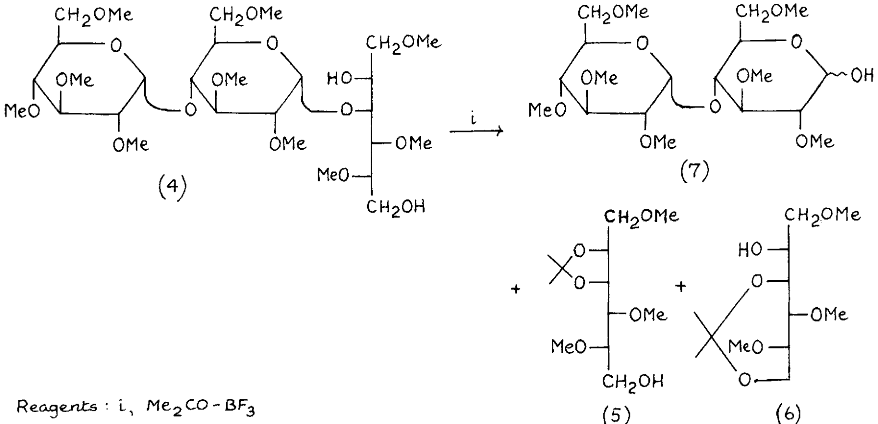

(1)


(2)




(3)

bonds fall in the order α(1→4) > α(1 → 6) > α(1 → 2) > β(1 → 2).[4] In a related study, the reducing terminus of maltotriose was released from the derived methylation-reduction product (4) as the mixed alditol acetals (5) and (6) together with the maltose ether (7) on acid-catalysed acetonation (Scheme 1).[5]



Reagents : i, Me_2CO-BF_3

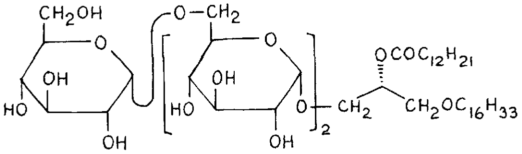
Scheme 1

An important paper on the determination of the solution conformations of oligosaccharides by ^1H n.m.r. and theoretical methods is referred to in Chapter 21, as is a report on the use of ^{13}C n.m.r. spectroscopy in the structural analysis of oligosaccharides. Oligosaccharides from human milk have been examined by ^1H n.m.r. spectroscopic analysis (360 MHz) of the derived peracetates. All signals can be recognized and assigned, sites of glycosidic bonding can be recognized by the shieldings of the protons at these positions [e.g., Galβ(1 → 3)GlcNAc and Galβ(1 → 4)GlcNAc can be distinguished] and n.O.e. experiments on the protons at the inter-unit linking positions can be used to determine sugar sequences.[6]

The sequncing of oligosaccharides by chemical ionization m.s. methods is mentioned in Chapter 22.

2 Trisaccharides

In the group of D-glucotrioses, cellotriose and homologues have been synthesized by successive glycosylations using benzyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside,[7] and benzyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside has been condensed with cellobiose and laminaribiose derivatives having free anomeric positions (p-nitrobenzenesulphonyl chloride, silver triflate, and triethylamine used for condensing) to give 1 → 4, 1 → 6- and 1 → 3, 1 → 6-linked products.[8] In related work on nephritogenic glycosides, the β-(1 → 6)-β-(1 → 6)-[9] and the β-(1 → 6)-α-(1 → 6)-linked trimers[10] were made as their 1-α-azides and converted into aspartic acid amides by reduction and amide linking to a partially protected aspartic acid derivative. The same Japanese group have also described syntheses of the α-(1 → 6)-α-(1 → 6) trisaccharide as a 1-glyceryl glycoside which has the structure (8) which has been proposed for the glycero-glucolipid of human gastric secretion.[11]



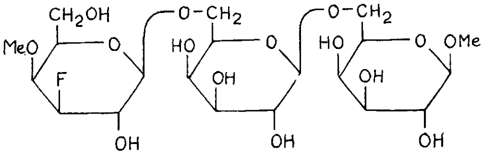
(8)

Related β-(1 → 6)-β-(1 → 4) glycosides with 2-hydroxypropyl aglycones, which are related to rhynchosporoside, have also been described.[12]

Controlled acetolysis of a glucan from fungal fruit bodies followed by chromatographic separations gave the peracetates of nigerose (3-O-α-D-glucopyranosyl-D-glucose) and nigerotriose and in the course of the work conventional syntheses of specific glycosides of these oligosaccharides were described.[13] Some bacterial glucansucrases were found to utilize a number of D-glucose oligosaccharides as D-glucose donors and acceptors. When donors also acted as acceptors, disproportionation reactions occurred, e.g., isomaltotriose gave initially isomaltose and the tetraose.[14]

In the D-mannose series, α-D-Man(1 → 2)α-D-Man(1 → 2)-D-Man, the repeating unit of the O8-antigen of E. coli, has been synthesized by stepwise procedures involving 2,3:4,6-di-O-benzylidene-D-mannosyl glycosylating reagents. In the products, the 2,3-acetals can be selectively converted to the 3-benzyl ethers with lithium aluminium hydride-aluminium chloride.[15]

In the deoxy series of homotrisaccharides, α-L-Cym-(1 → 4)-α-L-Cym(1 → 4)-β-L-Cym (Cym = cymerose = 2,6-dideoxy-3-O-methyl-D-ribo-hexose) has been isolated from dried twigs,[16] and phenyl 4"-amino-4",6"-dideoxymaltotrioside octabenzyl ether (a derivative of the acarbose terminal trisaccharide) has been made in connection with studies on α-glucosidase inhibitors.[17] The fluorinated trisaccharide glycoside (9) was made by use of the appropriate acetobromo derivative of the 3-fluorinated sugar.[18]

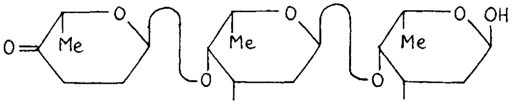


(9)

The following heterotrisaccharides are subdivided into linear and branched compounds and each set is categorized by the nature of the reducing moiety. One non-reducing compound, α-lactosyl β-D-fructofuranoside, has however been described as the product of action of levansucrase on lactose and sucrose and, in the course of the work, β-D-fructofuranosyl α-D-galactopyranoside was made by similar enzymic means.[19]

2.1 Linear Heterotrisaccharides.- A bacterial endo-(1 → 4)-β-D-xylanase caused transfer of xylosyl units from phenyl β-D-xylopyranoside to cellobiose and gave 6'-O-β-D-xylopyranosylcellobiose as well as the corresponding xylobiosyl- and xylotriosyl-cellobiose.[20] Conventional Koenigs Knorr procedures were used to prepare α- and β-L-Fuc(1 → 4)β-D-Gal(1 → 4)D-Glc and α-L-Fuc(1 → 6)β-D-Gal(1 → 4)D-Glc, and the isomeric 4'- and 6'-O-fucopyranosyllactose were prepared in the same study.[21] Another D-glucose compound to have been reported is β-D-Gal(1 → 3)-α-D-GalNAc(1 → 6) D-Glc and the D-galactose isomer was also prepared.[22] The synthesis of β-D-Man(1 → 4)α-L-Rha(1 → 3)D-Gal as the p-trifluoroacetamidophenyl glycoside has also been described.[23] The D-mannose-containing linear trisaccharides to have been described are derivatives of β-D-Gal(1 → 4)β-D-GlcNAc(1 → 2)D-Man[24] (for related pentasaccharides; see below), β-D-GalNAc(1 → 3)β-D-Glc(1 → 6)D-Man and β-D-GalNAc(1 → 4)β-D-Glc(1 → 6)D-Man.[25] In the L-rhamnose series β-D-Gal(1 → 6)β-D-Man(1 → 4)L-Rha has been made as a p-trifluoroacetamidophenyl glycoside.[23]

The following 2-acetamido-2-deoxy-D-glucose derivatives have been reported: α-D-Gal(1 → 4)β-D-Gal(1 → 4)GlcNAc,[26] α-D-Man(1 → 6) β-D-Man(1 → 4)GlcNAc,[27] α-D-Man(1 → 3)β-D-Man(1 → 4)GlcNAc,[27,28] α-D-Man(1 → 2)β-D-Man(1 → 4)GlcNAc,[28] α-L-Fuc(1 → 2)β-D-Gal(1 → 4) GlcNAc,[29] β-D-Man(1 → 4)β-D-GlcNAc(1 → 4)GlcNAc[30] and α-L-Fuc (1 → 2)β-D-Gal(1 → 4)GalNAc.[31] The 3-amino-3-deoxy sugar trisaccharide (10), which is related to that found in the antitumour antibiotic aclacinomycin, was prepared by procedures which included a final alcohol oxidation step.[32]



(10)

2.2 Branched Heterotrisaccharides.- The following have been reported (often as derivatives): 3-O-(β-D-glucopyranosyl)-2-O-(α-L-rhamnopyranosyl)-D-galactose,[33] 2,3-di-O-(β-D-galactosyl)-D-galactose and the 3-O-α-2-O-β-isomer,[34] 3,4-di-O-(β-D-glucopyranosyl)-L-rhamnose,[35] 2,3-di-O-(β-D-glucopyranosyl)-L-fucose,[36] and 2,3-di-O-(β-D-galactopyranosyl)-L-fucose,[36] the last four compounds being obtained by use of the photolabile o-nitrobenzylidene acetal. Derivatives of 2-amino-2-deoxyhexoses have attracted appreciable attention and the following trisaccharides have been synthesized (usually as glycosides): 2-acetamido-2-deoxy-4-O-(α-L-fucopyranosyl)-3-O-(β-D-galactopyranosyl)-D-glucose,[37,38] 2-acetamido-2-deoxy-3,4-di-O-(β-D-galactopyranosyl)-D-galactose[39] and 2-acetamido-3,6-di-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-galactose.[40]

3 Tetrasaccharides

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

3.1 Linear Tetrasaccharides.- From the partial hydrolysate of levan, the component fructotetraose (and the pentaose and hexaose) have been isolated by combined chromatographic methods.[41] The following isomers have been isolated from human milk and characterized: β-D-Gal(1 → 4)β-D-GlcNAc(1 → 3)β-D-Gal(1 → 4)D-Glc[42] and β-D-Gal(1 → 3)β-D-GlcNAc(1 → 3)β-D-Gal(1 → 4)D-Glc.[43] The latter was characterized by 2D n.m.r. studies carried out on the peracetylated, reduced tetrasaccharide. The α- and β-L-fucose-containing compounds β-D-Gal(1 → 4)α- and β-L-Fuc(1 → 4)α-L-Fuc (1 → 3)D-Glc have been made by Koenigs Knorr procedures modified to favour each isomer[44] and the repeating unit of the polysaccharide from *Shigella flexneri* variant 7 has been synthesized. It is α-L-Rha(1 → 3)α-L-Rha(1 → 3)β-D-GlcNAc(1 → 2)L-Rha.[45]

3.2 Branched Tetrasaccharides.- Syntheses of the following have been reported:

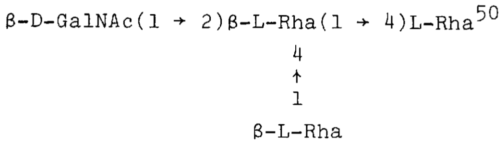
$$\alpha\text{-D-Man}(1 \rightarrow 3)\underset{\substack{6\\ \uparrow\\ 1\\ \alpha\text{-D-Man}}}{\beta\text{-D-Man}}(1 \rightarrow 4)\text{D-GlcNAc}\;[27]$$

$$\alpha\text{-L-Fuc}(1 \rightarrow 2)\underset{\substack{3\\ \uparrow\\ 1\\ \alpha\text{-D-GalNAc}}}{\beta\text{-D-Gal}}(1 \rightarrow 3)\text{D-GlcNAc}\;[46]$$

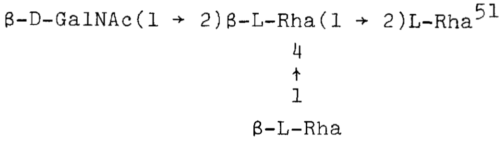
$$\alpha\text{-L-Fuc}(1 \rightarrow 2)\underset{\substack{4\\ \uparrow\\ 1\\ \alpha\text{-D-Gal}}}{\beta\text{-D-Gal}}(1 \rightarrow 4)\text{D-GlcNAc}\;[47]$$

$$\alpha\text{-L-Fuc}(1 \rightarrow 2)\underset{\substack{4\\ \uparrow\\ 1\\ \alpha\text{-D-Gal}}}{\beta\text{-D-Gal}}(1 \rightarrow 3)\text{GlcNAc}\;[48]$$

$$\beta\text{-D-Gal}(1 \rightarrow 4)\beta\text{-D-GlcNAc}(1 \rightarrow 6)\underset{\substack{3\\ \uparrow\\ 1\\ \beta\text{-D-GlcNAc}}}{\text{D-GalNAc}}\;[49]$$



$$\beta\text{-D-GalNAc}(1\rightarrow 2)\underset{\substack{4\\ \uparrow\\ 1\\ \beta\text{-L-Rha}}}{\beta\text{-L-Rha}}(1\rightarrow 4)\text{L-Rha}$$ [50]



$$\beta\text{-D-GalNAc}(1\rightarrow 2)\underset{\substack{4\\ \uparrow\\ 1\\ \beta\text{-L-Rha}}}{\beta\text{-L-Rha}}(1\rightarrow 2)\text{L-Rha}$$ [51]

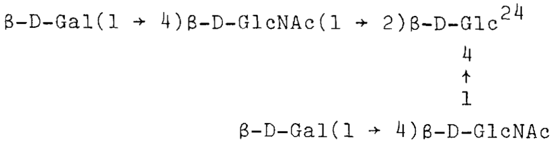
4 Higher Oligosaccharides

4.1 Pentasaccharides.- The following compounds have either been isolated from natural sources or have been synthesized:

α-L-Fuc(1 → 2)β-D-Gal(1 → 3)β-D-GlcNAc(1 → 3)β-D-Gal(1 → 4)-D-Glc[43]

β-D-Glc(1 → 4)β-D-Glc(1 → 3)β-D-Glc(1 → 4)β-D-Glc(1 → 4)D-Glc[52]

β-D-Glc(1 → 2)β-D-Glc(1 → 2)β-D-Glc(1 → 2)β-D-Glc(1 → 2)β-D-Glc[53]



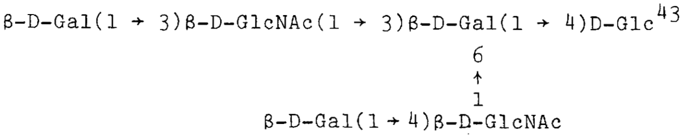
$$\beta\text{-D-Gal}(1\rightarrow 4)\beta\text{-D-GlcNAc}(1\rightarrow 2)\underset{\substack{4\\ \uparrow\\ 1\\ \beta\text{-D-Gal}(1\rightarrow 4)\beta\text{-D-GlcNAc}}}{\beta\text{-D-Glc}}$$ [24]

An antibiotic-derived pentasaccharide is noted in Chapter 19.

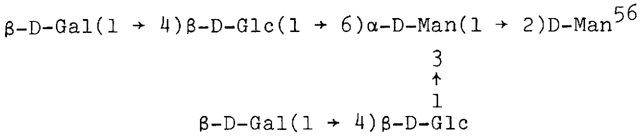
4.2 Hexasaccharides.-

α-D-Glc(1 → 2)α-D-Glc(1 → 3)α-D-Glc(1 → 3)α-D-Man(1 → 2)α-D-Man(1 → 2)D-Man[54]

β-D-Gal(1 → 4)β-D-GlcNAc(1 → 3)β-D-Gal(1 → 4)β-D-GlcNAc(1 → 3)β-D-Gal(1 → 4)D-GlcNAc[55]

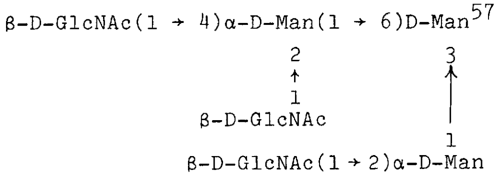


$$\beta\text{-D-Gal}(1\rightarrow 3)\beta\text{-D-GlcNAc}(1\rightarrow 3)\underset{\substack{6\\ \uparrow\\ 1\\ \beta\text{-D-Gal}(1\rightarrow 4)\beta\text{-D-GlcNAc}}}{\beta\text{-D-Gal}}(1\rightarrow 4)\text{D-Glc}$$ [43]



$$\begin{array}{rrcl}
\beta\text{-D-Gal}(1\rightarrow 4) & \beta\text{-D-Glc}(1\rightarrow 6) & \alpha\text{-D-Man}(1\rightarrow 2) & \text{D-Man} \\
 & & 3 & \\
 & & \uparrow & \\
 & & 1 & \\
 & \beta\text{-D-Gal}(1\rightarrow 4) & \beta\text{-D-Glc} &
\end{array}$$

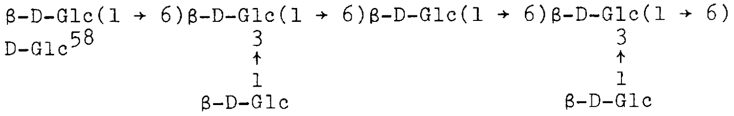
[56]



$$\begin{array}{rcc}
\beta\text{-D-GlcNAc}(1\rightarrow 4) & \alpha\text{-D-Man}(1\rightarrow 6) & \text{D-Man} \\
 & 2 & 3 \\
 & \uparrow & \uparrow \\
 & 1 & \\
 & \beta\text{-D-GlcNAc} & \\
 & & 1 \\
 & \beta\text{-D-GlcNAc}(1\rightarrow 2) & \alpha\text{-D-Man}
\end{array}$$

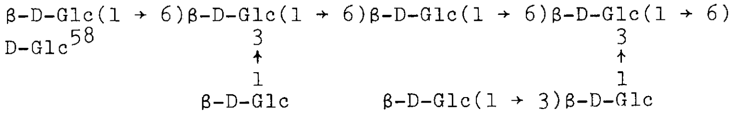
[57]

4.3 Higher Saccharides.-



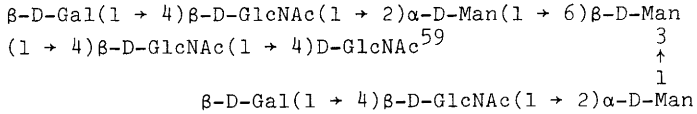
$$\begin{array}{lclcl}
\beta\text{-D-Glc}(1\rightarrow 6) & \beta\text{-D-Glc}(1\rightarrow 6) & \beta\text{-D-Glc}(1\rightarrow 6) & \beta\text{-D-Glc}(1\rightarrow 6) & \text{D-Glc} \\
 & 3 & & 3 & \\
 & \uparrow & & \uparrow & \\
 & 1 & & 1 & \\
 & \beta\text{-D-Glc} & & \beta\text{-D-Glc} &
\end{array}$$

[58]



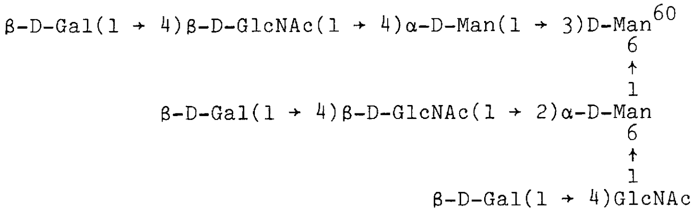
$$\begin{array}{lclcl}
\beta\text{-D-Glc}(1\rightarrow 6) & \beta\text{-D-Glc}(1\rightarrow 6) & \beta\text{-D-Glc}(1\rightarrow 6) & \beta\text{-D-Glc}(1\rightarrow 6) & \text{D-Glc} \\
 & 3 & & 3 & \\
 & \uparrow & & \uparrow & \\
 & 1 & & 1 & \\
 & \beta\text{-D-Glc} & \beta\text{-D-Glc}(1\rightarrow 3) & \beta\text{-D-Glc} &
\end{array}$$

[58]



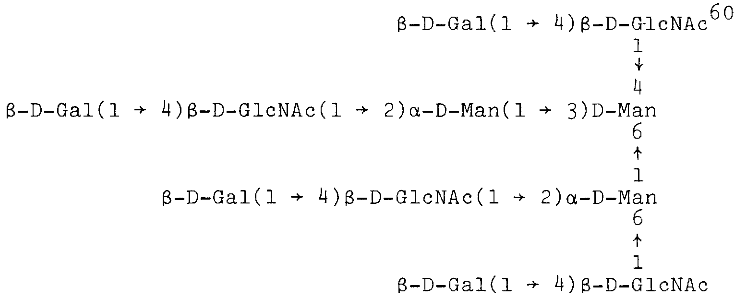
$$\begin{array}{rrrcl}
\beta\text{-D-Gal}(1\rightarrow 4) & \beta\text{-D-GlcNAc}(1\rightarrow 2) & \alpha\text{-D-Man}(1\rightarrow 6) & \beta\text{-D-Man}(1\rightarrow 4) & \beta\text{-D-GlcNAc}(1\rightarrow 4)\text{D-GlcNAc} \\
 & & & 3 & \\
 & & & \uparrow & \\
 & & & 1 & \\
 & \beta\text{-D-Gal}(1\rightarrow 4) & \beta\text{-D-GlcNAc}(1\rightarrow 2) & \alpha\text{-D-Man} &
\end{array}$$

[59]



$$\begin{array}{rrrc}
\beta\text{-D-Gal}(1\rightarrow 4) & \beta\text{-D-GlcNAc}(1\rightarrow 4) & \alpha\text{-D-Man}(1\rightarrow 3) & \text{D-Man} \\
 & & & 6 \\
 & & & \uparrow \\
 & & & 1 \\
 & \beta\text{-D-Gal}(1\rightarrow 4) & \beta\text{-D-GlcNAc}(1\rightarrow 2) & \alpha\text{-D-Man} \\
 & & & 6 \\
 & & & \uparrow \\
 & & & 1 \\
 & & \beta\text{-D-Gal}(1\rightarrow 4) & \text{GlcNAc}
\end{array}$$

[60]



$$\begin{array}{r}
\beta\text{-D-Gal}(1\rightarrow 4)\beta\text{-D-GlcNAc}^{60}\\
1\quad\;\;\\
\downarrow\quad\;\;\\
4\quad\;\;\\
\beta\text{-D-Gal}(1\rightarrow 4)\beta\text{-D-GlcNAc}(1\rightarrow 2)\alpha\text{-D-Man}(1\rightarrow 3)\text{D-Man}\\
6\quad\;\;\\
\uparrow\quad\;\;\\
1\quad\;\;\\
\beta\text{-D-Gal}(1\rightarrow 4)\beta\text{-D-GlcNAc}(1\rightarrow 2)\alpha\text{-D-Man}\\
6\quad\;\;\\
\uparrow\quad\;\;\\
1\quad\;\;\\
\beta\text{-D-Gal}(1\rightarrow 4)\beta\text{-D-GlcNAc}
\end{array}$$

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5

Ethers and Anhydro-sugars

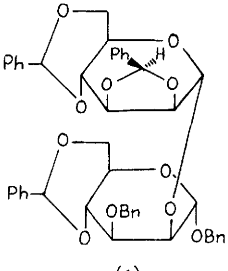
1 Ethers

Methyl Ethers.- Techniques used in the preparation of 3-*O*-[^{11}C]-methyl-D-glucose from di-*O*-isopropylidene-D-glucose and [^{11}C]methyl iodide have been described.[1] All the partially methylated derivatives of methyl α-D-manno- and -gluco-pyranoside have been synthesized by partial methylation of the corresponding 6-*O*-methyl and 6-*O*-trityl ethers, the products being separated by h.p.l.c.[2] 3'-And 4'-*O*-methylsucrose have been isolated by preparative h.p.l.c. from partially methylated sucrose, and their rates of alkaline degradation determined.[3] Partial methylation of β-D-*gluco*-heptopyranoside (of unspecified configuration at C-6) has yielded a total of 29 mono- to tetra-*O*-methyl ether derivatives isolated as their peracetates and identified by g.l.c.-m.s.[4,5] The expected mixtures of monomethyl ethers were obtained on partial methylation of methyl 2,6-dideoxy-α-D-hexopyranoside and 1,6-anhydro-2-deoxy-β-D-*arabino*-hexopyranose.[6] The *O*-isopropylidene derivatives of the naturally occurring 2-*O*-methyl-D-arabinose, 2- and 3-*O*-methyl-D-xylose, 3- and 6-*O*-methyl-D-galactose, 3-*O*-methyl-D-glucose, and 2-*O*-methyl-L-fucose have been characterized by g.l.c.-m.s.[7] The alkaline conversion of 2,3-di-*O*-methyl-D-glyceraldehyde into 2-methoxypropenal,[8] as a model for alkaline degradation of sugars, and the acid-catalyzed hydrolysis of 2-methoxypropenal to 2-oxopropanal,[9] as a model for related unsaturated sugar reactions, have been the subjects of kinetic and mechanistic investigations. Methyl, ethyl, and benzyl ethers of isopropylidene derivatives of D-galactose, D-glucose, and D-fructose and of methyl 4,6-*O*-benzylidene-D-gluco- and galacto-pyranoside anomers, can be prepared in high yield by phase transfer procedures.[10]

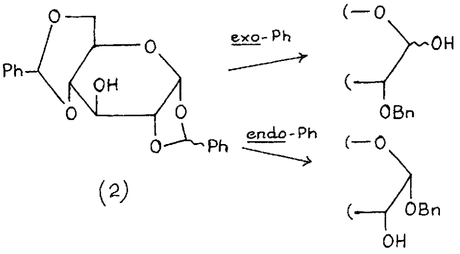
Other Alkyl and Aryl Ethers.- 3'-*O*-Allyl ethers of methyl β-lactoside and two *N*-acylated 2-amino-2-deoxy-lactose β-glycosides were obtained by reaction of the dibutylstannylene complexes of these disaccharides with allyl bromide-tetrabutylammonium bromide.[11]

The products from perbenzylation (BnBr-KOH-DMSO) of six aldoses have been determined by ^{13}C-n.m.r. spectroscopy. After chromatographic removal of dibenzyl ether, the β-pyranoside could be isolated in $\geqslant$60% yield from D-xylose, D-glucose, and D-mannose; D-galactose yielded an inseparable mixture of α-furanoside and β-pyranoside (present in 53 and 8% yields respectively), while L-arabinose and D-ribose gave more complex anomeric and ring size isomeric mixtures.[12] Partial benzylation (BnCl-LiOH) of methyl α-D-glactopyranoside gave the 2,3,6-triether, but the use of other bases (KOH, RbOH) led to the 2,4,6-isomer. Methyl β-D-galactopyranoside gave mainly the 3,4,6-triether, irrespective of the alkali used.[13] In a re-examination of the partial benzylation of methyl 4,6-O-benzylidene-α-D-glucopyranoside, it was shown that the production of either the 2- or 3-monoether could be optimized, depending upon the conditions used (BnBr-DMF-Ag_2O or BaO respectively).[14]

Reductive cleavage of benzylidene acetals has been further examined. Phenyl 2,3-di-O-benzyl-4,6-O-benzylidene-1-thio-β-D-gluco- and galacto-pyranosides were converted to the corresponding 2,3,4-tri-O-benzylated derivatives with a free 6-hydroxy group through the action of lithium aluminium hydride-aluminium chloride; analogous conversions of 1-thio-cellobiose and -lactose derivatives were also reported.[15] With the same reagent, the tri-O-benzylidenated disaccharide (1) underwent stepwise cleavage of the exo-2',3'-acetal at room temperature (to give a 3'-O-benzyl ether), and then the 4',6'-acetal on heating (to give a 3',4'-diether).[16] The configuration of the 1,2-acetal moiety in 1,2:4,6-di-O-benzylidene-α-D-glucopyranose (2) determined the course of its selective hydrogenolysis ($LiAlH_4$-$AlCl_3$) as shown on Scheme 1.[17] The regioselectivity of the borane-trimethylamine-aluminium chloride induced



(1)



Scheme 1

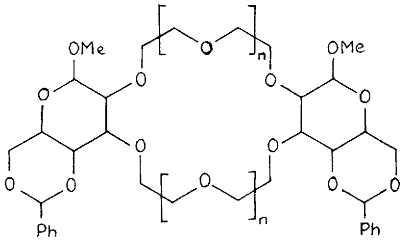
reductive cleavage of 4,6-O-benzylidene acetals in D-galacto- and gluco-pyranoside derivatives was strongly solvent dependent; in toluene, moderate yields of 4-O-benzylated derivatives with a free 6-hydroxy group were obtained, while in tetrahydrofuran, good yields of 6-O-benzylated derivatives with a free 4-hydroxy group resulted.[18]

Four alternative procedures for synthesizing benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranoside, each involving selective 6- over 4-O-benzylation as the overall result, were detailed and compared.[19] Slow hydrogenolysis of benzyl ethers was effected by heating them in propan-2-ol with palladium catalysts, the solvent providing the required hydrogen. Considerable selectivity was observed, with benzyl ether groups cleaving faster than benzylidene acetals. Partial removal of ethers was demonstrated by the conversion of methyl 2,3-di-O-benzyl-α- and β-D-glucopyranoside to mixtures of the 2- and 3-monoethers. A possible relationship between the orientation of a benzyl group and the ^{1}H-n.m.r. chemical shifts of its diastereotropic benzylic protons was also discussed.[20]

Muramyl dipeptide analogues which have 2-O-(1-carboxyethyl)-substituents on an amino-sugar ring are covered in Chapter 9.

The O-hydroxyethyl-D-glucoses released on acid hydrolysis of hydroxyethylstarch have been characterized, and the presence of 2-O-(2'-hydroxyethoxy)ethyl-D-glucose amongst the products was confirmed following its synthesis by conventional procedures.[21] The ^{13}C-n.m.r. spectra of the 2-, 3-, and 6-mono-, 2,3-, 2,6-, and 3,6-di-, and 2,3,6-tri-O-(carboxymethyl)-D-glucoses were reported in connection with the analysis of carboxymethylcellulose by a hydrolysis-^{13}C-n.m.r. procedure.[22] Phosphonylmethyl derivatives of ribonucleosides are covered in Chapter 20.

Crown ether compounds of general structure (3, n=1) were synthesized from methyl 4,6-O-benzylidene-α- and β-D-galactopyranoside and diethylene glycol di-p-toluenesulphonate, while α-D-gluco-analogues (3, n=2) were obtained using triethylene glycol di-p-toluenesulphonate; their association with metal ions was examined.[23] Crown ether derivatives and accompanying uncyclized products were obtained similarly from the condensation of 1,2-O-cyclohexylidene-3-O-methyl-α-D-glucofuranose with mono- to tetra-ethyleneglycol di-p-toluenesulphonate.[24] Heteromacrocyclic compounds of general structure (4) were constructed from methyl 4,6-O-benzylidene-α-D-mannopyranoside after initial phase-transfer catalyzed alkylation using t-butyl bromoacetate ($BrCH_2CO_2Bu^t$), and reduction to the corresponding 2,3-di-O-(2-hydroxyethyl) derivative.[25,26]



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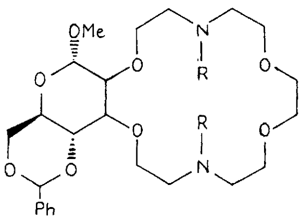


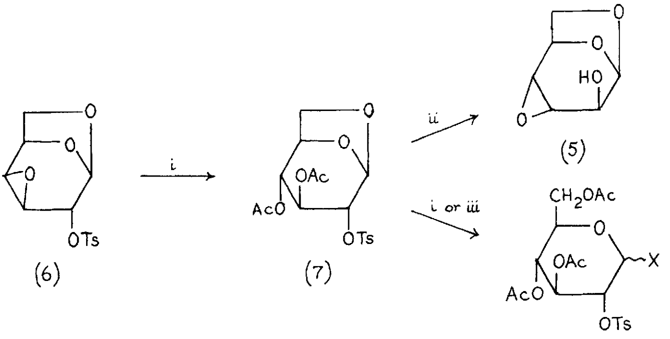
(4) R = H or CO_2Et, or R,R =

All the monotrityl ethers of methyl α- and β-D-xylopyranoside have been obtained following partial tritylation.[27] Ditritylation of methyl and benzyl α-D-hexopyranosides yielded the following major products: the 2,6-diethers from the glucosides, 3,6-diethers from the mannosides, and both the 2,6- and 3,6-diethers from the galactosides.[28] Further investigation of the dimolar tritylation of β-maltose has detected, in addition to the previously reported 6- and 6'-mono- and 6,6'-ditrityl ethers (see Vol.8, p.31), small amounts of trityl 6'-mono- and 6,6'-di-O-trityl-β-maltoside and 2,6'-di-O-trityl-α-maltose.[29] The selective removal (Cl_3CCO_2H-MeOH-$MeNO_2$) of 5'-O-(dimethoxytrityl)ethers from protected 2'-deoxyadenosine derivatives was achieved without detectable N-glycoside cleavage.[30]

Silyl Ethers.- Carbohydrate trityl and benzyl ethers can be converted into trimethylsilyl ethers using trimethylsilyl iodide, with primary benzyl ethers reacting preferentially. Since the products can be readily desilylated, this constitutes a good detritylation and debenzylation method.[31] The O-trimethylsilylation of partially protected monosaccharides using phase transfer procedures has been reported.[32] A highly selective *tert*-butyldimethylsilylation reagent (${}^{t}BuMe_2SiCl-AgNO_3-THF$), reacting with primary in preference to secondary hydroxy groups, has been demonstrated in the derivatization of glycerol, and 1,2-*O*-isopropylidene-α-D-gluco- and xylo-furanose; in presence of pyridine, however, quantitative persilylation resulted.[33] Other procedures, employing polymeric reagents, were effective for the selective 6-*O*-*tert*-butyldimethylsilylation (${}^{t}BuMe_2SiCl$ - polyvinylpyridine) and then desilylation (Amberlite A26 resin, F^--form) of methyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside.[34] The preparation and h.p.l.c. analysis of per(dimethylphenylsilyl)ated alditols, and mono- and di-saccharides have been described.[35] The use of the tetraisopropyldisiloxane-1,3-diyl group in oligonucleotide synthesis has been reviewed.[36]

2 Intramolecular Ethers (Anhydro-sugars)

Oxirans.- Methyl 2,3-anhydro-α-D-lyxofuranoside has been synthesized from methyl α-D-arabinofuranoside using triphenylphosphine-diethyl azodicarboxylate, mercury(II) ion mediated methanolysis of D-arabinose diethyl dithioacetal being used to prepare the starting glycoside.[37] 1,6:3,4-Dianhydro-β-D-altropyranose (5) was obtained from the D-*galacto*-dianhydride (6) by sequential acetolysis and base treatment (Scheme 2); the 1,6-anhydro-ring in the intermediate (7) could be cleaved to provide 2-*O*-tosyl-D-glucopyranose derivatives (8).[38] Other oxirans are referred to in Chapters 9, 13, 14, and 20.

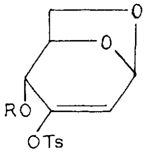


Reagents: i, Ac_2O ; ii, NaOMe-MeOH ; iii, HBr-HOAc

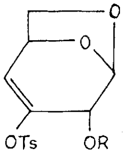
Scheme 2

Other Anhydrides.- Improvements to the synthesis of the 2,4,6-tri-O-benzyl and p-bromobenzyl ethers of 1,3-anhydro-β-D-mannopyranose have been described.[39] (See Vol.15, p.55).

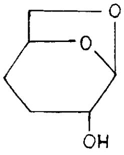
The titanium tetrachloride induced conversion of 1,2,3,4-tetra-O-acetyl-6-O-trityl-β-D-glucopyranose to 1,6-anhydro-β-D-glucopyranose triacetate has been shown to involve rapid detritylation followed by a slower cyclization reaction.[40] The mechanism of the analogous stannic chloride catalyzed conversion of 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose has also been studied.[41] Cellotriose, cellobiose, D-glucose and their 1,6-anhydrides (i.e., cellotriosan, cellobiosan, and 1,6-anhydro-β-D-gluco-furanose and -pyranose) have been identified as the water soluble pyrolysis products from cellulose resulting from infra-red absorption on irradiation with a CO_2-laser.[42] Reaction (NaOAc-DMF) of 1,6-anhydro-β-D-glucopyranose tritosylate (which exists preferentially in the boat conformation) yielded a mixture containing the D-erythro-2,3- and 3,4-unsaturated derivatives (9) and (10) respectively; reduction of the latter (10, R=H) led to the 3,4-dideoxy-derivative (11).[43] Improved syntheses of the 2,4-ditosylate and the 4-deoxy derivative of 1,6-anhydro-β-D-glucopyranose, and of 1,6:3,4-dianhydro-2-O-tosyl-β-D-galactopyranose were reported in a paper concerning the preference of 1,6-anhydro-β-D-glucopyranose derivatives substituted on O-3 with bulky groups for the boat or twisted-boat conformation.[44]



(9) R = H or Ac

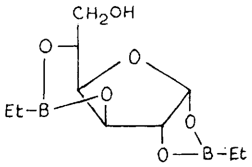


(10) R = H or Ac



(11)

The reaction of sucrose with triethylboroxine [$(EtBO)_3$-py-PhMe, 130°, azeotropic removal of H_2O] resulted in a 67% conversion to 1,2:3,5-diethylborandiyl-α-D-glucofuranose (12) plus 2,6-anhydro-β-D-fructofuranose (13); a procedure was devised for the isolation of the latter as its triacetate without recourse to chromatography.[45]



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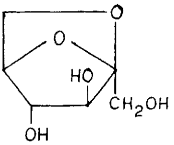
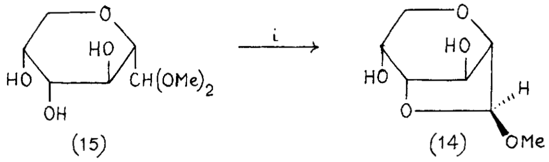


(13)

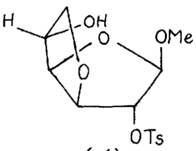
Methyl 2,6-anhydro-α-D-mannofuranoside (14) was obtained in >30% yield by intramolecular cyclization of the dimethyl acetal (15) (Scheme 3).[46]



Reagents: i, TsOH-xylene, Δ

Scheme 3

Hexopyranosides (D-*gluco*, D-*manno*, D-*galacto*, 2-acetamido-2-deoxy-D-*gluco*, and α,α-trehalose) were converted into their 3,6-anhydrides by treatment of their previously reported stable crystalline 6-oxytris(dimethylamino)phosphonium hexafluorophosphate salts with alkali (MeOH-MeONa).[47] The four possible 3,6-anhydrohexofuranoses, together with their triacetates, methyl glycosides, and glycoside diacetates, have been synthesized, mainly from the known 3,6-anhydrohexopyranoses, and equilibria between the anomeric forms of the free sugars and of the methyl glycosides were examined.[48] The selective tosylation of the methyl 3,6-anhydro-D-gluco-, -manno-, and -gulo-furanosides has been investigated. For example, the α-mannoside gave the 5-tosylate, which reacted with nucleophiles to provide 5-substituted β-L-*gulo*-compounds, while the β-mannoside gave the 2-tosylate, which similarly provided 2-substituted β-D-*gluco*-compounds.[49] Monotosylation of the β-D-glucofuranoside gave the 2-tosylate (16) as a minor product, and this gave the 2,5:3,6-dianhydride (17) on treatment with base. The α-anomer (18) was obtained from similar treatment of methyl 3,6-anhydro-5-*O*-tosyl-β-L-gulofuranoside.[50] The 3,6:3',6'-dianhydride



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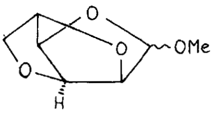
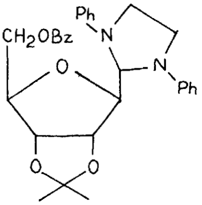


(17) β-anomer

(18) α-anomer



(19)

of methyl β-sophoroside (i.e., methyl 2-*O*-β-D-glucopyranosyl-β-D-glucopyranoside) was obtained by conventional synthesis and alkaline treatment of the 6,6'-ditosylate.[51]

2,5-Anhydro-D-allose, a useful substrate for C-nucleoside synthesis, has been prepared from D-ribose via the intermediate (19).[52]

A reaction of sedoheptulosan is covered in Chapter 24.

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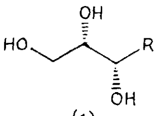
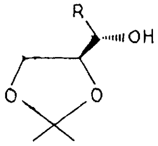
6
Acetals

1 Isopropylidene acetals

The products of reaction of glycerol with 2,2-dimethoxypropane in the presence of 1,2-dimethoxy-ethane have been characterized in ^{1}H n.m.r. Besides the 1,2- and 1,3-acetals, dimers of the 1,2-acetal were obtained, linked through isopropylidene groups, together with a mixed acetal of glycerol and methanol.[1] The kinetic product of isopropylidenation of the 1-C-substituted L-threo-glycerol (1) under Ohlah conditions was found to be the terminal acetal (2) which is transformed under thermodynamic control to the acetal (3).[2]


(1)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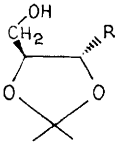
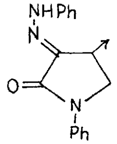
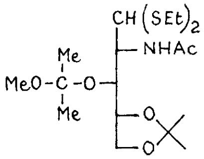

(3)

R =


Acid-catalyzed acetonation of L-sorbose gave a mixture of di-*O*-isopropylidene and mono-*O*-isopropylidene derivatives, easily separated by the solubility of the former in benzene.[3] Isopropylidenation of 2-acetamido-2-deoxy-D-xylose diethyl dithioacetal gave the 4,5-*O*-isopropylidene derivative accompanied by some 3-*O*-(1-methoxy-1-methylethyl)-derivative (4) when copper(II) sulphate was used as catalyst with either propanone - 2,2-dimethoxypropane or propanone - 2-methoxypropene. The 3,4-*O*-isopropylidene derivative was obtained when sulphuric acid was used as catalyst in propanone - 2,2-dimethoxypropane. The former was considered the kinetic, and the latter the thermodynamic product.[4] 3,4-*O*-Isopropylidene-L-fucopyranose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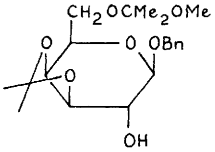
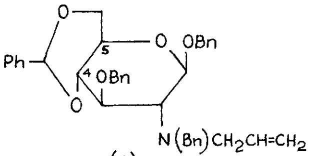

(5)

(mainly α), 2,3-O-isopropylidene- -L-rhamnofuranose, and 2-deoxy-3,4-O-isopropylidene-D-*erythro*-pentopyranose (mainly α) were obtained in good yield by isopropylidenation of the corresponding free sugars using 2-methoxypropene - DMF - tosic acid at 0 °C. Under these conditions, the kinetic products are obtained.[5] Reaction of benzyl β-D-galactopyranoside with 2,2-dimethoxypropane under tosic acid catalysis gave the 6-O-(methoxydimethyl)methyl derivative (5) along with the more usual 3,4-O- and 4,6-O-isopropylidene products in a 4:5:1 ratio. Similar reactions of 2,2-dimethoxypropane or acetophenone dimethyl acetal with 2,3-disubstituted (and hence 4,6-unsubstituted) D-galacto- and -glucopyranosides gave 6-O-(methoxydimethyl)methyl and 6-O-(methoxymethylphenyl)methyl derivatives selectively as kinetic products, demonstrating that mixed acetals, formed as intermediates in transacetalation reactions, can be isolated.[6] The 5,6-isopropylidene acetal of 1,4-anhydro-D-mannitol may be obtained by kinetically controlled acetonation of the parent compound.[7]

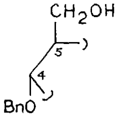
2 Benzylidene acetals

The 2,3-, 3,5- and 5,6-benzylidene acetals of 1,4-anhydro-D-mannitol with the (*R*)- and (*S*)-acetal configurations have all been obtained.[7] Interconversion of the *exo*- and *endo*-2,3-O-benzylidene acetal in methyl 2,3:4,,6-di-O-benzylidene-α-D-mannopyranoside using catalytic aluminium(III) chloride has been described. The *exo*-isomer is capable of separation from an equilibrating mixture by crystallization.[8]

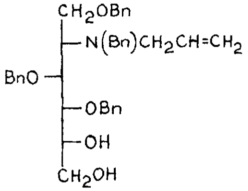
References to reductive cleavage of benzylidene acetals using lithium aluminium hydride - aluminium(III) chloride will be found in Chapters 4 and 5. Oxidative ring-opening to yield β-hydroxy aroyl derivatives is described in Chapter 4.



(6)



(7)

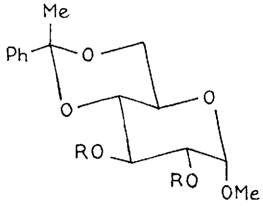


(8)

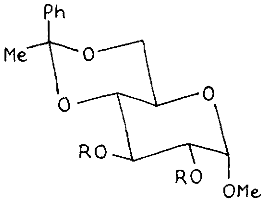
An unusual benzylidene acetal ring-opening using lithium aluminium hydride - aluminium(III) chloride occurred in the glucosamine derivative (6), which after formation of the 4-*O*-benzyl-6-hydroxy compound (7) went on to yield the acyclic derivative (8).[9]

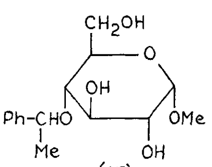
3 Other acetals

Mixtures of 2,6-dideoxy-3-*O*-methyl-DL-*lyxo*-, -*arabino*-, -*xylo*-, and -*ribo*-hexose dimethyl acetals, obtained by addition of methyl vinyl ether to but-2-enal dimethyl acetal followed by oxidation with potassium permanganate or perbenzoic acid, were separated by preparative g.l.c. of their diacetates. The parent dimethyl acetals were obtained by deacetylation.[10] 1-Phenylethylidene acetals (9) - (14) have been prepared by reaction of acetophenone dimethyl acetal with the appropriate D-glucopyranoside. A similar reaction was carried out on the corresponding D-galactose derivatives. Reductive cleavage of the (*R*)-*gluco* acetal (9) by means of lithium aluminium hydride - aluminium(III) chloride gave the 4-*O*-phenylethyl derivative (15) whereas the (*S*)-isomer (12) yielded the 6-*O*-ether (16).[11] Transacetalation of D-glucitol with chloroacetaldehyde diethyl acetal in the presence of concentrated hydrochloric acid gave a 1,2- or 5,6-monoacetal initially, then the triacetal (17). The 1,2:5,6-diacetal



(9) R = H (12)
(10) R = Me (13)
(11) R = Bn (14)





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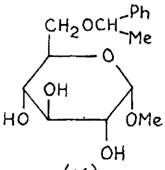

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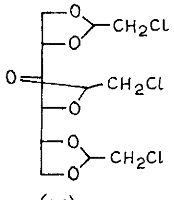
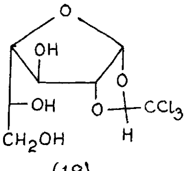
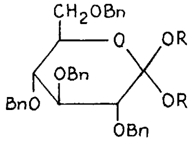


(17)



(18)



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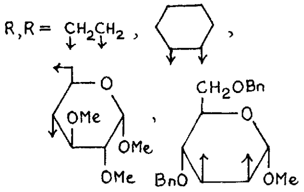
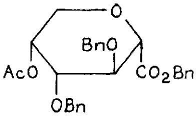


was produced from D-mannitol, while reaction of bromoacetaldehyde diethyl acetal gave the 1,3:4,6-diacetal with galactitol.[12] Reaction of D-galactose with chloral in the presence of sulphuric acid gave 1,2-O-trichloroethylidene-α-D-galactofuranose (18).[13] The intermediacy of 2-cyanoethylidene acetals in the preparation of glycosyl cyanides is mentioned in Chapter 3.

A new synthesis of 2,3,4,6-tetra-O-benzyl-D-glucopyranosylidene acetals of type (19) utilizes 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone and the appropriate bis-O-(dimethylsilyl)-1,2-ethers in the presence of trimethylsilyl trifluoromethylsulphonate. When the 6-O-acetyl-2,3,4-tri-O-benzyl-D-glucono-1,5-lactone was used 52% of the rearrangement product (20) was obtained.[14]



(20)

The presence of di-D-fructofuranose-2',1:2,3'-dianhydride in the digest from treatment of inulin with a root homogenate of Lycoris radiata has been quoted as evidence for the existence of inulin fructotransferase activity in this plant.[15]

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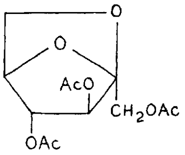
7
Esters

A review on the role of lone pair interactions in the selective functionalization of some 4,6-O-benzylidene-hexopyranosides by phase-transfer esterification and tin-mediated esterification and alkylation reactions has appeared.[1] A further discussion of these interactions in the chemistry of monosaccharides included mechanistic proposals to account for observed patterns of esterification, based on roles of β- and γ-effects which determine the relative energies of the orbitals of oxygen containing the lone pairs.[2] Three papers describing the two-phase esterification of glycosides using quaternary ammonium salts and sodium hydroxide or carbonate have been published;[3-5] 4,6-O-benzylidene-α-hexosides of allose, altrose, galactose, glucose and mannose gave primarily 2-O-mono-esters, whereas 3,6-anhydro-α-D-glucosides gave mainly 4-O-mono-esters. It was concluded that the reactivity of hydroxy groups was governed mainly by relative acidity and by hydrogen bonding rather than by steric effects.[3] Whereas methyl 4,6-O-benzylidene-α-D-galactopyranosides gave predominantly the 2-ester on tosylation using this system, the β-analogue gave the 3-ester. Benzoylation gave a mixture of the 2- and 3-ester due to benzoyl migration in the product; addition of saturated sodium perchlorate solution to the two-phase reaction system prevented equilibration, the α-anomer then giving the 2-ester and the β-anomer the 3-ester.[4,5]

1 Acetates

The additivity of ^{13}C- and ^{1}H-n.m.r. shifts for mono-, di-, and tri-O-acetyl-β-D-xylopyranosides has been critically evaluated. The conformer populations of the pyranoid rings are changed by such substitution and deviations from acceptable additivity rules result.[6] Transesterification using sodium hydride in ethyl acetate at 60 - 65°C has been used on carbohydrates. Methyl α- and β-D-glucopyranoside, which are poorly soluble in the reaction mixture, gave 40% yields of the 6-O-acetate, while more soluble substrates underwent further acetylation at secondary hydroxy groups.[7] The stereoisomeric composition of products of acetolysis and acetylation of methyl arabino-furanosides and -pyranosides has been investigated. The latter with acetic acid-acetic anhydride and low concentrations of sulphuric acid gave acyclic semi-acetates as intermediates which then led to the acyclic diacetylacetal. The arabinofuranosides gave mainly 1,2,3,5-tetra-O-acetyl-α-D-arabinofuranose.[8] 1,3,6-Tri-O-acetyl- and 1,3,6-tri-O-acetyl-4-O-mesyl derivatives of N-acetyl-D-mannosamine and the corresponding N-trifluoroacetyl derivative have been synthesized and used to test the effect on the proliferation of cancer cells.[9] The preparation of the 1,3,4-tri-O-acetyl-2,6-anhydrofructofuranose (1) from sucrose has been effected by means of an intermediate boroxine derivative (see Chapter 5).[10] Selective acetolysis of the 2',3,3',4',6,6'-hexa-O-trimethylsilylated disaccharide (2) using acetic anhydride-acetic acid-pyridine resulted



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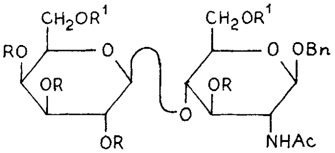


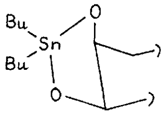
(2) $R = R^1 = Me_3Si-$
(3) $R = Me_3Si-$, $R^1 = Ac$

in replacement of the primary silylether groups by acetates to yield the diacetate (3).[11] Among many 6,6'-diesters of α,α-trehalose prepared for in vitro testing for antitumour activity and anti-leukaemic activity were the diacetates (see also section on other carboxylic esters).[12]

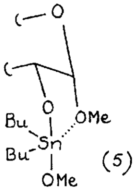
Acetyl migration from O-4 to O-6, induced by aqueous pyridine, has been shown to be a useful general method for regiospecific deprotection of hydroxy groups at C-4 of hexopyranosides, particularly for 2- and 3-aminodeoxyhexopyranosides (where the yields are generally higher). Aqueous pyridine was shown to possess greater selectivity than other alkalis, and a number of useful general conclusions regarding acetyl migrations in pyranosides were drawn.[13] Selective removal of O-acetyl groups in the presence of O-benzoyl groups has been effected with methanolic hydrogen chloride prepared by addition at 0° of acetyl chloride to dry methanol. Many examples showed that most other groups do not interfere with the reaction although cyanoethylidene compounds gave the corresponding imidate and its subsequent hydrolysis product.[14]

2 Benzoates

Phase transfer benzoylation of methyl 4,6-O-benzylidene-α-D-hexopyranosides using benzoyl chloride (1 mol) - dichloromethane - tetra-n-butylammonium chloride in 40% aqueous sodium hydroxide in the presence of sodium iodide has been shown to proceed with benzoyl chloride as the acylating agent rather than benzoyl iodide as previously claimed.[5] Selective benzoylation of methyl 4,6-O-benzylidene-α-D-glucopyranoside avoiding benzoyl migration, which generally accompanies phase-transfer methods, was achieved with sodium hydride in THF in the presence of tetra-n-butyl ammonium iodide and benzoyl chloride. A yield of 65% of the 2-benzoate was obtained with less than 5% of the 3-benzoyl derivative. The yields were improved by using potassium carbonate instead of sodium hydride, which was simply removing the hydrogen chloride produced, and by using benzene instead of THF. The reaction was extended to methyl 4,6-O-benzylidene derivatives of the α-alloside and α-galactoside and to the use of p-nitrobenzoyl chloride. It was shown that the lower the polarity of the medium used, the more selective was the reaction.[15]



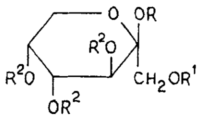
(4)



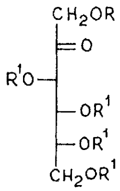
(5)

Monobenzoylations of a range of pento- and hexopyranosides by direct acylation, or after treatment with di- or tri-butyltin oxide, were compared by ^{13}C-n.m.r. examination of the products. Activation by dibutyltin oxide was considered to occur by preferential formation of a five membered stannylene of type (4) as found in arabino-, galacto-, and manno-pyranosides, with resultant activation of the equatorial hydroxy group. In the absence of such a cis-diol, a five membered co-ordination complex of type (5) was preferred, as found in α-D-gluco- and -xylopyranosides. In contrast, tributyltin oxide first enhances the reactivity of the most reactive hydroxy group by forming a tin ether which can be stabilized by co-ordination to a neighbouring oxygen atom. Some 50 benzoate derivatives are detailed and some inconsistencies of the literature were corrected.[16] The benzoylation of D-fructose with benzoyl chloride in pyridine and chloroform has been reinvestigated. In addition to (6), (7), and (8), previously obtained, the perbenzoylated derivatives (9) and (10) were isolated. When 1-O-allyl-D-fructose was benzoylated in a similar way, the products were the tri- and tetra-benzoylated derivatives (11) and (12). During the work, the fully benzoylated 1-O-allyl-D-fructopyranose (13) was obtained together with the elimination product (14).[17]

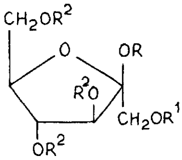
Partial benzoylation of L-rhamnono-1,4-lactone gave mainly the 2,5-dibenzoate (48%), while similar treatment of D-mannono-1,4-lactone gave the 2,5,6-tribenzoate in 60% yield, accompanied by lesser amounts of the 3,6-dibenzoate (5%) and the 2,3,5,6-tetrabenzoate (25%).[18]



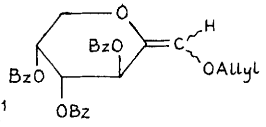
(6) $R=R^1=H$, $R^2=Bz$
(9) $R=R^1=R^2=Bz$
(11) $R=H$, $R^1=Allyl$, $R^2=Bz$
(13) $R=R^2=Bz$, $R^1=Allyl$



(7) $R=R^1=Bz$
(12) $R=Allyl$, $R^1=Bz$



(8) $R=H$, $R^1=R^2=Bz$
(10) $R=R^1=R^2=Bz$



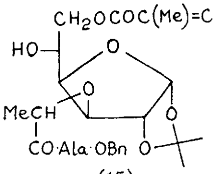
(14)

Selective benzoylation of 1,5-anhydrogalactitol occurs with the hydroxy groups showing the following order of preference for esterification: OH-6>OH-3>OH-2>OH-4.[19] All five possible benzoates from monomolar benzoylation of 1,5-anhydroxylitol, using benzoyl chloride in pyridine at -40°C, have been isolated. It was concluded that the C-2 (or 4) hydroxy groups have much the same reactivity as the C-3 hydroxy group.[20] Treatment of the 5,6-dibenzoate of 1,4-anhydro-D-mannitol with pyridine hydrochloride gave the 2,6-dibenzoate by ester migration.[21]

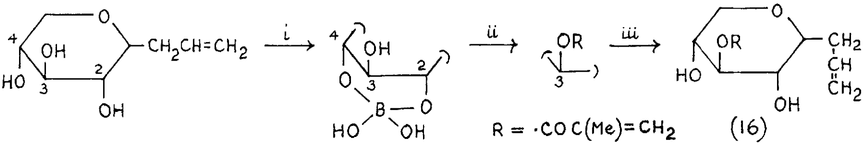
3 Other Carboxylic Esters

A detailed investigation of O-acyl migration in D-glucose derivatives has been conducted by examining the products formed from treatment of all possible mono-O-myristoyl esters of methyl α- and β-D-glucopyranoside and of D-glucopyranose under acidic, basic, thermal, and solvolytic conditions. In addition to the well known O-1α → O-2 and O-4 → O-6 migrations, the O-2 → O-3 process involving trans-related substituents was confirmed, while the O-1β → O-2 and O-3 → O-4 related migrations were not observed. Migrations involving a $^{1}C_{4}$ (D) conformation included the common O-6 → O-3 and the rarer O-4 → O-2 processes. The reversibility of many of these migrations was also confirmed.[22] In a related study, it was shown that migration in 1-O-myristoyl-β-D-glucopyranose occurs by an O-1β → O-3 → O-6 path.[23]

An eight-step synthesis of the monomer (15) from D-glucose has been described. The derived lipophilic polymer was a model of N-acetylmuramyl-L-alanyl-D-isoglutamine.[24] The synthesis of the monomethacrylic ester (16) of 1-deoxy-1-C-allyl-D-xylose has been achieved (Scheme 1). The product was polymerized with aluminium boronitride to yield a soluble linear polymer.[25]



(15)

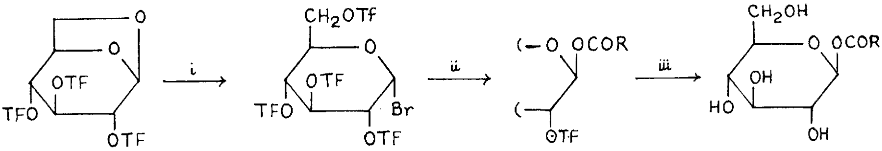


(16)

Reagents: i, B_2O_3-Me_2CO; ii, $(CH_2{=}C(Me)CO)_2O$-Py; iii, MeOH-H_2SO_4

Scheme 1

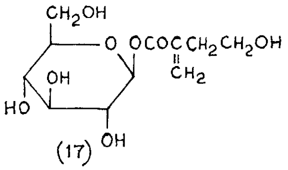
A new method for preparing 1-O-acyl-β-D-glucopyranoses has been described (Scheme 2). Tuliposide-A (17) was prepared by this method.[26] Selective substitution at the anomeric centre of



Reagents: i, $TiBr_4$-CF_3CO_2H; ii, RCO_2Ag-C_6H_6; iii, MeOH or Al_2O_3; TF = CF_3CO-

Scheme 2

lactose to yield 1-esters has been achieved by means of acyl derivatives of type (18) in pyridine.[27]



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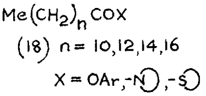
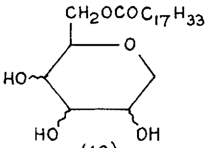


(18) n = 10,12,14,16



(19)

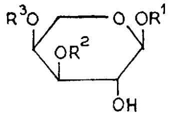
Selective esterification of 2-acetamido-2-deoxy-D-glucose in pyridine and of benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside with long-chain fatty acid chlorides gave the 6-O-acyl and 3-O-acyl derivatives respectively. The products were used as surfactants (after removal of the benzylidene acetal from the latter).[28] An improved procedure for preparing Span-80 (19) on a large scale has been described.[29]

A study of the binding of sucrose monoesters of caprylic, capric and lauric acids with proteins has been carried out using measurements of critical micelle concentrations, micellar sizes and ellipticities. The esters were shown to bind in a similar fashion to Triton X-100, a widely used non-ionic detergent. It was suggested that the esters of caprylic and capric acids might be promising detergents for membrane protein research.[30] Many 6,6'-diesters of α,α-trehalose with long-chain acids, some new to the literature, have been prepared and tested for antitumour or antileukaemic activity. All showed some activity in vitro, with the dilaurate having the lowest ID_{50} value in antileukaemia tests. In vivo antitumour activity was shown by the derivatives with ester chains longer than decanoyl.[12] The synthesis of deoxy-sugars by deoxygenation of pivaloyl esters is referred to in Chapter 12.

The synthesis of 6-O-(ω-aminoacyl)-derivatives of the methyl glycoside of N-acetyl-muramyl-L-alanyl-D-isoglutamine has been reported, and their coupling to the meningococcal group C polysaccharide investigated. The ω-aminocarboxylic acids selectively esterified the 6-hydroxy group when DCC and 4-(dimethylamino)-pyridine in DMF were used, a benzoyl protecting group on the dipeptide fragment being removed by subsequent trimethylsilane - palladium(II) chloride treatment.[31]

Mixed acetyl and toluoyl esters of D-ribofuranose have been prepared.[32]

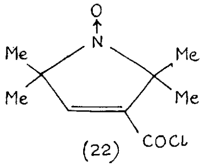
The synthesis of 1-O-(p-methoxycinnamoyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose by a phase-transfer catalysed procedure has been described. The glycosyl ester was obtained in a 60% yield from the acetobromoglucose.[33] The triterpenoid 4'-O-p-coumaroyl-α-L-arabinosides (20) have been synthesised by selective 3'-O-coumaroylation using a 3',4'-O-stannylated intermediate followed by acyl migration to give an equilibrium mixture containing similar amounts of the 3'- (21) and 4'-O-substituted derivatives.[34] The gallotannins in Paeoniae radix have been shown to be a homologous series of tetra- to undeca-galloylglucoses, based upon a 1,2,3,4,6-penta-O-galloyl-β-D-glucose core. The compounds were separated by reverse-phase h.p.l.c.[35] References to naturally-occurring esters of the sugar moieties of antibiotics will be found in Chapter 19.



R^1 = Cholester-3-yl or Serratanediol-3-yl

(20) $R^1 = -COCH{=}CH{\cdot}C_6H_4{\cdot}OH\text{-}p$, $R^2 = H$

(21) $R^1 = H$, $R^2 = COCH{=}CHC_6H_4{\cdot}OH\text{-}p$



(22)

Mixed monoesters prepared by esterification of methyl α-D-glucopyranoside with the nitroxide spin-label (22) have been examined by e.s.r. spectroscopy as part of a study on a simple method for spin-labelling polysaccharides.[36]

The synthesis of 2'- and 3'-aminoacyl derivatives of adenosine by acylation of 5'-O-(4-methoxytrityl)adenosine with the appropriate N-benzyloxycarbonyl or N-t-butyloxycarbonyl amino-acids with DCC-pyridine has been reported.[37] Amino-acid residues have been used as protecting groups for sugars, being readily removed by saponification or enzymic hydrolysis. No deaminoacylation occurs under acidic conditions. Carboxyacyl groups can also serve as sugar hydroxy protecting groups.[38]

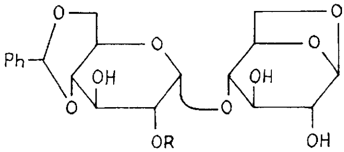
Four new dammarane-type triterpene oligoglycosides with 6-O-malonyl-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl moieties have been isolated from the root of *Panax ginseng* (White ginseng).[39]

Selective deprotection under mild conditions has been achieved by the use of hydrazine dithiocarbonate for removal of chloroacetyl and bromoacetyl groups. The halogenated groups were removable without affecting other ester groups including acetate, benzyl ethers and glycosides, methyl glycosides, or methyl esters of uronic acid groups. The removal of the haloacetates was accomplished within 2-10 min. at room temperature and gave yields of 95-99% of the deprotected alcohol.[40]

4 Sulphonates

The danger of formation of sugar pyridinium salts when using trifluoroacetic anhydride in pyridine may be avoided by using 2,6-di-t-butyl-4-methylpyridine.[41] Reaction of carbohydrate triflates with cyanide ion allows inversion at the hydroxy carrying centre; either sodium cyanide or tetra-n-butylammonium cyanide were used in a one-pot reaction.[42]

Selective tosylation of 1,5-anhydro-D-galactitol showed that the order of reactivity of the hydroxy groups was OH-6>OH-3>OH-2>OH-4. Useful amounts of the 2,3,6-tritosylate or of the 3,6-ditosylate could be obtained on tri- and dimolar tosylation respectively.[43] Contrary to an earlier report (G.G.S.Dutton and K.N.Slessor, Can. J. Chem., 1966, 44, 1069) benzyl 4',6'-O-benzylidene-β-maltoside was successfully monotosylated at the 6-position with tosyl chloride (1.7 mole) in pyridine at -20°C, in a fashion analogous to that reported for the methyl glycoside analogue. The peracetylated 6-O-tosylate was isolated in 72% yield by chromatography and converted via the iodide into the 6-deoxy derivative.[44] Selective tosylation patterns of methyl 3,6-anhydro-gluco-, -manno-, and -gulo-furanoside have been rationalized by steric and polar considerations.[45] Phase transfer catalyzed tosylation of 1,6-anhydro-4',6'-O-benzylidene-β-maltose (23) using 1.2 mol tosyl chloride gave 64% isolated yield of the 2'-O-tosyl derivative (24).[46] Methyl β-sophoroside was converted to its peracetylated 6,6'-ditosylate and thence to a variety



(23) R = H

(24) R = Ts

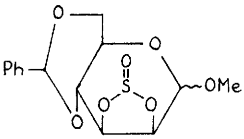
of 6,6'-disubstituted derivatives (Cl, Br, I, SAc, N_3, NHAc, H) via sulphonate displacement reactions, and the 3,6:3',6'-dianhydride was obtained using methoxide. Several 6- and 6'-monosubstituted derivatives were prepared via the 4,6-O-benzylidene derivative, and methyl 2-O-β-D-glucopyranosyl-β-D-allopyranoside was obtained by a standard C-3 sulphonate inversion procedure.[47] Tosylations under phase transfer catalysis are mentioned in the introduction to this chapter (Ref. 3-5).

Selective demesylation of 2-O-mesyl-D-mannopyranoside derivatives has been achieved by means of sodium amalgam and 2-propanol. Most other protecting groups are stable to these conditions.[48]

5 Sulphates, Sulphites and Related Esters

Autohydrolysis of 1,2-*O*-isopropylidene-α-D-glucofuranose 5-(hydrogen sulphate) led to D-fructopyranose 5-sulphate in high yield in 30 min. at 70°C, rather than to the expected D-glucofuranose 5-sulphate.[49] 2,5-Anhydro-4-*O*-β-D-galactopyranosyl-[1-^{3}H]mannitol 6-sulphate and its 6,6'-disulphate were prepared from keratan sulphate by a sequence of *N*-deacetylation with hydrazine, deamination with nitrous acid, followed by sodium borotritiide treatment. The products were used as substrates for β-D-galactosidases and 6-*O*-sulphogalactose sulphatase.[50] Two steroidal oligoglycosides bearing α-L-rhamnopyranosyl-(1→2)-4-*O*-sulpho-α-L-arabinopyranosyl moieties have been isolated from the roots of *Ophiopogon planiscapus*, the first report of a steroidal glycoside bearing a sulphate group on the sugar portion.[51]

Reactions of cyclic sulphites and sulphates with tetramethylammonium fluoride have been studied. The cyclic sulphites (25) gave the corresponding de-esterified mannoside, whereas the α-glycoside cyclic sulphate (26) yielded the enone (27). The β-anomer of the cyclic sulphate (26) gave, after acid hydrolysis of the benzylidene acetal, the 2-deoxy-2-fluoro-glycoside (28) which was converted into the free 2-fluoro-sugar.[52]



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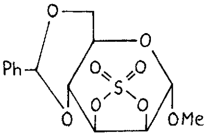
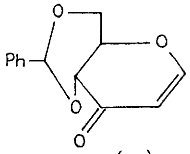
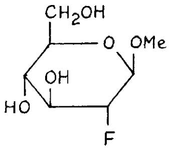


(26)



(27)



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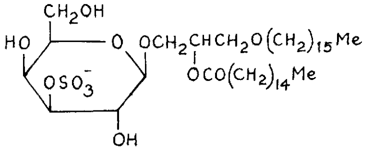


(29)

The rates of desulphation of many monosaccharide and glycoside sulphates by 0.25 M hydrochloric acid at 100°C and by 0.25 M sodium hydroxide at 60°C have been determined. The generalization, that desulphation in alkali will occur only when an adjacent trans-hydroxy group is present was shown to hold for methyl α-D-galactopyranoside

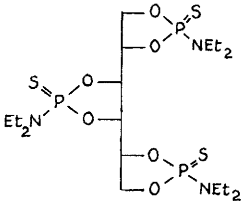
4-sulphate which is stable; in contrast, the corresponding glucoside had a half-life of 50 min.[53] Anhydrous propanone-hydrogen chloride is a mild reagent for desulphation without deacylation or degradation. The method was applied to sulpholipids and cerebrosides: e.g., the time to desulphate the lipid (29) was found[54] to be 1.5h. Intermediate chlorosulphates in the synthesis of chlorodeoxy sugars are mentioned in Chapter 8.

6 Phosphates, Phosphites, and Related Esters

D-[1-^{13}C]Ribose 5-phosphate and D-[1-^{13}C]arabinose 5-phosphate have been synthesized by condensation of D-erythrose 4-phosphate with labelled potassium cyanide and the consequent epimeric aldononitrile phosphates hydrogenated over palladium on barium sulphate after chromatographic separation.[55] Various mono-, di-, and cyclic phosphate esters of 1,2-O-isopropylidene-α-D-ribo- and -xylo-furanoses have been prepared and their ^{1}H, ^{13}C, and ^{31}P n.m.r. spectral characteristics determined.[56]

A one-step procedure for the isolation of α-D-glucose 1-phosphate has been described: using an anion exchange resin and potassium acetate as eluting buffer, the carbohydrate, inorganic phosphate and the required phosphate from a reaction mixture were separated, finally precipitating the latter from the eluant by addition of ethanol.[57] The synthesis of D-galactose 6-phosphate has been achieved by direct phosphorylation using polyphosphoric acid, partial acid hydrolysis, and purification by ion-exchange chromatography. D-Tagatose 6-phosphate was prepared from D-galacturonic acid in six steps, the key steps being isomerization to D-tagaturonic acid and phosphorylation of 1,2:3,4-di-O-isopropylidene-D-tagatose with diphenyl phosphoryl chloride.[58] Treatment of pyridinium D-fructose 1,6-diphosphate with DCC-triethylamine in pyridine gave 30-50% yields of D-fructose 1,2-cyclophosphate 6-phosphate which was isolated by column chromatography and saponified with sodium hydroxide to yield D-fructose 2,6-bisphosphate.[59] Enzymes of the glycolytic pathway have been used to prepare ^{13}C-labelled ketose phosphates from ^{13}C-enriched pyruvate. Three primary steps were used: phosphocreatine kinase, adenylate kinase, and enolpyruvate synthetase on the three-carbon precursor yielded enolpyruvate phosphate; yeast enolase, phosphoglycerate mutase and phosphoglycerate kinase caused conversion to glycerate 3-phosphate and glycerate itself; finally, β-NADH, D-glyceraldehyde 3-phosphate dehydrogenase gave 1,3-dihydroxy-2-propanone phosphate which was converted to D-fructose 1,6-diphosphate on addition of aldolase. Throughout the synthesis the ATP to ADP ratio was kept high by enzymic rephosphorylation of the latter by phosphocreatine.[60] A new monosaccharide, 1-deoxy-D-altro-heptulose phosphate, has been synthesized from DL-acetoin and D-ribose 5-phosphate using a transketolase mutant of B. pumilus, the other product being ethanal.[61]

Phosphorylation of galactitol with tris(diethylamino)phosphine, followed by treatment with sulphur, gave a mixture of diastereoisomeric phosphorus(V) esters including the cyclic phosphoryl derivatives (30) and (31) and the 1,6-di-O-phosphoryl derivative (32).[62]



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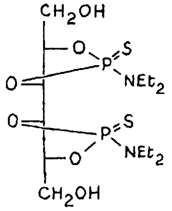

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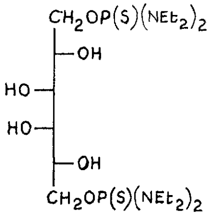
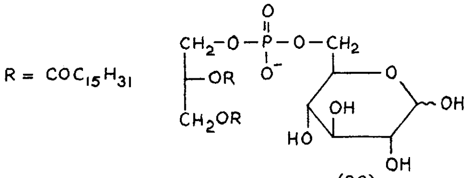


(32)

The phospholipid (33) has been synthesized by condensation of 1,2-dipalmitoyl-sn-glycerol and 2,3,4-tri-O-benzyl-D-glucose with the cyclic enediol reagent (34). The product was used for studies of bilayer formation and associated phase-transition properties of aqueous dispersions of phosphatidylglucoses.[63] A novel platelet activating



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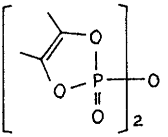

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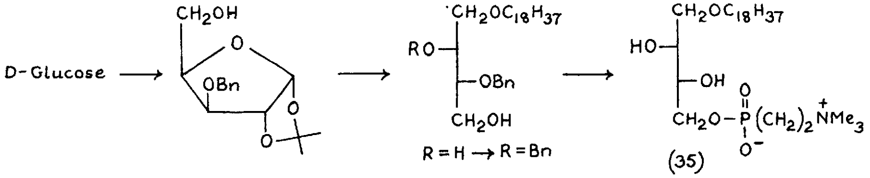


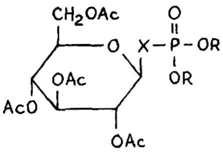
Scheme 3

factor congener (35) has been synthesized from D-glucose via the intermediates indicated in Scheme 3.[64] The synthesis of the _S_- and _Se_-glycosyl thio- and selenophosphates (36) by reaction of 2,3,4,6-tetra-_O_-acetyl-α-D-glucopyranosyl bromide with dicyclohexylammonium _O_,_O_-di-_t_-butylphosphoro-thioate or -selenoate and their conversion by trifluoroacetic acid to the free phosphoro-thioic and -selenoic acids (37) have been accomplished in good yield.[65]

Palladium complexes with alkylglycophosphite ligands (38) and with bisglycophosphite ligands (39) have been synthesized and shown to impart asymmetry in the hydrogenation of certain unsaturated acids.[66]

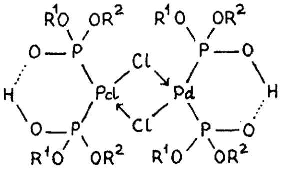
By using oxygen isotope labels, the barium hydroxide catalyzed hydrolysis of the nucleotide cyclophosphate (40) to yield a 4:1 mixture of 3'- and 5'-monophosphates was shown by ^{31}P-n.m.r. to occur with inversion at phosphorus.[67]

Investigation of the biosynthesis of a D-glucosyl polyisoprenyl diphosphate by _Micrococcus lysodeikticus_ has been carried out using UDP-D-[^{14}C]glucose.[68]



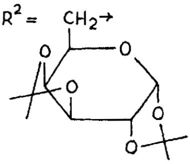
(36) X = S or Se, R = Bu^t

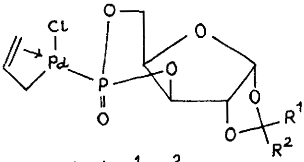
(37) X = S or Se, R = H



(38) R^1 = Et, Pr^n, or Pr^i;

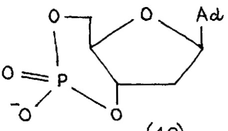
R^2 =





(39) $R^1 = R^2$ = Me, or

$R^1, R^2 = (CH_2)_5$



(40)

7 Other Esters

The competitive formation of 1,3-orthoacetate derivatives in the Koenigs-Knorr glycosidation of various alcohols with 2,3,4-tri-_O_-

acetyl-β-L-arabinopyranosyl bromide using silver oxide in dichloromethane-ether has been investigated.[69]

Sucrose has been shown to yield sucrose 4,6-ethylboronate with 1,3-bis(2,2-dimethylpropanoyloxy)-1,3-diethyldiborane. The product is a useful intermediate for the synthesis of 2,3,1',3',4',6'-hexa-*O*-derivatives.[70]

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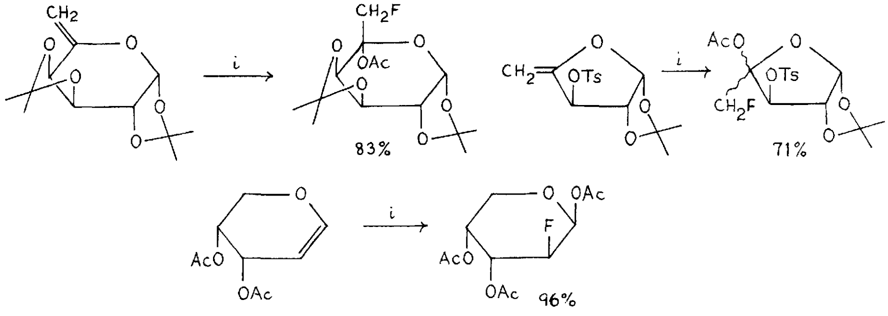
8
Halogeno-sugars

The synthesis of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride and its α-D-arabinofuranosyl analogue, has been accomplished by the reaction of the tri-*O*-benzylated sugar with 2-fluoro-1-methylpyridinium tosylate - triethylamine.[1]

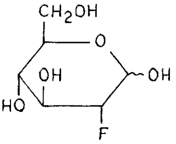
Addition of acetyl hypofluorite to unsaturated sugar derivatives which contain a vinyl ether substructure has formed the basis for syntheses of 2-deoxy-2-fluoro-sugars.[2-5] Thus the conversions of 3,4,6-tri-*O*-acetyl-D-*arabino*- and -*lyxo*-hex-1-enoses to the corresponding 2-deoxy-2-fluoro-glycosyl acetates were accomplished in high yield. The reaction is rapid (<5 min at -78 °C) and the products are isomerically pure; the mode of addition is exclusively *cis* with preferential stereo-facial attack. Other conversions and isolated yields are shown in Scheme 1.[2] The same addition has been used to prepare fluorine-18 labelled 2-deoxy-2-fluoro-D-glucose (1) from ^{18}FOAc, prepared by fluorine-18 on sodium acetate - acetic acid, and 3,4,6-tri-*O*-acetyl-D-*arabino*-hex-1-enose. The yields of 98% radiochemically pure product after deacetylation were about 20%.[3-5] High yields of the labelled fluoro-sugar (1) have also been obtained by reaction of labelled xenon difluoride with tri-acetyl-D-glucal in the presence of boron trifluoride etherate, followed by hydrolysis of the acetyl groups and the glycosyl fluoride by 1M hydrochloric acid. The reaction, which was accomplished in 45 min, gave a yield of 75% and a radiochemical yield of 20%.[6] The



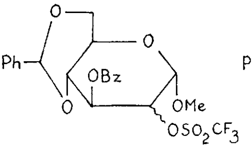
Reagent: i, AcOF

Scheme 1

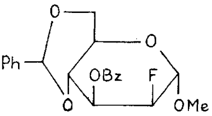
identical reaction was also described as taking 1h and giving 50% yields.[7] 2-Deoxy-2-fluoro-D-glucose (1) has been prepared from methyl 4,6-O̲-benzylidene-3-O̲-methyl-2-O̲-(trifluoromethyl)sulphonyl-β-D-glucopyranoside using cyclotron-produced $^{18}F^-$ at 130°C for 25 min, followed by hydrolysis.[8,9] [^{18}F]-2-Deoxy-2-fluoro-α-D-glucopyranosyl fluoride has been prepared from triacetyl-D-glucal by reaction with fluorine-18 in fluorotrichloromethane at -78°C, followed by separation and partial hydrolysis with methanolic sodium methoxide. The radiochemical yield was 28%.[10] 2-O̲-Triflate displacement by fluoride ion derived from tetra-n-butylammonium fluoride has been shown to proceed stereoselectively according to anomeric configuration and neighbouring group on C-3. Thus the α-gluco̲ or manno̲-3-O̲-benzoyl compounds (2) gave the 2-deoxy-2-fluoro-mannoside (3), as did the β-anomer (4), while the β-3-O̲-benzyl-gluco̲- or manno̲-glycosides (5) gave the glucoside (6).[11] The cyclic sulphate (7) on reaction with tetramethylammonium fluoride, followed by acid hydrolysis yields 2-deoxy-2-fluoro-D-glucose in 40% yield.[12]



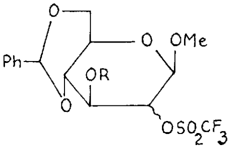
(1)



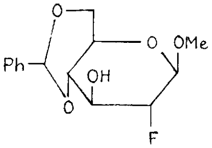
(2)



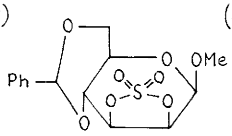
(3)



(4) R = Bz
(5) R = Bn



(6)



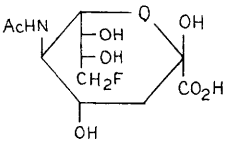
(7)

The synthesis of [^{18}F]-3-deoxy-3-fluoro-D-glucose has been carried out by treatment of 1,2:5,6-di-O̲-isopropylidene-3-O̲-triflyl-α-D-glucofuranose with fluoride-18 ion in an acetamide melt at 150°C, followed by acid hydrolysis. The yield of 30±5% was obtained in less time than the half-life for fluorine-18.[13] Conventional epoxide ring-opening of 1,6:3,4-dianhydro-D-altropyranose using potassium hydrogen difluoride in glycol has led to synthesis of 3-deoxy-3-fluoro-D-mannose. Reduction of the product to the corresponding fluoro-hexitol was carried out with sodium borohydride.[14] An improved preparation of methyl 3-deoxy-3-fluoro-β-D-galactopyranoside using diethylaminosulphur trifluoride (DAST) and 4-(dimethylamino)pyridine has been described.[15]

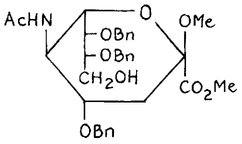
Using a modified Kiliani-Fischer cyanohydrin synthesis, 2-deoxy-2-fluoro-D-arabinose has been converted to 3-fluoro-3-deoxy-D-glucose and -D-mannose, and 3-fluoro-3-deoxy-D-arabinose similarly yielded 4-deoxy-4-fluoro-D-glucose and -D-mannose by chain extension; analogues containing $[1\text{-}^{13}\text{C}]$ and $[1\text{-}^{14}\text{C}]$ labels were similarly prepared using labelled cyanide.[16]

The DAST procedure has been used and investigated for its stereo- and regio-selectivity in glycoside fluorinations.[17-21]

Methyl α-D-gluco- and manno-pyranosides gave a mixture of 6-deoxy-6-fluoro- and 4,6-dideoxy-4,6-difluoro derivatives with inversion at C-4 in the latter, whereas methyl β-D-glucopyranoside gave a mixture of the 6-fluoro, 4,6-difluoro-galactoside, and 3,6-difluoro-alloside derivatives. Methyl 6-*O*-trityl-α-D-glucopyranoside gave methyl 4-deoxy-6-*O*-trityl-4-fluoro-α-D-galactopyranoside. The ^{19}F n.m.r. spectra of the products were given.[17] At low temperatures (-30°) the fluorination of methyl α-D-glucopyranoside by DAST may be restricted to C-6 giving the 6-fluoro product in 80% yield. Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-glucopyranoside was also synthesized using the DAST procedure on methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside.[18] Further extensions of the reaction to yield 4,6- and 3,6-difluoro-sugars have been reported. Use of phenyl glycosides in place of methyl analogues improved yields in some cases.[19] Methyl 6-deoxy-6-fluoro-β-D-galactopyranoside has been isolated in 15% yield by direct fluorination of methyl β-galactopyranoside with DAST. The ^{13}C n.m.r. spectra of methyl 2-,3-,4-, and 6-deoxyfluoro-β-D-galactopyranosides and their peracetates were detailed and fully assigned.[20] *N*-Acetyl-9-deoxy-9-fluoroneuraminic acid (8) has been synthesized by the action of DAST on the 9-unprotected *N*-acetylneuraminic acid derivative(9). Alternatively (8) could be obtained in 21% yield by alkaline epimerization - chain extension of 2-acetamido-2,6-dideoxy-6-fluoro-D-glucopyranose (10) as shown in Scheme 2.[21]

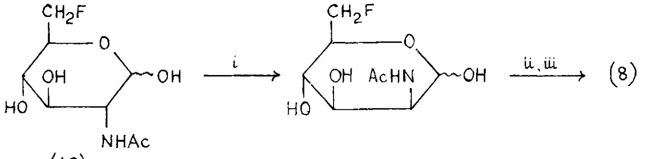


(8)



(9)

Specifically-fluorinated methyl β-glycosides of (1→6)-β-D-galacto-oligosaccharides have been synthesized by use of 3-fluoro sugar units in Koenigs-Knorr-type reactions. (See also Chapter 3).[22]

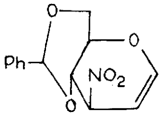


Reagents : i, OH^- ; ii, $[Bu^tO_2C\cdot CHCOCO_2Bu^t]^-K^+$; iii, H_3O^+

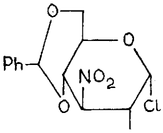
Scheme 2

Synthesis of sporaricin antibiotics fluorinated in the non-carbohydrate rings is referred to in Chapter 19.

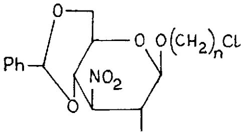
Efficient syntheses of glycosyl chlorides have been achieved by treating aldoses protected at all positions except the anomeric centre with N-dichloromethylene-N,N-dimethylammonium chloride (Viehe's salt). Compounds which have both C-1 and C-2 hydroxy groups free gave 2-O-(N,N-dimethylcarbamoyl)glycosyl chlorides.[23] Chlorination of the 3-nitro-glycal (11) gave the expected dichloride (12) when the reaction was carried out in carbon tetrachloride or dioxane, but with THF, THP, and oxetane the solvent participated in the reaction to yield the ω-chloroalkyl β-glycosides (13), while diethyl ether gave ethyl β-glycosides. Separations of (13) on silica gel caused partial elimination giving the nitroenes (14).[24]



(11)



(12)



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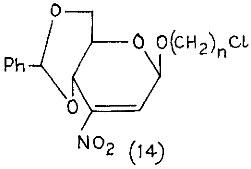
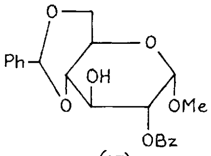


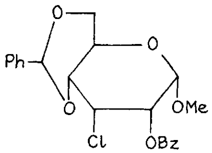
(14)

The products of treatment of aldopyranoside 2,3-epoxides with dichlorobis(benzonitrile)palladium(II) are the 3-chloro-3-deoxypyranosides, with trans diaxial ring-opening being predominant.[25] Viehe's salt reacts with secondary hydroxy groups to yield the inverted chloro-deoxy compounds. Thus the 3-hydroxy-glucoside (15) gives rise to the 3-chloro-3-deoxy-alloside (16). With methyl α-D-lyxofuranoside the 2-O-carbamoyl-3,5-dichloro-derivative (17) was produced. The products were used in the synthesis of deoxy and amino sugars using conventional methods.[26] The full paper on the reaction of 1,2-O-isopropylidene-α-D-glucofuranose with sulphuryl chloride-pyridine at 0° has been published (see Vol 9, Ref. 271,

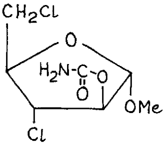
p. 56). The product is the 6-chloro-3,5-bis(chlorosulphate) (18), which was dechlorosulphated with sodium iodide-sodium hydrogen carbonate in methanol to yield the diol (19). Treatment of the bis-(chlorosulphate) (18) with pyridine afforded the 3,5-cyclic sulphate (20). Raising the temperature of the sulphuryl chloride reaction to 50° led to the 5,6-dichloro-L-ido-derivative (21), which on de-chlorosulphation to the alcohol (22) and acid hydrolysis gave the 3,6-anhydride (23). Similar treatment of D-glucofuranurono-6,3-lactone derivatives led to 5-chloro-5-deoxy-L-idofuranurono-6,3-lactone derivatives, e.g., (24).[27]



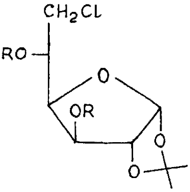
(15)



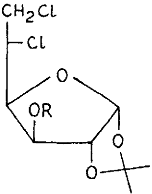
(16)



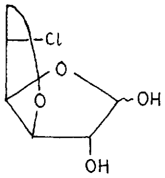
(17)



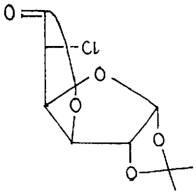
(18) R = SO_2Cl
(19) R = H
(20) R,R = $>SO_2$



(21) R = SO_2Cl
(22) R = H

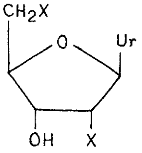


(23)

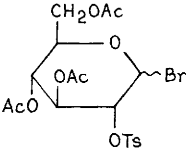


(24)

2',5'-Dibromo- and dichloro-2',5'-dideoxyuridines (25) have been obtained by treatment of the parent nucleoside with Vilsmeier reagent.[28]

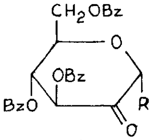


(25) X = Cl, Br

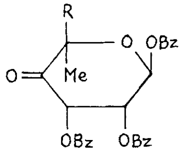


(26)

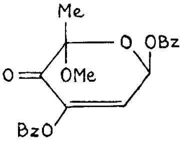
Treatment of 1,6-anhydro-3,4-di-O-acetyl-2-O-tosyl-β-D-glucopyranose with hydrogen bromide in acetic acid yields the glycosyl bromide (26).[29] Photobromination at the "pro-anomeric centre" of such ketones as (27) gave rise to glycosulosyl bromides, e.g. (28). Photobromination of 4-uloses resulted in bromination at the α-position giving 5-bromo-products. Thus the ketone (29) yielded the bromosugar (30), which with methanol-silver carbonate gave the enone (31).[30]



(27) R=H
(28) R=Br

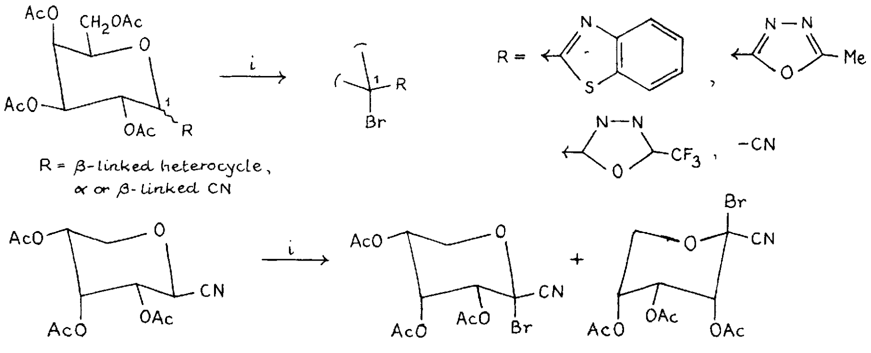


(29) R=H
(30) R=Br



(31)

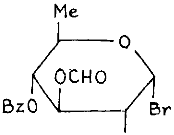
The reactions of acetylated C-(D-glycosyl) heterocycles and of D-glycosyl cyanides with NBS in hot carbon tetrachloride or with bromine in the presence of u.v. light gave axial bromination at the anomeric centre. Both methods gave the same results, with a wide range of heterocycles. Scheme 3 shows some examples of reactions carried out.[31]



Reagents: NBS-CCl$_4$ or Br$_2$-hν

Scheme 3

2-Bromo-2-deoxy-3-O-formyl-α-D-quinovosyl bromide (32) has been obtained by the reaction of dibromomethyl methyl ether (DBE) with the blocked rhamnose derivative (33). Reaction of the 4-hydroxy analogue of (33) with DBE-zinc bromide gave the pyranosyl and furanosyl bromides (34) and (35), whereas the 4-O-benzyl analogue underwent stepwise reactions via the α-glycosyl bromide, the 4-O-formyl ester, and cleavage of the isopropylidene acetal to yield finally the dibromide (34).[32] Treatment of the digitoxose triacetates (36), or the olivose triacetates (37) with trimethylsilyl halide led to the glycosyl halides (38) and (39), and, on further reaction with these reagents, to the 3-halo-D-arabino-halides (40) and (41), apparently by way of the 3,4-acetoxonium ion intermediate.[33] Reaction of glycal esters with NBS or NIS in the presence of alcohols has been shown to yield 2-haloglycosides, e.g., (42) gave (43), whereas with the peracetylated 2-hydroxy glycals the bromouloses are formed, e.g., (44) yielded (45). The method was also applied to cellobiose- and lactose-derived hydroxyglycal esters. Several reactions were carried out on the products.[34]



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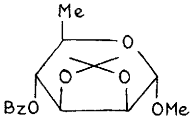

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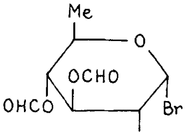

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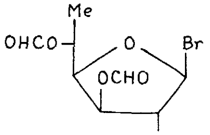

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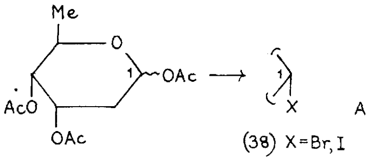
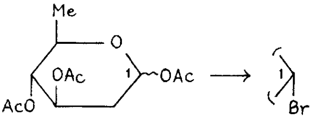


(36)
(38) X=Br,I



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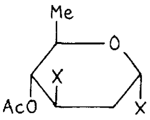
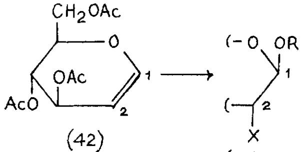
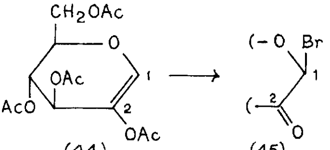


(40) X=Br
(41) X=I



(42)
(43) X=Br, I
R = C_6H_{11}, Pr^i, Bz

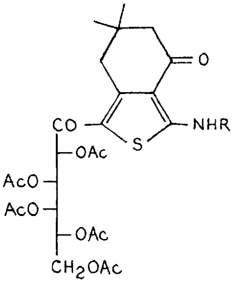


(44)
(45)

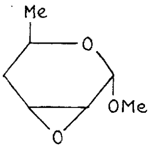
D-Glucose derivatives labelled with bromine-75, bromine-77 and iodine-123 have been prepared by standard procedures from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose to yield the 3-halo-compounds and from tri-O-acetyl-D-glucal to give the 2-halo compounds.[35]

The synthesis of the heterocyclic derivatives (46) from 1-bromo-1-deoxy-3,4,5,6,7-penta-O-acetyl-D-galacto-heptulose by reaction with cyclohexane-1,3-diones has been reported.[36]

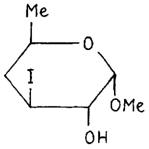
The stereospecific photobromination at C-6 of 1,6-anhydrosugars as intermediates for isotopic labelling at this centre by hydrogen isotopes is covered in Chapter 2.



(46) R = Me, substituted phenyl



(47)



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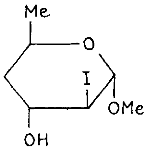

(49)

Opening of the epoxide ring in the 4,6-dideoxy sugar (47) with magnesium iodide in THF gave 80% trans-3-deoxy-3-iodo-2-hydroxy product (48), whereas with sodium iodide the product was the corresponding trans-2-iodo compound (49). Tetra-n-butylammonium iodide gave no reaction.[37]

Xylitol has been converted to its 1,5-dideoxy-1,5-diiodo derivative via the intermediate 1,2:5,6-anhydro-xylitols and epoxide ring opening with hydriodic acid.[38]

Iodinolysis by means of iodotrimethylsilane in carbon tetrachloride as an alternative to acid hydrolysis of glycosidic linkages is mentioned in Chapter 3.

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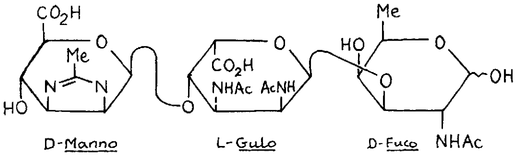
9

Amino-sugars

1 Natural Products

3-[(N-Acetyl-L-seryl)amino]-3,6-dideoxy-D-glucose has been identified as a component sugar of the O-specific polysaccharide of an *Escherichia coli* strain, and a related aminosugar reported previously to be 3,6-dideoxy-3-(L-glyceroylamino)-D-glucose (W. Kondo *et al.*, *Carbohydr. Res.*, 1980, **83**, 129) has been shown instead to have the *galacto*-configuration.[1] A new acidic amino-sugar, 2,3-diacetamido-2,3-dideoxy-L-guluronic acid, has been identified as a component of the O-specific polysaccharide of a *Pseudomonas aeruginosa* strain; this polysaccharide, on solvolysis with hydrogen fluoride, released the trisaccharide repeating unit (1) in almost quantitative yield.[2] 1,5-Dideoxy-1,5-imino-D-mannitol, a recently isolated plant natural product (Vol. 13, p.78), has been shown to be a potent inhibitor of various glucosidase enzymes.[3] Temperature dependent ^{13}C-n.m.r. spectroscopy has been used to show that binding of 2-acetamido-2-deoxy-D-glucose to lysozyme dramatically reduces the conformational flexibility of the protein.[4]



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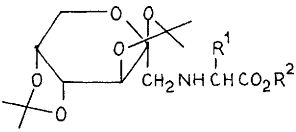


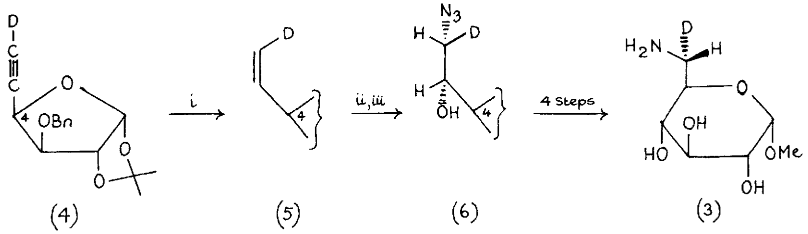
(2) $R^1 = H, Me, Pr^i, Bu^i, Bu^s$
$R^2 = Me, Et$

2 Synthesis

The protected Amadori compounds (2), from which the free N-substituted 1-amino-1-deoxy-D-fructoses can be released for biochemical studies, have been synthesized by displacement of a 1-

triflate group by an amino-acid ester.[5] ε-N-(1-Deoxylactulos-1-yl)-L-lysine has been isolated from the reaction of lactose and lysine in low yield, by h.p.l.c. on a cation-exchange resin, and then used as a substrate for monitoring β-galactosidase activity.[6] Fourteen mutarotated N-(1-deoxy-D-fructos-1-yl)-L-amino-acids have been examined by high field ^{1}H- and ^{13}C-n.m.r. spectroscopy in D_2O solution, and shown to be mixtures of α- and β-pyranose, and α- and β-furanose forms in the ratio ca. 6:64:15:15 respectively, independent of pH, although the L-alanine derivative was shown to contain 2% of the keto-form; on prolonged storage, H-1 in these compounds underwent H/D-exchange, presumably via enamine intermediates.[7]

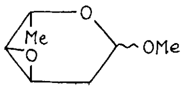
Methyl (6S)-[6-$^2H_1$]-6-amino-6-deoxy-α-D-glucopyranoside (3) has been synthesized from the deuterated acetylene derivative (4) as shown in Scheme 1, involving selective epoxidation of alkene (5) and azide opening of the resulting epoxide to give (6).[8] The



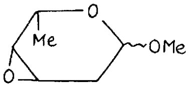
Reagents: i, Lindlar cat.-H_2; ii, MCPBA; iii, NaN_3

Scheme 1

epoxide rings in the anomeric 2,6-dideoxy-L-lyxo-derivatives (7) undergo preferential attack at C-3 with a variety of nucleophilic reagents (MeONa, NaN_3, Me_2NH, $MeNH_2$, NH_3), as does that in the α-anomer of the 2,6-dideoxy-L-ribo-derivative (8) with the first three reagents. A mixture of products resulting from attack at



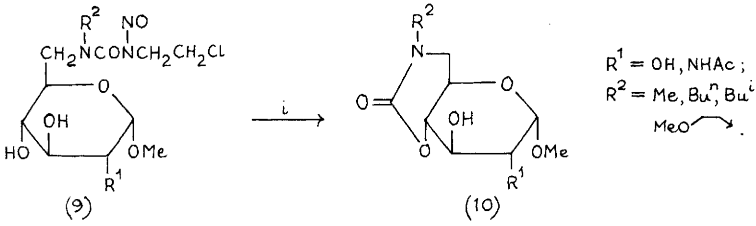
(7)



(8)

both C-3 and C-4, however, was obtained in other cases.[9] 6-Deoxy-6-piperazino-D-glucose, and various N-substituted derivatives therefrom, have been synthesized in a search for cytostatic activity.[9a]

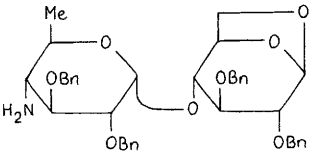
Introduction of nitrogen functionality by sulphonate displacement continues to be a popular strategy. Eight nitrosourea derivatives (9) have been synthesized by displacement of a 6-sulphonate by



Reagent: i, $NaHCO_3$-H_2O

Scheme 2

alkylamine, and shown to form cyclic carbamates [i.e. (10) in Scheme 2] more slowly than their C-1 and C-3 positional isomers, consistent with their lower antitumour activity.[10] Full details of the synthesis of the 4'-aminodisaccharide (11) have been published (Vol. 16, p. 72).[11] The 2-amino-3,6-anhydro-heptonic acids (12) have been synthesized from D-ribose via cyanohydrin chain extension of a 2,5-anhydro-hexose derivative, the 2-amino-functionality being introduced by displacement of sulphonate by azide.[12] Various 4-amino- and 4,6-diamino-hexosides including the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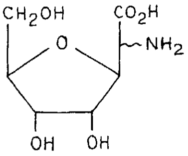
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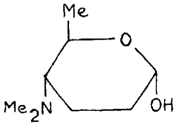
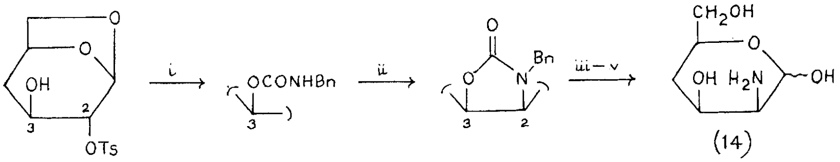

(13)

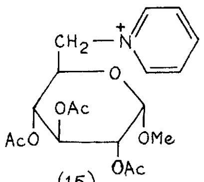
aminodeoxysugar (13) have been synthesized from ethyl α-D-erythro-hex-2-enopyranoside, again using azide displacement of sulphonate.[13] 4-Deoxy-D-mannosamine (14) has been synthesized from 1,6-anhydro-β-D-glucopyranose utilizing the intramolecular sulphonate displacement strategy shown in Scheme 3.[14] The conditions frequently used to



Reagents: i, BnNCO; ii, NaH-DMF; iii, OH^--H_2O; iv, H_2-Pd; v, H_3O^+

Scheme 3

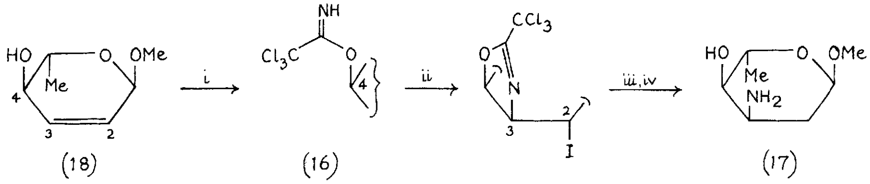
prepare triflate esters (Tf_2O-CH_2Cl_2-py) can lead to the formation of pyridinium salts such as (15) when applied to primary alcohols.[15]



(15)

Syntheses of carminomycine analogues with 3-amino- and 3,5-diamino-hexofuranosyl moieties, and of 3'-amino-nucleoside and -deoxy-nucleoside analogues, which involve displacement of sulphonate with azide, are covered in Chapters 19 and 20 respectively.

Guided addition of the elements of ammonia to an allylic alcohol has been demonstrated in syntheses of 3-amino-2,3-dideoxy-sugars. Thus, two groups employed the halocyclization of the 4-O-trichloroacetimido-derivative (16) in the synthesis of methyl α-L-ristosaminide (17) (Scheme 4),[16,17] while a daunosamine derivative,

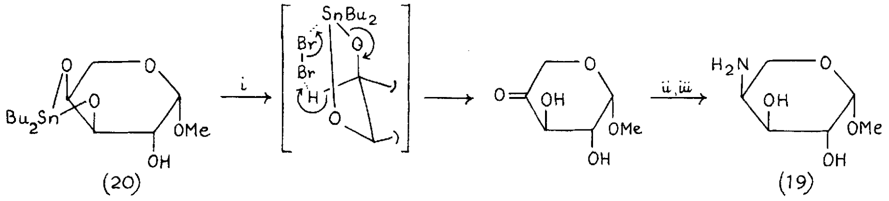


Reagents: i, CCl_3CN-NaH; ii, NIS or I(Collidine)$_2ClO_4$; iii, H_3O^+; iv, Bu_3SnH

Scheme 4

related to (17) by inversion at C-3 and -4, was obtained by applying the same strategy after first inverting the configuration at C-4 in the starting material (18) using the Mitsunobo reaction.[18] p-Trifluoroacetamidophenyl 2-acetamido-2-deoxy-4-O-α-D-glucopyranosyl-β-D-glucopyranoside has been synthesized from maltose via azidonitration of maltal hexaacetate, while the (1 → 6)-linked isomer was synthesized by conventional bromide-ion catalyzed glycosidation procedures.[19]

Amino-functionality has also been introduced via ulose derivatives. 4-O-(2-Acetamido-2-deoxy-α-D-glucopyranosyl)-D-glucopyranose was synthesized from a protected 1,6-anhydro-2'-O-tosyl-β-maltose derivative. Removal of the 2'-O-tosyl group by alkaline hydrolysis, oxidation of the resulting alcohol, oximation, and reduction (LAH) provided a 6:1 mixture of disaccharides having the gluco- and manno-configuration in the non-reducing terminal respectively.[20] The 4-amino-4-deoxy-β-L-arabinoside (19) was synthesized as shown in Scheme 5, using the novel bromine oxidation

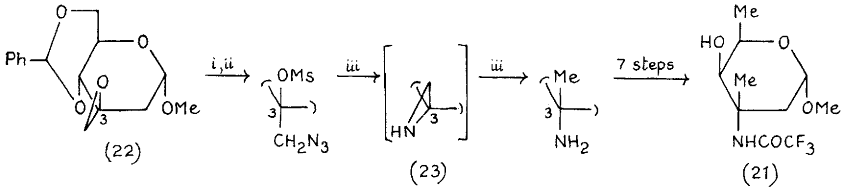


Reagents: i, Br_2-$CHCl_3$; ii, NH_2OH ; iii, PtO_2-H_2-AcOH

Scheme 5

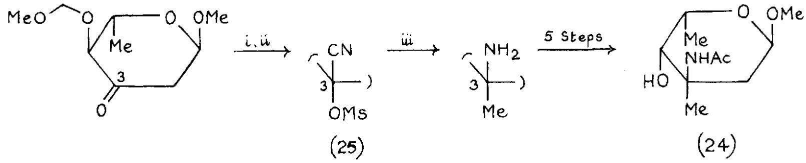
of the stannylene derivative (20) in which the equatorial hydrogen was specifically abstracted, as shown in the postulated cyclic mechanism.^{21}

The branched-chain amino-sugar (21) has been synthesized as shown in Scheme 6, the amino-function being introduced in a stereo-controlled manner by conversion of spiro-oxiran (22) to spiro-aziridine (23).^{22} The enantiomeric L-xylo-derivative (24) was synthesized as shown in Scheme 7, with the presumed intermediacy of a spiro-aziridine in the reduction of the cyano-mesylate (25).^{23}



Reagents: i, NaN_3 ; ii, MsCl-Py ; iii, H_2-PtO_2-MeOH

Scheme 6



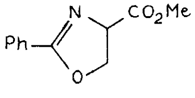
Reagents : i, KCN ; ii, MsCl-Py ; iii, LAH

Scheme 7

In both syntheses, epimerization at C-4 was effected by an oxidation-reduction sequence. Details have been published on the syntheses of the four configurational isomers of 2,3,6-trideoxy-3-C-methyl-3-benzamido-L-hexose from a yeast-produced α-methylcinnamaldehyde-acetaldehyde adduct (see Vol.15, p.97).^{24}

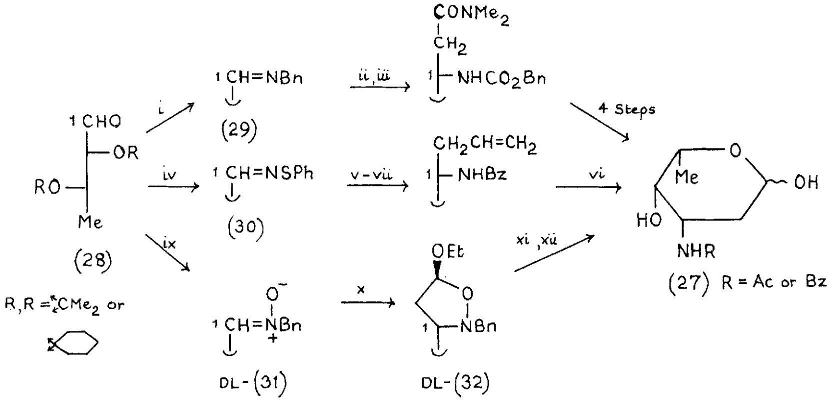
A number of amino-sugars have been elaborated from 3- and 4-

carbon chiral compounds. The two isoxazolidines reported last year (Vol.16, p.93) from the condensation of 2,3-O-isopropylidene-D-glyceraldehyde with ethyl isocyanate, have been independently obtained in the same way and converted into lactones of 2-amino-2-deoxy-D-arabinonic and -D-xylonic acid.[25] These workers also examined the base-catalyzed condensation of the same aldehyde with the heterocycle (26), but found that four isomeric branched-chain amino-sugar acid derivatives were obtained, and that they were racemic due to partial epimerization of the starting aldehyde.



(26)

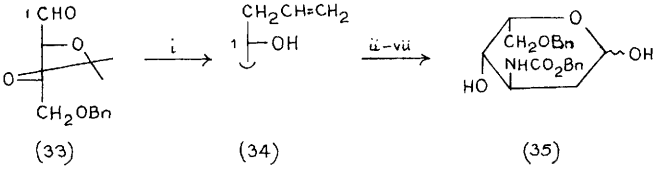
N-Acyl-L-daunosamines (27) have been synthesized from the 4-deoxy-L-threose acetals (28), available from diethyl L-(+)-tartrate, by the three alternative routes shown in Scheme 8. Thus carbon substituents were added to the imine (29)[26] and the sulphenimine (30)[27] in an *erythro*-fashion, while dipolar cycloaddition of ethyl vinyl ether to the nitrone (31) led to the isoxazolidine (32).[28]



Reagents: i, $BnNH_2$; ii, $LiCH_2CONMe_2$-$ZnBr_2$; iii, BnO_2CCl-$NaHCO_3$; iv, PhSSPh-$AgNO_3$-NH_3; v, $(CH_2{=}CHCH_2)_2Zn$; vi, H^+; vii, BzCl; viii, O_3; ix, BnNHOH; x, $EtOCH{=}CH_2$; xi, H_2-$Pd(OH)_2$-HCl, 50psi; xii, Ac_2O

Scheme 8

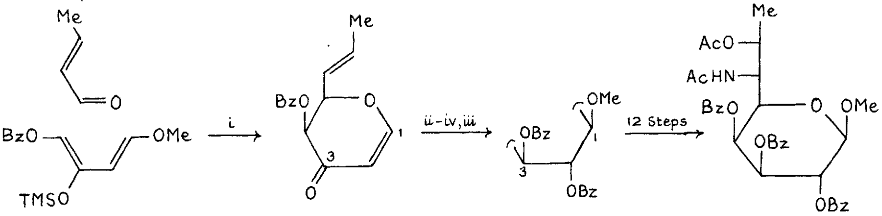
This latter synthesis actually employed racemic material, but it could equally well be applied to optically pure compounds. N-Benzoyl-L-ristosamine [the methyl α-glycoside (17) of L-ristosamine is shown in Scheme 4] was similarly obtained *via* a sulphenimine derivative of 4-deoxy-2,3-O-isopropylidene-L-threose.[27] The C-allylation of the L-threose derivative (33) also yielded an *erythro*-adduct (34) as the major product, from which the 3-amino-2,3-dideoxy-L-xylo-hexose derivative (35) was synthesized by employing a new procedure for amination with inversion (steps ii-iv, Scheme 9).[29]



Reagents: i, $(CH_2=CHCH_2)_2SnBr_2$; ii, $\overset{+}{N}Me.\bar{O}Ts-Et_3N$; iii, LiN_3; iv, LAH; v, BnOCOCl; vi, OsO_4-NaIO_4; vii, H_3O^+

Scheme 9

The approach developed by Danishefsky and co-workers for the construction of sugar derivatives (see Vol.16,p.126), which employs the initial synthesis of a dihydropyrone derivative by a Lewis acid-catalyzed hetero-Diels-Alder reaction, has been extended to the synthesis of the glycoside derivative (36) of DL-lincosamine (Scheme 10). Introduction of the amino-function at C-6 required a circuitous approach involving 6,7-bromohydrin, 6,7-epoxide, and N-substituted 6,7-aziridine intermediates.[30]

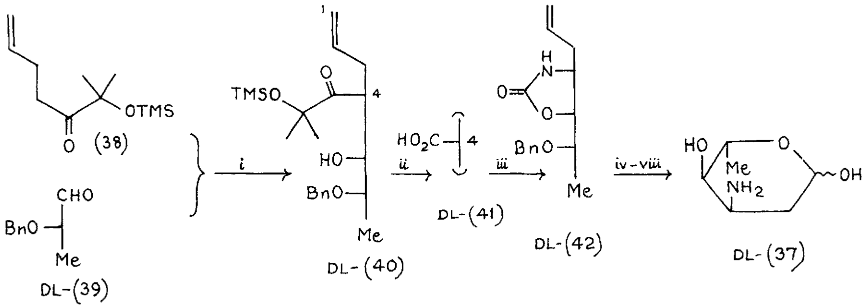


Reagents: i, BF_3; ii, $NaBH_4-CeCl_3$; iii, BzCl-Py; iv, MCPBA-MeOH

DL-(36)

Scheme 10

A further synthesis of ristosamine (c.f. refs.16, 17, and 26),

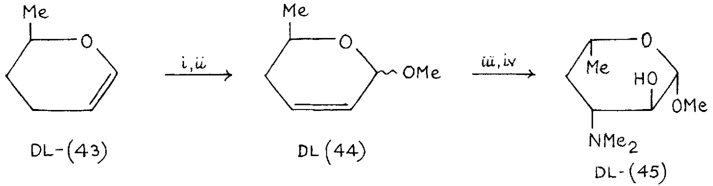


Reagents: i, LDA; ii, HIO_4-THF; iii, $N_3PO(OPh)_2-Et_3N-Bu^tOH$; iv, $NaIO_4-OsO_4$; v, H^+-MeOH; vi, H_2-Pd/C; vii, $Ba(OH)_2-H_2O$; viii, H_3O^+

Scheme 11

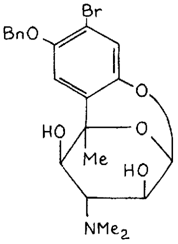
this time of the racemic material (37), is shown in Scheme 11, involving the stereoselective aldol condensation of ketone (38) with *O*-benzyl-DL-lactaldehyde (39) to give adduct (40) as the major product, and the introduction of the amino-function through a modified Curtius degradation [(41) → (42)].[31]

Other non-carbohydrate starting materials have been converted into amino-sugars. Addition-oxidative elimination of a phenyl-selenium reagent has been used to convert the racemic dihydropyran (43) into the 2,3-unsaturated glycoside (44), which yielded α-*lyxo*, and α- and β-*ribo*-epoxides in the ratio 61:26:13; the minor epoxide was converted into methyl DL-desosaminide (45) (Scheme 12).[32] The racemic *C*,*O*-fused amino-sugar-aromatic derivative (46) has been synthesized from a 5-*C*-substituted hex-2-enos-4-ulose, available by oxidative ring expansion of an appropriately substituted furan derivative.[33]



Reagents: i, PhSeBr-MeOH; ii, H_2O_2; iii, MCPBA; iv, Me_2NH

Scheme 12



(46)

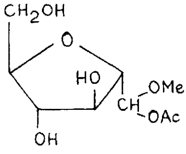
Syntheses of amino-alditol derivatives are covered in Chapters 18 and 19, and the introduction of a 2-acetamido-function into a sugar formazan derivative is covered in Chapter 10.

3 Reactions

N-Acetyl-muramoyl-L-alanyl-D-isoglutamine (MDP) analogues continue to be popular synthetic targets. Thus a Japanese group have used conventional procedures to convert amino-sugar derivatives into MDP-analogues bearing various 1-*O*-acyl,[34] 1-thio- and 1-*S*-acyl-1-

thio,[35,36] and C-6 substituents (OMe, halogen, N_3, and OMs),[37] and have tested the immunoadjuvant activity of their products. Others have synthesized 1- and 6-O-(ω-aminoacyl)-MDP-analogues, for subsequent coupling to meningococcal group C polysaccharide,[38,39] and a 4-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-MDP disaccharide.[40] The nature of MDP and its D-manno-, D-allo-, and D-gulo-analogues in solution has been studied by ^{1}H-n.m.r. spectroscopy at 400 MHz,[41,42] while the mutarotation rate constant of MDP has been determined from h.p.l.c. data.[43]

Nitrous acid deamination of methyl 2-amino-2-deoxy-α-D-glucopyranoside in anhydrous acetic acid has been shown to yield the ring-contracted acetal (47) in 76% yield, accompanied by the corresponding free aldehyde. The same treatment of tetra-O-acetyl-2-amino-2-deoxy-β-D-glucopyranose gave mainly the pentaacetates of D-gluco- and D-manno-pyranose, while tetra-O-acetyl-β-D-glucopyranosylamine gave mainly the pentaacetates of D-glucose.[44]

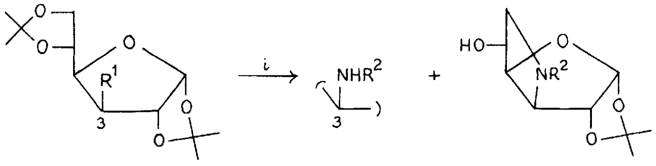


(47)

A new method for N-demethylation involved air oxidation over a palladium catalyst in aqueous 1,4-dioxan at alkatine pH; the dioxan was considered to form an unstable peroxide reagent. Methyl 2-amino-2-deoxy-N-methyl-6-O-(tert-butyldimethylsilyl)-α-D-glucopyranoside was thus N-demethylated in 94% yield.[45] The N-debenzylation of N-benzylacetamido groups with potassium tert-butoxide in DMSO has been shown to be an autoxidation requiring molecular oxygen.[46] The N-allylbenzylamino group has proved useful for protection of amino-sugars where vigorous O-alkylation without further N-alkylation is desired; the N-allyl group is readily removed by isomerization to N-prop-1-enyl, which spontaneously hydrolyses in moist air.[47]

The 3,6-N-alkylimino-derivatives (48) were formed along with the expected 3-alkylamino-derivatives (49) on reduction of 3-acylamido- and 3-alkylimino-derivatives (50) (Scheme 13), and predominated under forcing conditions.[48]

The photoaffinity labelling compound 6-(4-azido-2-hydroxybenzamido)-6-deoxy-D-glucopyranose, and its D-galacto-isomer, have been synthesized both by acylation of suitable O-protected amino-



(50) (49) (48)

R^1 = -NHCOR^2 or -N=CHR^2
where R^2 = Pr, Ph, etc.

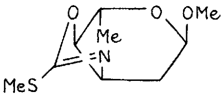
Reagent: *i*, LAH

Scheme 13

sugar derivatives, and by carbodiimide-induced coupling of the aromatic acid with the free amino-sugar; analogues with radioactive iodine in the aromatic residue were also synthesized.[49] Methyl 3,6-dideoxy-3-(L-glyceroylamido)-α-D-glucopyranoside has been synthesized by acylation of the 3-amino-glycoside, and its anti-Gram positive-bacterial activity recorded.[50]

The Schiff base formation between 2-amino-2-deoxy-D-glucopyranose and 4-nitrobenzaldehyde has been the subject of a kinetic study,[51] while N-(N',N'-dimethylformamidine) derivatives were formed on reaction of glucosamine or mycosamine with N,N-dimethylformamide dimethylacetal.[52]

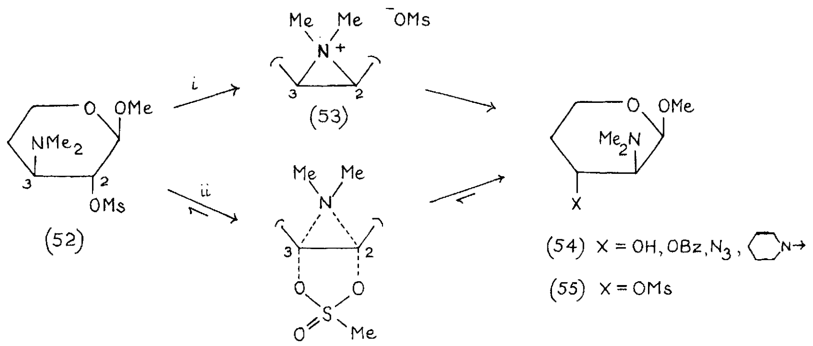
The oxazoline derivative (51) was formed in good yield upon attempted C-4 deoxygenation of a 3-azido-4-O-(methylthio)thiocarbonyl derivative with tributyltin hydride.[53]



(51)

The migration of the dimethylamino-group in the methyl pyranoside (52) (see Vol.11, p.81) has been investigated in detail. In polar solvents such as water, the aziridonium salt (53) is formed rapidly, and is then opened by a nucleophile to give derivatives (54), but in non-polar solvents the migration appears to be concerted, and an equilibrium mixture of compounds (52) and (55), in the ratio 1:2, is formed (Scheme 14).[54]

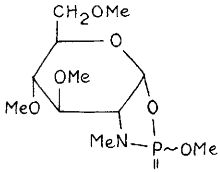
The O,N,P-heterocycles (56) and their 1,2-*trans*-isomers have been synthesized from 2-N-methyl-3,4,6-tri-O-methyl-D-glucopyranose and methylthiophosphonic dichloride ($MePSCl_2$) and their cleavage to



Reagents: i, H_2O ; ii, C_6H_6 (reflux, 8h)

Scheme 14

release chiral compounds [such as Me(MeS)(EtO)PO] has been studied.[55] The action of sodium alkoxides on the same starting sugar led to the substituted pyrrole (57), but the N-phosphorylated derivative (58) provided the aldulosylamine derivative (59) by way of an N → O phosphonate migration.[56]



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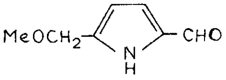

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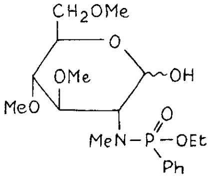
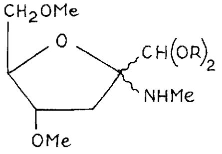


(58)



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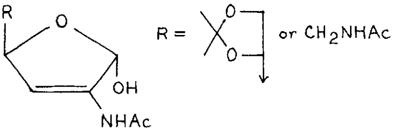


(60)

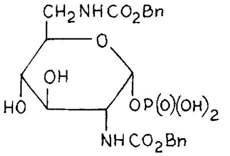
2-Amino-2-deoxy-3-thio-D-glucose has been synthesized conventionally by a route involving the opening of a D-altro-2,3-aziridine derivative with a thiol.[57]

The products formed on treatment of various 2-acetamino-2-deoxy-furanoses with alkaline ion-exchange resin have been shown to be the 2,3-unsaturated furanoses (60), formed through β-elimination of C-3 hydroxy, alkoxy, or tetrahydropyranyloxy substituents, rather than the 1,2-unsaturated isomers reported previously (Vol.13, p.114).[58]

Modifications of amino-sugars covered in other chapters include 6-deoxygenation of 2-amino-2-deoxy-D-galactose and -glucose, and synthesis of methyl 2-acetamido-2,3,6-trideoxy-β-L-*lyxo*-hexopyranoside (Chapter 12), syntheses of six 2-amino-2-deoxyheptonic acids (Chapter 16) and of pseudonucleosides (Chapter 20), and the tritiation of aminoglycoside antibiotics (Chapter 19).

4 Di- and Tri-amino-sugars

The glycosyl phosphate (61) has been synthesized from 2-amino-2-deoxy-D-glucose by standard methods, and condensed with appropriate nucleoside 5'-phosphate derivatives to give cytidine, uridine, and adenosine 5'-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl diphosphates) which are potential biosynthetic intermediates for aminocyclitol antibiotics.[59] Conventional syntheses of methyl 2,3-diacetamido-2,3-dideoxy-α-D-hexopyranosides with the *gulo*-, *allo*-, *galacto*-, *ido*-, and *altro*-configuration, and of 2,3-diacetamido-2,3-dideoxy-D-galactose, have been reported, along with comprehensive ^{13}C-n.m.r. data for all the eight possible glycosides in the D-series, and three of their corresponding free sugars.[60] Certain 4,6-diamino-sugars have been synthesized from glycals *via* hex-2-enosides, using sulphonate displacement with azide.[13,61] The tetra-amino-disaccharide (62) has been constructed by coupling known monosaccharides using the "azido method" (Vol.13, p.32, ref.122) and introducing the 6'-amino-functionality by sulphonate displacement with azide, and its activity against gram-negative organisms has been recorded.[62]



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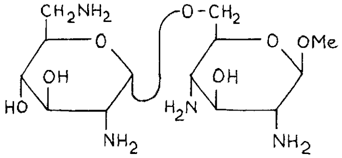

(62)

Benzyl 2,3,4-triacetamido-2,3,4,6-tetradeoxy-α-D-galactopyranoside has been synthesized from the corresponding 3,4,6-tri-*O*-mesyl-allopyranoside by selective reduction at C-6 ($NaBH_4$-DMSO), followed by azide-displacement of the sulphonates at 3 and 4 with inversion; mass spectral fragmentation of its derived alditol acetate was also recorded.[63]

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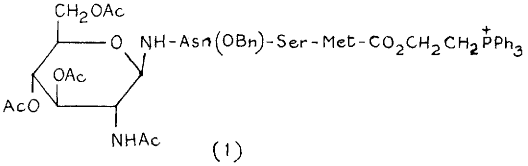
10
Miscellaneous Nitrogen Derivatives

1 Glycosylamines

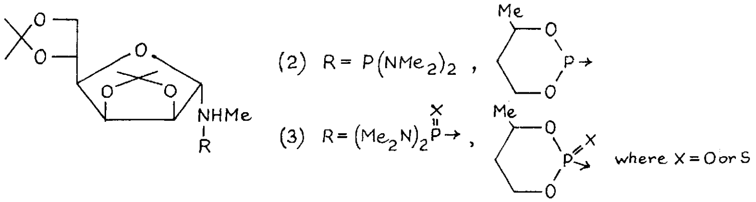
N-(Substituted-phenyl)-D-glycopyranosylamines and their O-acetyl derivatives have been synthesized conventionally for a study of their potential as modifiers of glycosaminoglycan formation; the p-methoxyphenyl D-xylo-derivative was found to be the most cytotoxic.[1,2] D-Ribosylamines formed on condensation of nine primary amines with D-ribose have been shown by ^{1}H- and ^{13}C-n.m.r. spectroscopy to be mainly the α-pyranose isomers in the $^{1}C_{4}$ conformation, the β-pyranose isomers assuming the $^{4}C_{1}$ conformation. Condensation of 2,3-O-isopropylidene-D-ribose with these same amines gave furanosylamines, and it was found that the Δδ value for the ^{13}C-n.m.r. signals of the isopropylidene methyl groups was a useful criterion of the anomeric configuration.[3] Various N-substituted D-galactosylamines have been used to probe the active site of β-D-galactosidase from Escherichia coli.[4] The e.i.-m.s. fragmentation patterns of acylated glycopyranosylamine derivatives have been investigated in detail.[5]

The stereoselective synthesis of N-(β-L-aspartyl)-α-D-glucopyranosylamine from 2,3,4,6-tetra-O-benzyl-α-D-glycopyranosyl azide has been detailed,[6] as has the synthesis of the protected glycosyl tripeptide (1), representing the partial unit of bovine deoxyribonuclease A, from the corresponding protected glycosylamine.[7] N-(α-Lactosyl)-urea has been prepared by heating lactose with urea (2 h, 60°); on hydrolysis it gave a mixture of galactosyl and glucosyl ureas.[8] Condensations of β-D-glucopyranosyl and α-L-arabinopyranosyl thiosemicarbazides with furfuraldehyde and



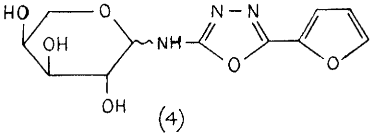
(1)

5-nitrofurfuraldehyde to give the corresponding semicarbazones, and of glycosyl isothiocyanates with furoyl hydrazides, have been reported.[9] *N*-Glycosylamidophosphites such as (2) have been synthesized through the phosphorylation of *N*-methyl-glycosylamines, and were readily oxidized to the corresponding phosphates and thiophosphates (3).[10] Mercury(II) oxide-induced desulphurization of



N-aroyl *N*'-glycosyl thiosemicarbazides yielded 5-glycosylamino-2-aryl-1,3,4-oxadiazole derivatives such as the arabinosylamine derivative (4).[11,12]

2-Amino-(1,2-dideoxy-β-D-arabinofurano)[1,2-*d*]-2-oxazoline (5) has been obtained by reaction of α-D-arabinopyranosylamine with cyanamide in methanol for 1-2 days; analogous products were obtained in the D-ribose, D-xylose, D-glucose and L-sorbose series,



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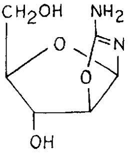

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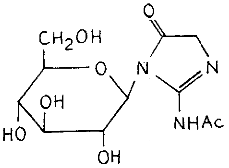


(6)

and both labelled nitrogen atoms were incorporated when doubly ^{15}N-labelled cyanamide was employed.[13,14] The *N*-glucosylimidazoline (6) has been obtained on acetylation of *N*-β-D-glucopyranosyl-*N*'-carboxymethylguanidine, and its conformation investigated by ^{1}H-n.m.r. spectroscopy.[15]

The proceedings of a symposium devoted to the Maillard reaction in food and nutrition have been published,[16] and reports made of a kinetic and mechanistic study on the Amadori rearrangement of *N*-(4,6-*O*-benzylidene-D-glucopyranosyl)glycine esters,[17] and a g.c.-m.s. study of the pentane soluble products from the Maillard reaction between glucose and phenylalanine.[18]

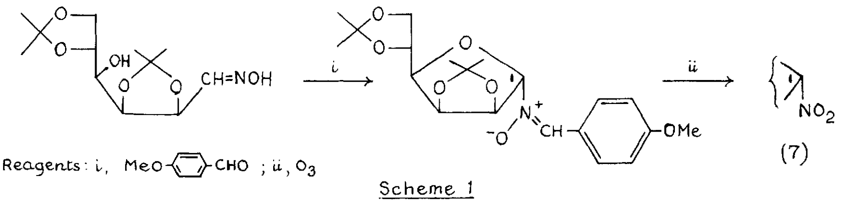
2 Azido-sugars

O-Protected D-ribofuranosyl azides have been synthesized from the Lewis acid catalyzed reaction of azidotrimethylsilane with the corresponding 1-O-acetates.[19] A set of 2-O-methyl-α-glycopyranosyl azides have been synthesized in the same way, while their β-analogues have been obtained from 2-O-levulinoyl-α-glycosyl bromides by displacement with azide and subsequent introduction of the 2-O-methyl substituent.[20] The influence of O-3,-4, and -6 substituents in D-glucal and D-galactal derivatives upon addition reactions of these sugars with chloroazide, yielding 2-azido-glycosyl chlorides, 2-chloro-glycosyl azides, and other products, has been examined both experimentally and by quantum chemical calculations. For O-acetyl and O-benzyl substituents, only that on O-3 influences the reaction rate, a 3-O-acetyl substituent markedly lowering reactivity by an inductive effect.[21]

The sulphonate groups in the 5,6-O-isopropylidene-3-O-tosyl-1,2-O-trichloroethylidene-α-D-galacto- and gluco-furanose isomers with exo-CCl_3 substituents were readily displaced by azide, the repulsion between the approaching charged nucleophile and the acetal oxygen atoms being diminished by the strong inductive effect of the Cl_3C-substituent. The gluco-isomer with an endo-CCl_3 substituent, as would be expected, failed to react.[22]

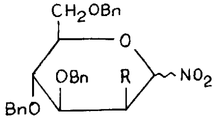
3 Nitro-sugars

1-Deoxy-1-nitroaldoses in the furanose or pyranose form have been synthesized from various oximes by the strategy shown in Scheme 1



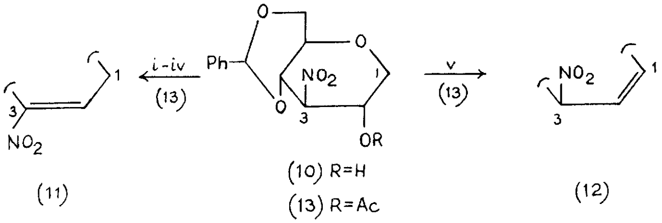
Scheme 1

for the synthesis of the mannofuranosyl nitrate (7).[23] On equilibration with base, the glycosyl nitrates (8) and (9) formed mixtures of anomers in the α:β-ratio 93:7 and 92:8 respectively,



(8) R = OBn
(9) R = H

from which the anomeric effect of the nitro-group in these molecules was calculated to be 3.4 and 2.4 kcal. mol^{-1} respectively.[24] 1,5-Anhydro-3-nitrohexitol derivatives with the D-gluco-[i.e. (10)], D-manno-, and D-galacto-configuration have been synthesized by periodate oxidation of 1,5-anhydro-D-mannitol followed by condensation with nitromethane and benzylidenation, and their conversion into nitroalkenes has been studied. Sulphonylation (MsCl-py) of nitroalcohol (10) yielded both the 2,3-alkene (11) and the glycal (12) through double-bond migration. The glycal (12)

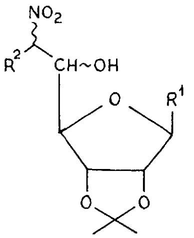


Reagents: i, $NaBH_4$-DMSO; ii, BuLi; iii, PhSeBr; iv, H_2O_2; v, $NaHCO_3$

Scheme 2

was the sole product from base treatment of the acetate (13), while a synthesis of the 2,3-alkene (11) from this acetate in 72% overall yield involved deoxygenation at C-2, phenylselenylation at C-3, and oxidative elimination (Scheme 2).[25]

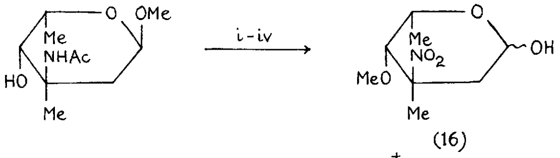
Improved yields of the chain-extended glycosides (14) and nucleosides (15) have been achieved by employing strictly anhydrous conditions for the condensation of nitroalkanes with 5-aldehydo-D-ribose derivatives.[26]



(14) R^1 = OMe ; R^2 = H, Me, Et, Bu

(15) R^1 = N^6-Benzoyladenine ; R^2 = H, Bu

2,3,4,6-Tetradeoxy-4-methoxycarbonylamino-3-*C*-methyl-3-nitro-β-D-*xylo*-hexopyranose has been identified as a constituent sugar unit in the antibiotic kijanimicin.[27] The synthesis of L-rubranitrose (16), the enantiomer of a naturally occurring antibiotic component, has now been completed as shown in Scheme 3, the key step being *N*-deacetylation using calcium in liquid ammonia.[28] ^{13}C-N.m.r. studies including branched-chain nitro-sugars are mentioned in Chapter 14.

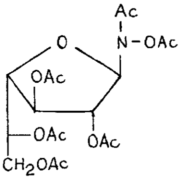


Reagents: i, Methylation; ii, Ca-$NH_3(\ell)$; iii, MCPBA; iv, H_3O^+

Scheme 3

4 Nitriles and Hydroxylamines

The procedure commonly employed for preparing the peracetylated aldononitrile derivatives from D-galactose and D-glucose for analysis by g.c., involving oximation (py-NH_2OH.HCl) then acetylation (py-Ac_2O), has been shown to yield substantial amounts of isomeric *N*-hexosylhydroxylamine hexaacetates. Thus the β-D-galactofuranose derivative (17) was isolated in 16% yield, along with its α-furanose (1%) and β-pyranose (2%) isomers.[29] The e.i.-m.s. fragmentation patterns of some benzoylated aldononitriles have been investigated.[30] The dipolar cycloadducts formed from a carbohydrate nitrile oxide are covered in Section 6.



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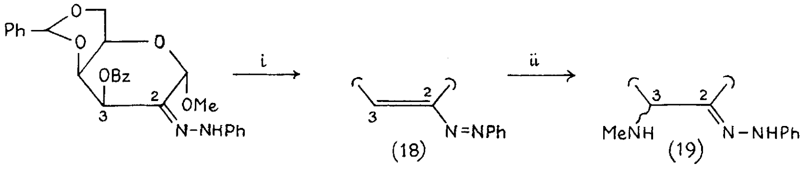
5 Hydrazones, Osazones, and Derived Heterocycles

Following earlier analogous work, 2,3-dideoxy-D-*threo*-hex-2-

enopyranosides with 2- and 3-phenylazo-substituents have been synthesized from monoesters of the corresponding glycosiduloses, followed by treatment with base, e.g.,to give (18) (Scheme 4);



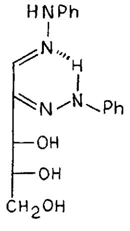
Reagents: i, KOBu^t ; ii, MeNH$_2$

Scheme 4

nucleophiles added in the 1,4-sense, but the adducts were unstable and tended to revert, but some amine adducts (e.g.,19) were isolated.[31] The E- and Z-isomers of 1,3,4,5,6-penta-O-acetyl-keto-D-fructose 2,4-dinitrophenylhydrazone have been separated chromatographically and characterized.[32]

Hydrazones of eight aldoses have been investigated by ^{1}H- and ^{13}C-n.m.r. spectroscopy. In hydrazine solution they exist mainly in the syn-acyclic form, but in D$_2$O they slowly tautomerize to the cyclic glycosylhydrazines. At pH 6 this process is rapid and the cyclic modifications preponderate for all but D-ribose and L-arabinose derivatives, which are $\sim$1:1 mixtures of cyclic and acylic forms. Nitrosation (NaNO$_2$-HOAc) of D-glucose hydrazone gave β-D-glucopyranosyl azide and D-glucose, presumably by reaction of the cyclic and acyclic forms of the hydrazone respectively.[33] Hydrazinolysis (at 105° for 10 h) of 2-acetamido-1-N-acetyl-2-deoxy-β-D-glucopyranosylamine, studied as a model for the hydrazinolysis of glycopeptides, led to 1-deoxy-D-fructose hydrazone (22%), possibly via a Wolf-Kishner-type reaction of a 1,2-bishydrazone intermediate.[34] Milder conditions were inefficient.[35] Hydrazinolysis of the 1-N-(L-β-aspartyl)-analogue proceeded much more rapidly, presumably due to an initial intramolecular carboxylate-assisted cleavage of the amide bond.[34] Hydrazinolysis of 2-amino-2-deoxy-D-glucose hydrazone also gave 1-deoxy-D-fructose hydrazone, the use of hydrazinium sulphate as catalyst providing this compound in 44% yield.[35]

The photochemical and thermal isomerization of D-arabino-hexulose phenylosazone in solution between the N- and O-chelate forms (20) and (21) respectively, has been studied in detail, the photoreaction being a fast efficient method for the synthesis of the O-chelate.[36,37] Lifetimes and quantum yields have been reported for the photochemical singlet to triplet intersystem crossing in D-glucose phenylosazone.[38] Reduction of the azomethine group in sugar hydrazones and osazones in aqueous and non-aqueous media has been the subject of a polarographic study. Four electrons were taken up, and it was concluded that chelated structures were cleaved prior to reduction.[39]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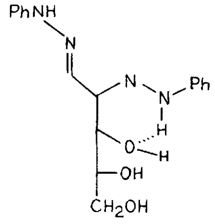
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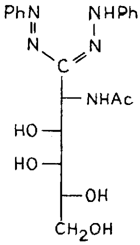
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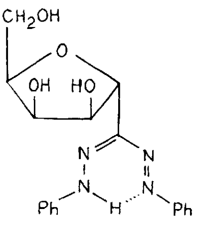
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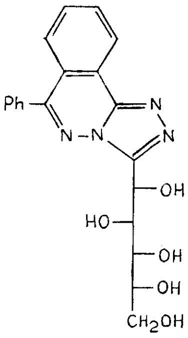
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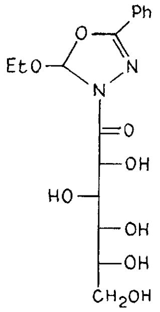
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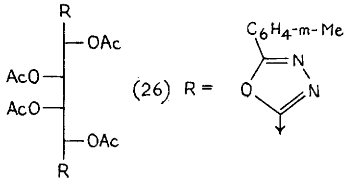
Ammonia-catalyzed O-deacetylation of sugar formazans unexpectedly gave 2-acetamido-2-deoxy-derivatives. The 2-acetamido-2-deoxy-D-glucose derivative (22) was thus obtained in high yield from both per-O-acetylated glucose and mannose formazans, presumably by way of a 1,4-elimination/addition process.[40] The 2,5-anhydride structure of the product (23), formed on irregular Zemplen deacetylation of both penta- and hexa-acetyl-D-galactose diphenyl formazans, has been confirmed by a ^{13}C-n.m.r. spin-lattice relaxation-time study.[41]

3-(Alditol-1-yl)-1,2,4-triazolo[3,4-a]phthalazines, such as the glucose derived product (24), were obtained by condensation of D-ribose, D-galactose, D-mannose, D-arabinose and D-glucose with 1-hydrazino-4-phenylphthalazine and subsequent dehydrogenation, which occurred spontaneously in the case of the last two sugars. D-Glucono-1,5-lactone gave the same product (24) by autodehydration of the acyl hydrazide derivative.[42] 5-Aryl-2-ethoxy-3-D-gluconyl-2,3-dihydro-1,3,4-oxadiazoles, such as the 5-phenyl derivative (25), have been prepared by condensative cyclization of the 1-aroyl-2-D-gluconylhydrazines (obtained from aroyl hydrazines and D-glucono-1,5-lactone) with triethyl orthoformate.[43] Similar condensation of 2,3,4,5-tetra-*O*-acetyl-galactaric bis(aroylhydrazides) with triethyl orthoformate yielded double-headed analogues of (25), while treatment of the bishydrazides with phosphorus oxychloride ($POCl_3$) gave compounds such as (26).[44] The synthesis of the (2,4-dichlorophenoxy)acetyl hydrazones of a number of monosaccharides has been reported, and the cyclized product (27) has been obtained from the D-galactose derivative along with the expected penta-*O*-acetate upon acetylation.[45]



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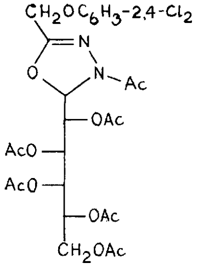

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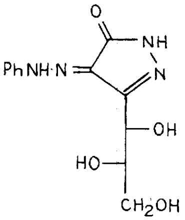


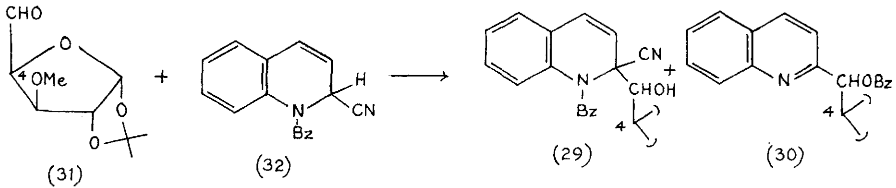
(28)

Dehydro-L-ascorbic acid 2-phenylhydrazone 3-semicarbazone has been found to rearrange on alkaline treatment to the 4,5-(1*H*)-pyrazoledione derivative (28), from which a variety of pyrazole derivatives were synthesized.[46] The synthesis of 1,2,3-triazole derivatives from dehydro-D-*arabino*-ascorbic acid, analogous to those reported last year (Vol.16, p.113) from dehydro-L-ascorbic acid, and their conversion to non-carbohydrate compounds has been described.[47] The synthesis of nucleoside analogues from *N*-glycofuranosylhydrazine derivatives is covered in Chapter 20.

6 Other Heterocyclic Derivatives

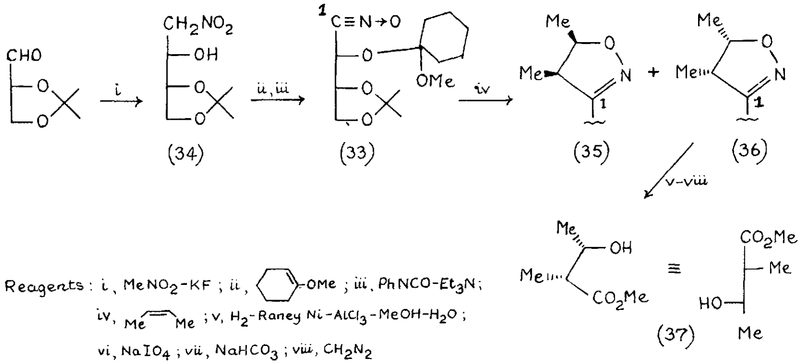
The 5-*C*-aryl derivatives (29) and (30) of xylose have been obtained in a 1:1 ratio by condensation of the xylodialdose (31) with the quinoline carbonitrile (32) (Scheme 5).[48]

Dipolar cycloaddition of an alkene such as (Z)-but-2-ene to the tetrononitrile oxide (33), generated *in situ* from nitroalcohol (34),



Scheme 5

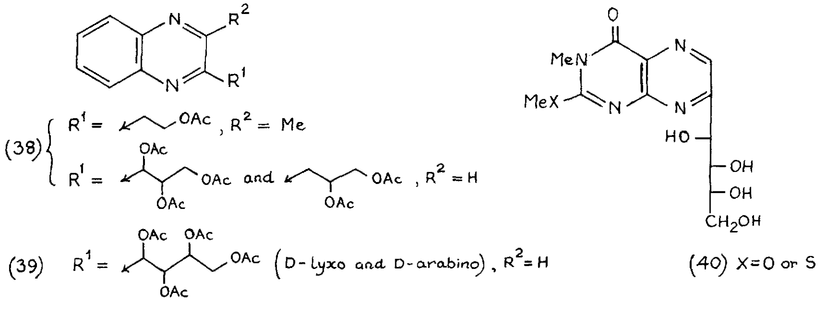
led to diastereoisomeric isoxazolines, e.g., (35) and (36), in the ratio 1:2.9 (Scheme 6). Separation and cleavage of the major isomer (36) yielded optically pure β-hydroxyacid (37).[49]



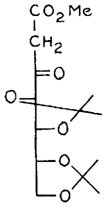
Reagents: i, $MeNO_2$-KF ; ii, OMe ; iii, PhNCO-Et_3N; iv, Me Me ; v, H_2-Raney Ni-$AlCl_3$-MeOH-H_2O ; vi, $NaIO_4$; vii, $NaHCO_3$; viii, CH_2N_2

Scheme 6

Included amongst the products from the reaction of D-xylose[50] and D-galactose[51] with o-phenylenediamine under acidic conditions were, after acetylation, 2-substituted quinoxalines such as (38) and (39). The pteridines (40) have been obtained from the condensation of D-



glucose with aminopyrimidines.[52] Condensation of 2,3:4,5-di-O-isopropylidene-aldehydo-D-arabinose with methyl diazoacetate ($BF_3.Et_2O$ catalysis) led to the chain-extended derivative (41) which reacted separately with S-methylthiourea, thiourea, and guanidine to give, after deacetalation, the alditolyl heterocycles (42).[53]



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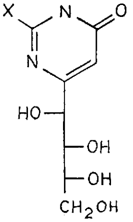
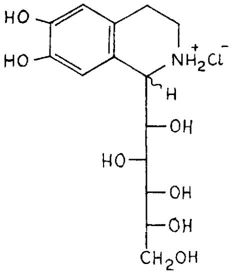


(42) X = SMe, SH, or NH_2

The e.i.-m.s. fragmentation patterns of some benzoylated 5-[poly(benzoyloxy)alkyl]tetrazoles have been reported.[30]

Pictet-Spengler condensation of dopamine with D-glucose gave a 4:1 mixture of 1-substituted tetrahydroisoquinoline diastereomers (43). Analogous reactions of dopamine and tryptamine with 2,5-anhydro-D-mannose were also studied, the latter combination giving the diastereomeric β-carbolines (44).[54] Acid-catalyzed dehydration of the D-galacto-pentitol-1-ylated heterocyclic derivative (45), obtained from the condensation of 2-(benzylamino)-2-deoxy-D-glycero-L-gluco-heptose with 5,5-dimethyl-1,3-cyclohexanedione, led to the D-lyxofuranosyl derivative (46) with a presumed α-configuration as the kinetic product, and thence to a 1:1 mixture of α-'and β-D-lyxopyranosyl derivatives (47) under thermodynamic



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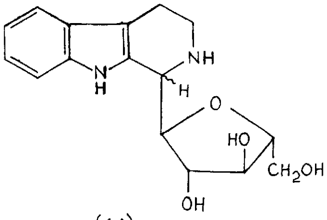

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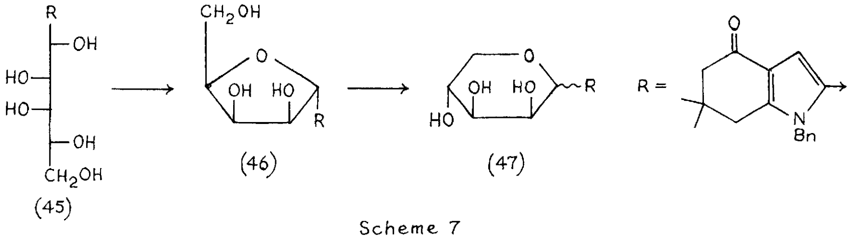

Scheme 7

control (Scheme 7).[55] These results are in contrast to earlier observations by the same authors (Vol.16, p.113) that pyranose derivatives were formed directly from related D-*galacto*-pentitol-1-ylated heterocycles, the formation of furanose rings being presumed to be disfavoured by steric congestion in the required transition stage.

Several pyranose-fused heterocyclic derivatives are covered in Chapter 9.

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11
Thio-sugars

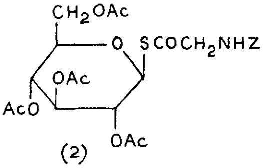
A review of the synthetic methods which have been developed for the preparation of monosaccharide thiocyanates and their transformations to deoxy sugars and thio sugars has appeared. A table of carbohydrate thiocyanates is included.[1]

Condensation of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose with *p*-(2-bromoethyl)aniline hydrobromide followed by treatment with methanolic sodium methoxide led to the corresponding substituted ethyl β-thioglycoside.[2] 1-Thioglucosyl aminoacid esters[3] transfer their acyl moiety with high efficiency upon ammonolysis with an amino acid ester, thereby constituting a peptide synthesis; thus the peptide (1) was formed in 90% yield on reacting the thioglucosyl derivative (2) with methyl glycinate, the other product being 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose.[4] Analogues of (2) have been prepared from peracetylated 1-thio-L- and -D-arabinopyranosyl and methyl 1-thio-β-D-glucopyranosyluronate esters of *N*-acylamino acids by coupling of the thiols to pentachlorophenyl esters of the *N*-acylamino acids in the presence of imidazole;[5] (see also reference 2 above).

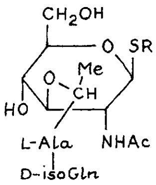
Z-Gly-Gly-OMe

(1)

$Z = Me_3COCO-$

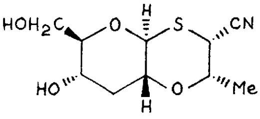


(2)

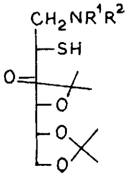


(3)

$R = H, \cdot CO(CH_2)_{14}Me, \cdot CO(CH_2)_{15}Me.$

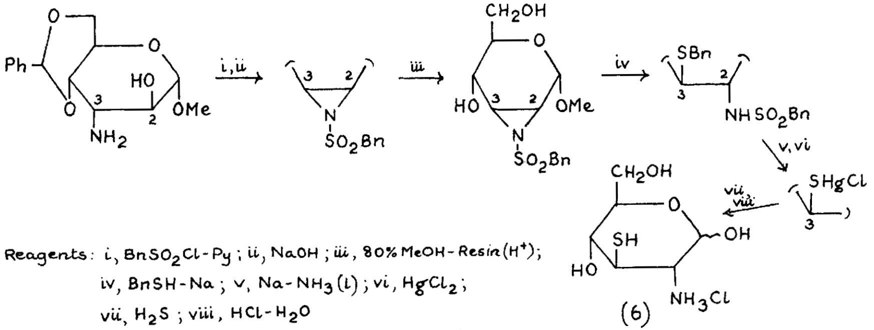


(4)



(5) $R^1 = H, R^2 = Bu^t$; $R^1 = R^2 = Et$

1-Thio-*N*-acetylmuramoyl-L-alanyl-D-isoglutamine and its lipophilic derivatives (3) have been synthesized conventionally. Some of these and other analogues showed potent biological activity.[6,7] The crystal structure of merosinigrin (4), an ap,ap-monothioacetal rearrangement product of allylglycosinolate, has been determined by direct methods.[8]



Reagents: i, $BnSO_2Cl$-Py; ii, NaOH; iii, 80% MeOH-Resin(H^+); iv, BnSH-Na; v, Na-NH_3(l); vi, $HgCl_2$; vii, H_2S; viii, HCl-H_2O

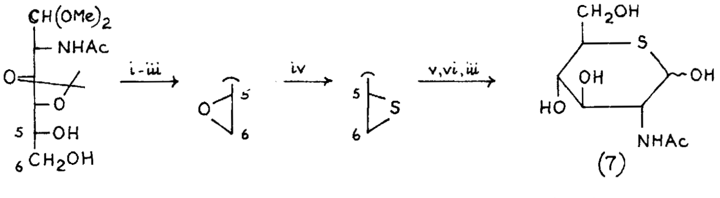
Scheme 1

Amination of epithiosorbitol by isobutylamine or diethylamine in dry benzene gave low yields of the 1-amino-2-thio-derivative (5).[9]

2-Amino-2-deoxy-3-thio-D-glucose (6) has been synthesized as shown in Scheme 1.[10]

The extent to which the sulphur atom in the ring of the anomers of 5-thio-D-xylopyranose and 6-thio-D-fructopyranose distorts the conventional chair conformation of their oxygenated counterparts has been determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy. The distortion was found to be more pronounced in the α-anomers.[11]

2-Acetamido-2-deoxy-5-thio-D-glucopyranose (7),[12] and -D-mannopyranose (8),[13] have been synthesized as shown in Schemes 2 and 3.

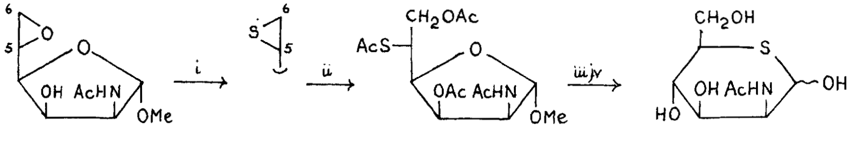


Reagents: i, BzCl-Py; ii, MsCl-Py; iii, MeONa-MeOH; iv, $CS(NH_2)_2$; v, KOAc-Ac_2O-AcOH; vi, H_3O^+

Scheme 2

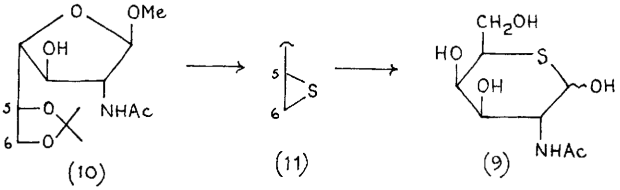
The corresponding D-galactopyranose (9) has been prepared from the 5,6-O-isopropylidene derivative (10) via the 5,6-epithio-galactofuranoside (11) with acetate ion (Scheme 4).[14] The acetamidothioglucose (7) has been converted by conventional methodology to the 3-

O-(L-lactate)ether (12) and thence to its L-alanyl-D-isoglutamine peptidyl derivative, corresponding to (3).[15]



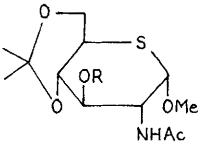
Reagents: i, $CS(NH_2)_2$; ii, KOAc-Ac_2O-AcOH ; iii, HCl ; iv, NaOMe

Scheme 3

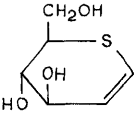


Scheme 4

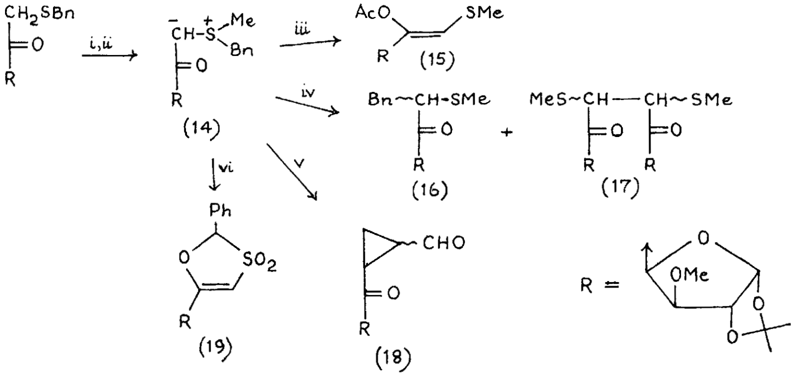
5-Thio-D-glucal (13), a competitive inhibitor of glycosidases, has been synthesized by the zinc-acetic acid method on the corresponding glycosyl bromide, followed by Zemplen deacetylation.[16]



(12) R = L-$CHMeCO_2Me$



(13)



Reagents: i, $MeFSO_3$; ii, NaOH ; iii, AcCl ; iv, Δ(95°) ; v, CH_2=CHCHO ; vi, PhCH=SO_2

Scheme 5

The sulphylid (14), prepared as shown in Scheme 5, underwent acylation to (15), facile Stevens rearrangement to (16) and the dimers (17), *via* initial loss of benzyl radical, and reaction with Michael acceptors to give cyclopropane derivatives, *e.g.*, (18), with acrolein. With benzene carbothioaldehyde-*S*,*S*-dioxide, generated *in situ*, however, the unexpected oxathiolenedioxide (19) was formed and isolated in 40% yield.[17]

Reference to *S*-3-indolemethyl derivatives of 5'-deoxy-5'-thioadenosine is to be found in Chapter 20, and to thio- and seleno-phosphates in Chapter 7.

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12
Deoxy-sugars

A branched-chain tetrasaccharide consisting of three units of 2,6-dideoxy-α-L-ribo-hexopyranose (i.e., L-digitoxose) and one of 2,6-dideoxy-4-O-methyl-β-L-ribo-hexopyranose (i.e., L-cymarose), is part of the antibiotic kijanimicin.[1] New antitumour-active polyoxypregnane oligoglycosides isolated from Drega volubilis contained mainly the 3-O-methyl-2,6-dideoxy-sugars cymarose and oleandrose, and 3-O-methyl-6-deoxy-β-D-allopyranose.[2] 6-Deoxy- and 4,6-dideoxy-gulopyranose units with an assumed D-configuration have been found in affinosides S-III and S-VIII, terpenoid glycosides isolated from Anodendron affine.[3] 2,3,6-Trideoxy-α-D-threo-hexopyranose, the enantiomer of L-rhodinose, has been found for the first time in sakyomicin, an anthracyclinone-type antibiotic metabolite from a Norcardia species.[4]

3-Deoxy-D-ribo- and -D-arabino-hexoses have been synthesized from 2-deoxy-D-ribose by a modification of the Kiliani-Fischer method, as a chromatographically separable 1:1 mixture; [1-^{13}C]-enriched analogues were also obtained, and from their ^{13}C-n.m.r. spectra it was deduced that significant amounts of the furanose forms were present in aqueous solution.[5]

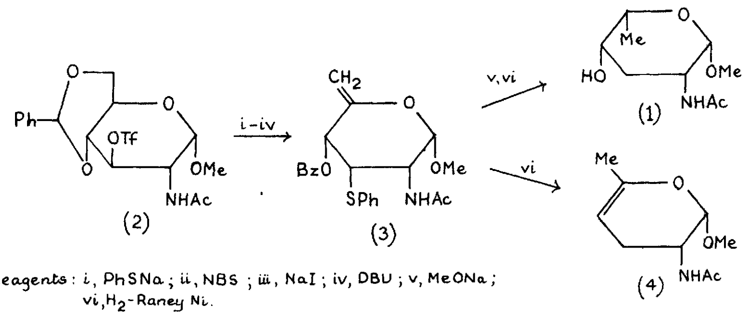
2-Deoxy-D-[1-^{11}C]-glucose, required as a radiopharmaceutical, has been conveniently prepared from 2,3:4,5-di-O-isopropylidene-1-O-triflyl-D-arabinitol using K^{11}CN.[6]

Methyl 2,6-dideoxy- and 3,6-dideoxy-α-D-arabino-hexopyranosides have been synthesized by photochemical deoxygenation of the 2,6-dipivaloate of methyl α-D-glucopyranoside, and of the 3,6-dipivaloate of methyl α-D-mannopyranoside respectively. While products resulting from incomplete ester removal and from ester migration were also present in the photolysis products, 20-25% yields of these dideoxy-sugars were isolated, and these syntheses were much shorter than alternatives. The required dipivaloates were readily obtained by selective diacylation of the methyl glycosides.[7]

Syntheses of a number of deoxy-sugars are covered in a review on modern methods of radical deoxygenation of alcohols.[8] A modified procedure for deoxygenating secondary alcohols, which involves the synthesis and radical-initiated tributyltin hydride reduction of *O*-phenoxythiocarbonyl derivatives, and apparently resulting in less byproduct and higher yields, has been used to prepare 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in 85% yield. Seven ribonucleosides were also deoxygenated at C-2' using this procedure on their 3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) derivatives, thereby mimicking a biosynthetic radical deoxygenation path.[9] Related radical deoxygenation and dehalogenations of nucleoside antibiotics are covered in Chapter 19.

6- And 6'-deoxylactose[10] and benzyl 4',6'-*O*-benzylidene-6-deoxy-β-maltoside[11] have been synthesized conventionally by displacement of primary tosyloxy groups with iodide and reductive dehalogenation. 6,6'-Dideoxysucrose was readily synthesized by radical dehalogenation (Bu_3SnH) of the peracetate of the known 6,6'-dichloro-6,6'-dideoxysucrose (available from reaction of sucrose with Ph_3P-CCl_4-py).[12] Three preparatively useful routes to methyl 2-acetamido-2,6-dideoxy-α-D-glucopyranoside from 2-acetamido-2-deoxy-D-glucose have been reported, involving catalytic reduction of 6-bromo-derivatives, the halogen having been introduced either by the action of *N*-bromosuccinimide on a 4,6-*O*-benzylidene derivative, or by the selective replacement of a primary hydroxy-group using triphenylphosphine-carbon tetrabromide.[13] Benzyl 3,6-dideoxy-β-D-*xylo*-hexopyranoside (*i.e.* benzyl abequoside) has been synthesized by radical dehalogenation of chloro-sugar derivatives mentioned in Chapter 8,[14] while certain amino-deoxy-sugar syntheses are covered in Chapter 9.

Methyl 2-acetamido-2,3,6-trideoxy-β-L-*lyxo*-hexopyranoside (1), a regioisomer of daunosamine having the 2-deoxy- and 3-amino-groups

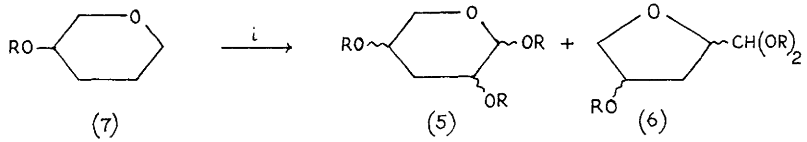


Reagents: i, PhSNa; ii, NBS; iii, NaI; iv, DBU; v, MeONa; vi, H_2-Raney Ni.

Scheme 1

interchanged, has been synthesized in nine steps from 2-acetamido-2-deoxy-D-glucose by way of the sulphonate derivative (2) (Scheme 1) which underwent displacement at C-3 without neighbouring-group participation. Direct treatment of the alkene (3) with Raney nickel led to the endo-alkene (4), but after debenzoylation, simultaneous stereoselective reduction of the 5,6-double bond and reductive desulphurization could be effected.[15]

A number of deoxy-sugars have been synthesized from non-carbohydrate starting materials. All possible isomers of the 3-deoxy-DL-pentose derivatives (5) and (6) were obtained on oxidation of the cyclic ether (7) with iodine(III) tris(trifluoroacetate) (Scheme 2), and these were separated by preparative g.c.[16] Treatment of the alkene (8) with potassium permanganate led to dimethyl derivatives of 2,6-dideoxy-DL-hexoses whose stereochemistry and separation were examined.[17]



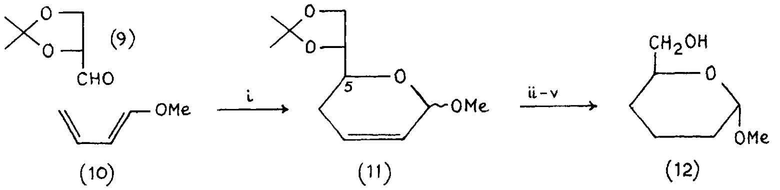
Reagent: i, $I(O_2CCF_3)_3$

Scheme 2

$Me\text{-}CH{=}CH\text{-}CH(OH)CH_2CH(OMe)_2$

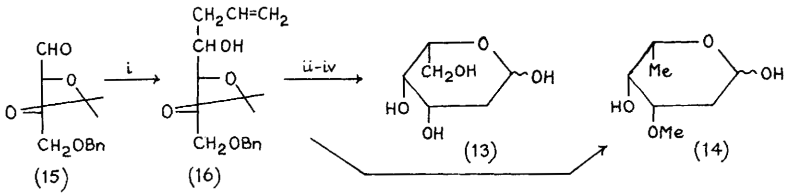
(8)

High-pressure cycloaddition of 2,3-O-isopropylidene-D-glyceraldehyde (9) and diene (10) gave the unsaturated derivatives (11) as the major products (65%), accompanied by their C-5 epimers (15%); these major products (11) were converted into the 2,3,4-trideoxy-D-glycero-hexoside (12) (Scheme 3).[18] The 2-deoxy-L-sugars, 2-deoxy-L-galactose (13) and L-diginose (14), have been synthesized from the L-threose derivative (15) via the common homoallyl alcohol intermediate (16) (Scheme 4); the synthesis of (14) involved conventional methylation and reductive detosylation reactions prior



Reagents: i, 22 Kbar, 50°C; ii, H_2-Pt; iii, MeOH-HCl; iv, $NaIO_4$; v, LAH

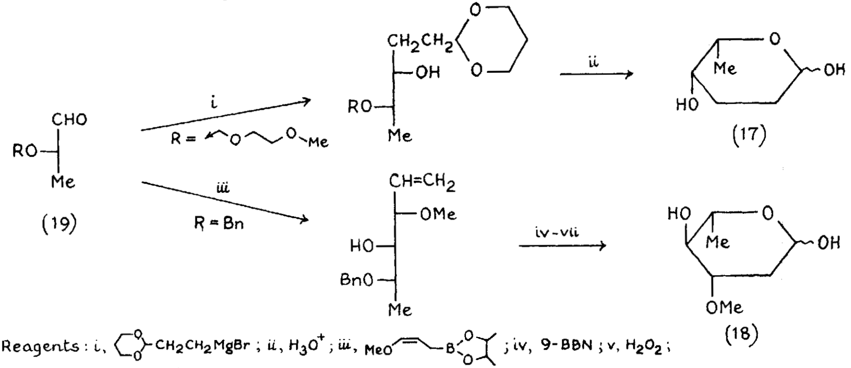
Scheme 3



Reagents: i, $(CH_2=CHCH_2)_2SnBr_2$; ii, OsO_4-$NaIO_4$; iii, H_3O^+ ; iv, H_2-Pd/C-HCO_2H

Scheme 4

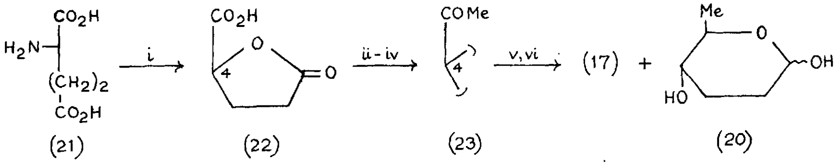
to applying steps ii-iv.[19] L-Rhodinose (17)[20] and L-oleandrose (18)[21] have been synthesized as shown in Scheme 5, starting from



Scheme 5

the chiral three-carbon aldehydes (19), derived from ethyl (S)-lactate. A 3:1 mixture of α- and β-(1→4)-linked L-oleandrose disaccharides, the major anomer of which is the disaccharide unit of avermectin, was synthesized by lead(II) ion-induced coupling of benzyl α-L-oleandropyranoside with 2-pyridyl 4-O-acetyl-1-thio-α-L-oleandropyranoside.[21] An eight step synthesis of 2-deoxy-D-glycero-tetrose from 4,6-O-isopropylidene-D-glucitol via 2,4-O-isopropylidene-D-erythrose has been reported.[22]

A further synthesis of L-rhodinose (17), as well as of D-amicetose (20), has been achieved through the deamination of L-glutamic acid (21) (Scheme 6). The 5-carboxylate (22) was converted to the chain-extended ketone (23), reduced with diborane, and the resulting C-5 epimeric lactones separated chromatographically and reduced.[23]



Reagents: i, HNO_2; ii, $(COCl)_2$; iii, CH_2N_2; iv, HI; v, B_2H_6-Me_2S; vi, Bu^i_2AlH

Scheme 6

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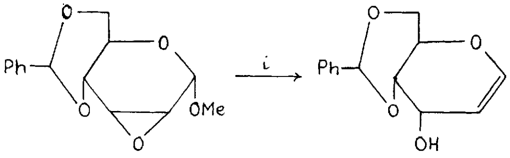
13
Unsaturated Derivatives

1 Glycals

Treatment of the epoxide (1) with Grignard reagents in the presence of copper(I) iodide gives 4,6-O-benzylidene-D-allal (2) in high yield (Scheme 1); C-4 epimers underwent the same reaction.[1]

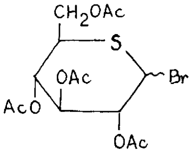


(1) (2)

Reagents: i, EtMgBr-CuI-THF

Scheme 1

Orthodox reaction of the 5-thiopyranosyl bromide (3) with zinc-acetic acid followed by deacetylation gave 5-thio-D-glucal (4) which is a competitive inhibitor of glycosidases.[2]



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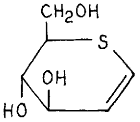
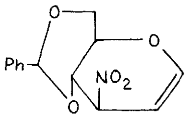


(4)

The three possible D-galactal monoacetate dibenzyl ethers have been prepared, and their rates of reaction with chloroazide to give 2-azido-2-deoxyglycosyl chlorides were examined. When the ester group is at O-3, the glycal reactivity is markedly reduced.[3] When chlorination of the nitroglycal (5) is carried out in, for example, carbon tetrachloride, standard addition occurs, but when ethers, e.g., THF, tetrahydropyran, oxetane or diethyl ether are used as solvents, O-glycosides are formed, e.g., (6) following participation of the solvent. From such compounds eliminations occur readily, as for example on column chromatography, and nitroalkenes, e.g., (7), result.[4]



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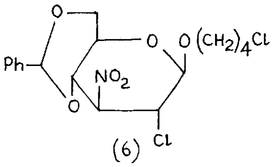

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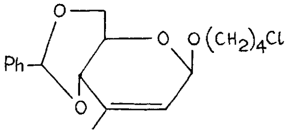

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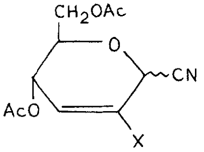
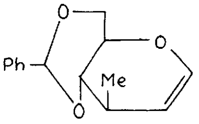


(8) X = H or OAc



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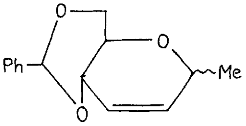
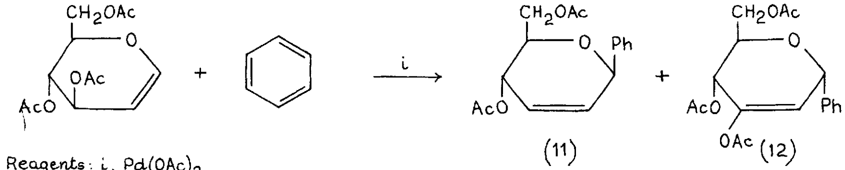


(10)

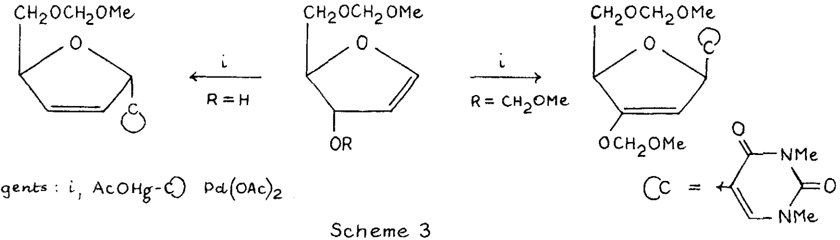
The conversion of glycal derivatives into 2,3-unsaturated compounds continues to attract attention and is referred to in Chapter 3 as a means of making C-glycosides. Four approaches to the preparation of methyl 2,3,6-trideoxy-α-D-erythro-hex-2-enopyranoside have been compared; the favoured route involves treatment of tri-O-acetyl-D-glucal with methanol in the presence of boron trifluoride, deacetylation of the 2,3-unsaturated product and deoxygenation at C-6 by way of the tosylate.[5] The same type of rearrangement process has afforded several unsaturated C-glycosides. Glycal or 2-hydroxyglycal acetates react with trimethylsilyl cyanide to give such compounds (e.g., 8) and cannot be induced to give 3-cyano-derivatives.[6] When compound (2), however, was treated with butyllithium followed by a sulphonyl chloride and the product then treated with lithium dimethyl copper, products of direct (9) and rearranged (10) substitution were isolated. Grignard reagents were used to introduce complex aliphatic groups at positions 1 and 3.[7] When tri-O-acetyl-D-glucal (tri-O-acetyl-D-galactal behaves similarly) is treated with benzene or methoxy-substituted benzenes in the presence of palladium acetate, the rearranged product (11) is obtained but only in 10% yield, the main product being the tri-



Reagents: i, $Pd(OAc)_2$

Scheme 2

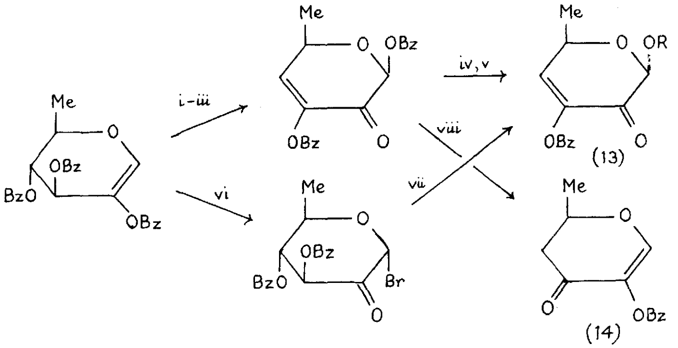
acetate (12) (Scheme 2). The reaction is believed to involve cis-addition of Ph, PdOAc followed by cis-elimination of $Pd(OAc)_2$ and HPdOAc.[8] Furanoid glycals in the presence of palladium acetate react with pyrimidine-mercury derivatives to give analogous products depending upon the specific compounds taken (Scheme 3).[9]



Reagents: i, AcOHg-C $Pd(OAc)_2$

Scheme 3

In connection with the investigation of the 2,3-diketopyranose unit in spectinomycin, Lichtenthaler et al. have made the enolones (13) and (14) (Scheme 4) and have examined their chiropticality.[10] Oxidation of 1,2,4,6-tetra-O-acyl-β-D-glucopyranoses give analogous enones to the latter by oxidation at C-3 followed by elimination. Bromo-adducts of the enones were reported.[10a]



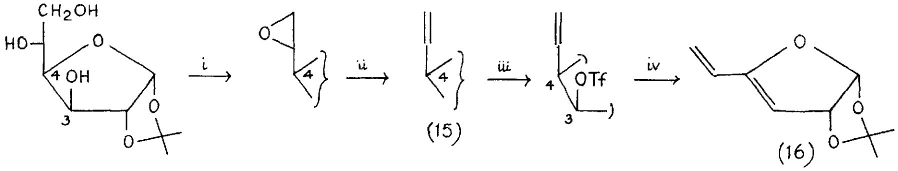
Reagents: i, Cl_2; ii, H_2O; iii, $NaHCO_3$; iv, HCl; v, ROH; vi, NBS-MeOH; vii, ROH-Ag_2CO_3; viii, $Zn(BH_4)_2$

Scheme 4

2 Other Unsaturated Derivatives

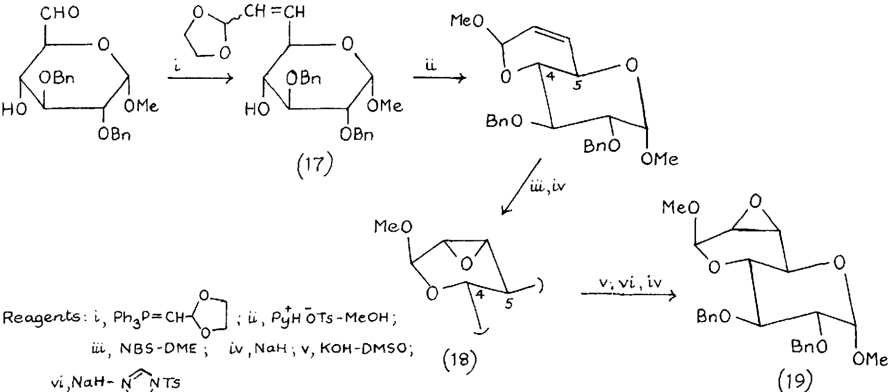
Several other chapters refer to the use of 2,3-unsaturated pyranoid substances in synthesis: in Chapter 3,and in the earlier part of this Chapter,2,3-unsaturated C-glycosides are noted and further references are given to the use of 2,3-unsaturated compounds as follows: Chapter 9 (synthesis of 3-amino-3-deoxy compounds), Chapter 12(2,3,4,-trideoxy-sugars), Chapter 14 (3- and 2,3-branched-chain sugars), and Chapter 20 (nucleosides). References to 4',5'-unsaturated nucleosides and to 5,6-unsaturated hexopyranosyl compounds appear in Chapters 20 and 18, respectively.

The 5,6-unsaturated furanoid compound (15) and the diene (16) have been prepared as indicated in Scheme 5,[11] and the 6,7-unsaturated pyranoid derivative (17) has been used as precursor of "bipyranosides" (18) and (19) (Scheme 6).[12]



Reagents: i, TPP-DEAD; ii, 3-Methyl-2-selenoxobenzothiazole; TFA; iii, $(TfO)_2O$; iv, DBU

Scheme 5

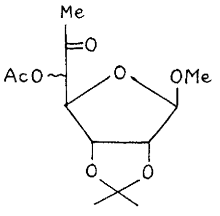


Reagents: i, $Ph_3P=CH-$; ii, $Py\overset{+}{H}\,\overset{-}{O}Ts$-MeOH; iii, NBS-DME; iv, NaH; v, KOH-DMSO; vi, NaH-NTs

Scheme 6

Mercury(II) catalysed hydration of the corresponding 6-alkynes gave access to the epimeric methyl ketones (20).[13]

Base-catalysed condensation of 2,3-O-isopropylidene-D-glyceraldehyde with monoethyl methylmalonate occurs with racemization by pre-equilibration, giving the DL-pentonic acid, whereas the faster reaction with α-methylacetoacetic acid gives largely unracemized product.[14] Reaction of 2,4:3,5-di-O-ethylidene-L-xylose with Wittig-Horner phosphonate reagents in benzene-aqueous sodium hydroxide in the presence of a phase transfer catalyst gave about



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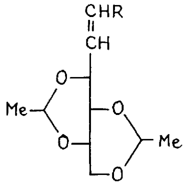
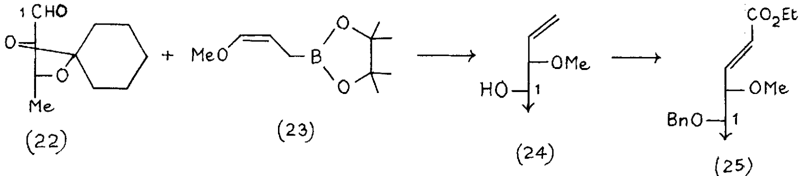


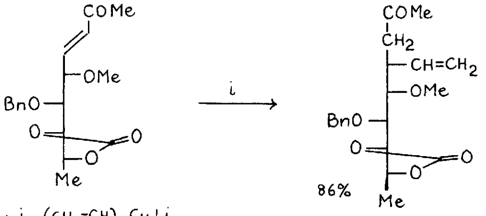
(21) R = CN, CO_2Et

40-50% yields of the unsaturated aldonic acid compounds (21).[15]

A more novel reaction involves conversion of the acetal (22) into the heptose compound (24) by use of the allyl-boronic ester (23). The product was then extended by way of the <u>aldehydo</u>-hexose into the octenoic acid derivative (25) for use in the synthesis of aureolic acid (Scheme 7).[16] Continuation of the work revealed how vinyl cuprate reagents can add with high stereoselectivity to carbohydrate enones (Scheme 8). Several related reactions, concerned with the synthesis of olivin were discribed.[17]



Scheme 7



Reagent : i, $(CH_2=CH)_2CuLi$

Scheme 8

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14

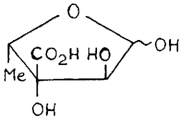
Branched-chain Sugars

1 Sugars Containing an R-C-OH Branch

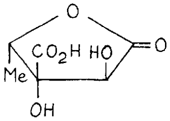
3-*C*-Carboxy-5-deoxy-L-xylose (1) has been identified for the first time as a plant cell-wall component; the *xylo*-configuration was confirmed by X-ray crystal analysis on the derived lactone (2), and the L-series assignment by conversion to L-lactic acid.[1]

Some recent advances in the chemistry of branched-chain sugars have been reviewed.[2]

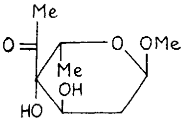
Most syntheses have used well-documented procedures involving nucleophilic additions to glycosulose derivatives. Methyl α-trioxacarcinoside B (3) was prepared by the dithiane route using a 2,6-dideoxy-L-hexopyranosid-4-ulose intermediate.[3]



(1)



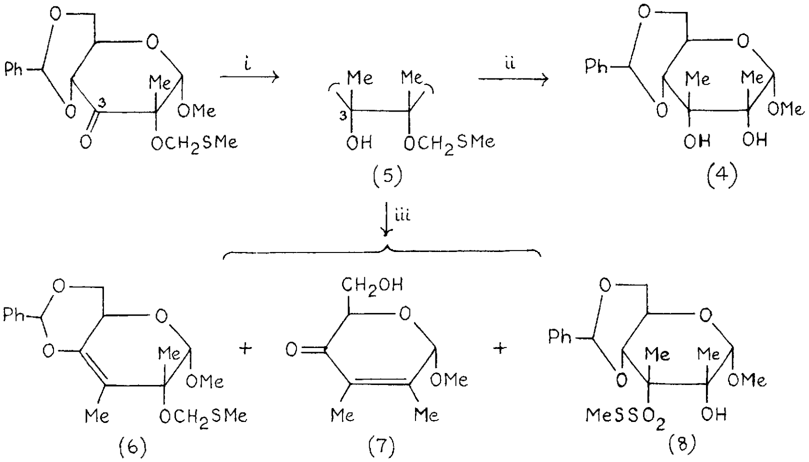
(2)



(3)

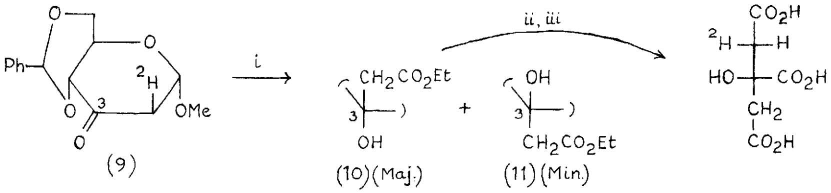
The 2,3-Di-*C*-methyl-hexose (4) has been obtained from the 3-ulose of the corresponding 2-*C*-methyl sugar as illustrated in Scheme 1. The intermediate (5), characterized by X-ray analysis, yielded a mixture of products (6)-(8) on treatment with sulphuryl chloride in pyridine.[4] Reformatsky reaction of the 2-deuterio-2-deoxy-3-ulose (9) gave an isomeric mixture of the corresponding branched-chain sugars (10) and (11), the former then being used as a source material for stereospecifically labelled citric acid, as shown in Scheme 2; it was noted that, under base catalysis, the axial 2-hydrogen in (9) (^{2}H = H) inexplicably exchanges 1000 times faster than the axial 2-hydrogen in 4-t-butylcyclohexanone.[5]

A study of the reaction of diazomethane with the standard 3-ulose (12) derived from glucose has shown that both cyclo-addition and methylene insertion occur, giving spiro-epoxides having five, six, and seven-membered sugar rings, as indicated in Scheme 3;[6] this conforms with results observed previously with other glycosulose derivatives.



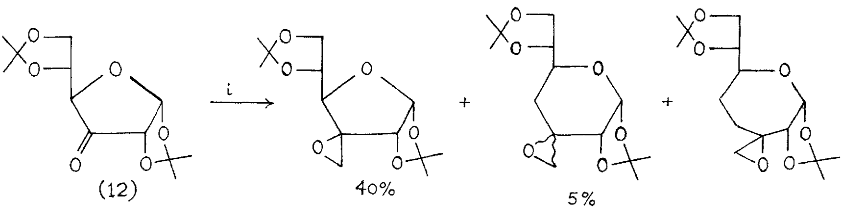
Reagents: i, MeMgI ; ii, $MeI-K_2CO_3$; iii, SO_2Cl_2-Py

Scheme 1



Reagents: i, Zn-$BrCH_2CO_2Et$; ii, HOAc-H_2O ; iii, $KMnO_4$-NaOH

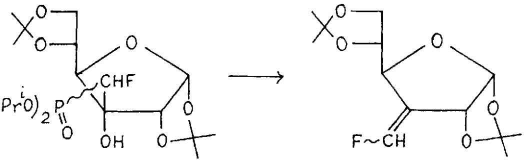
Scheme 2



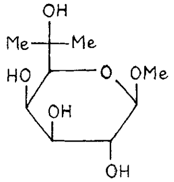
Reagents: i, CH_2N_2

Scheme 3

Reaction of (12) with diisopropyl fluoromethylphosphonate anion gave the corresponding *C*-fluoromethylenephosphonate allose derivatives (13) (a 1:1 mixture of C-1' epimers), which underwent elimination to give the fluoromethylene unsaturated sugar mixture (14).[7] D-Galactose has been converted to its 6,6-di-*C*-methyl analogue (15) by standard reactions using its 1,2:3,4-di-*O*-isopropylidene-dialdose derivative.[8]



(13) (14)



(15)

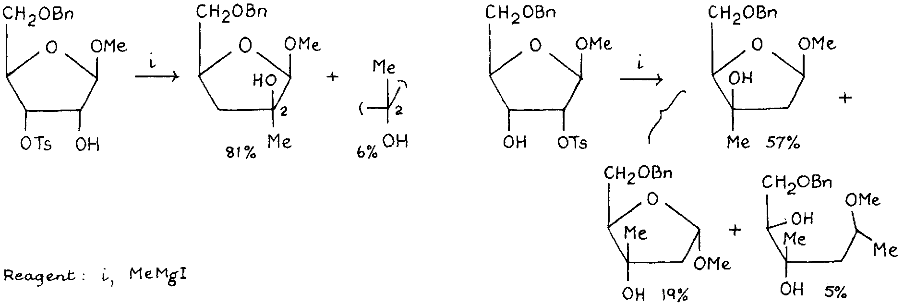
The stereochemistry of the reaction of methyl lithium and methyl magnesium iodide with a range of glyco-4-ulose derivatives has been studied to test proposals said to govern stereoselectivity (Miljhovic *et al.*; see Vol. 8, p. 106). Differences can arise where magnesium coordination to oxygen causes a conformational change; equatorial attack predominates, modified by axial groups α- to the carbonyl group.[9]

Conventional Grignard reaction of levoglucosenone followed by hydroxylation has been used to prepare 1,6-anhydro-2-*C*-tetradecyl altropyranose.[10]

Reaction of Grignard reagents with sulphonate derivatives of methyl D-ribofuranoside leads to rearranged, branched-chain sugars as outlined in Scheme 4; anomerization of these compounds by acidic methanolysis or with Grignard reagents was also studied, the latter favouring the thermodynamically less-stable anomers.[11]

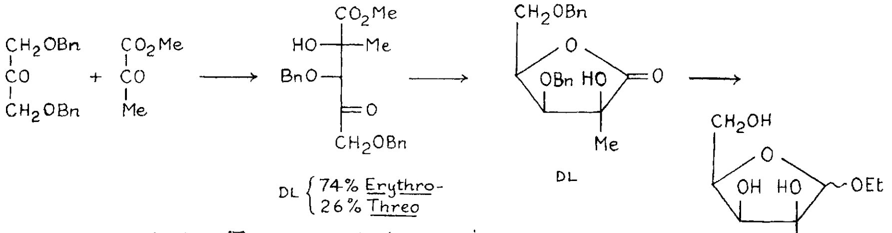
DL-Hamamelose has been synthesized by alkaline treatment of a 2,2'-*O*-methylene dimer of D-glyeraldehyde, the D-form crystallizing preferentially from the mixture. At equilibrium in water, the free sugar consisted of 39% α-furanose, 28% β-furanose, 13% α-furanose and 20% β-pyranose.[12]

Ethyl 2-*C*-methyl-DL-lyxofuranoside (16) has been obtained using a directed cross-aldol reaction between dihydroxyacetone and pyruvic acid derivatives, as outlined in Scheme 5. *Cis*-hydroxylation of 4-benzyloxy-methyl-2-methyl-γ-butenolide gave mainly the stereochemically expected DL-*ribo*-lactone (37%) together with DL-*lyxo*-lactone (9%), the latter being correlated with (16).[13]



Reagent: i, MeMgI

Scheme 4

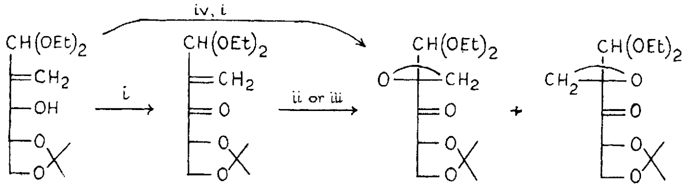


Reagents: i, $Sn(OTf)_2$–N-Et; ii, $LiBH(Bu^s)_3$; iii, Bu^i_2AlH; iv, $KOBu^t$–EtI; v, H_2–Pd

DL-(16)

Scheme 5

Swern oxidation of the unsaturated branched-chain sugar (17) gave the corresponding enone (18), which on enzymatic epoxidation gave the threo-oxiran (19) exclusively; chemical methods yielded some of the isomeric erythro-oxiran (20) as well (Scheme 6).[14]

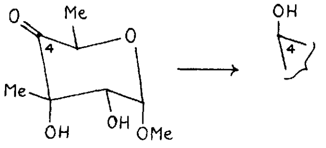


(17) (18) (19) (20)

Reagents: i, $(COCl)_2$–DMSO–NEt_3; ii, H_2O_2–NaOH; iii, Cytochrome P450–O_2–NADPH; v, Bu^tO_2H–$VO(acac)_2$

Scheme 6

The 4-ulose (21) underwent anticipated stereoselective reduction with L-selectride to yield the axial alcohol (methyl α-virenoside).[15] The branched-chain aldonic acid (22), related to orthosomycin components, has been prepared from the corresponding benzyl aldopyranoside.[16]



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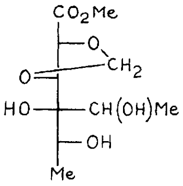
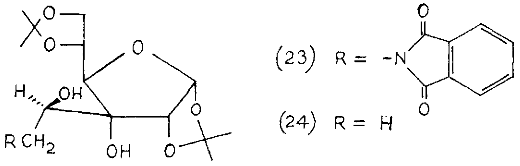


(22)

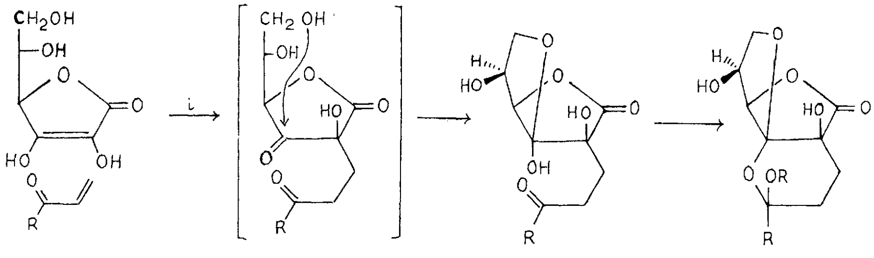
α-D-Apiofuranosyl 1-phosphate and 1,2-cyclic phosphate have been synthesized.[17] X-Ray analysis on the branched-chain sugar (23) has established that both (23) and the hydroxyethyl analogue (24) have the (R)-configuration at C-1', since they are both obtained from the same oxiranyl precursor.[18]



(23) R =

(24) R = H

L-Ascorbic acid undergoes Michael addition to acrolein and butenone to yield 2-C-substituted ulosonic acid derivatives as indicated in Scheme 7, the structure of the tricycle (25) (R = H) being established by X-ray analysis.[19]



Reagents : i, H_2O, pH 4

R = H or Me

(25)

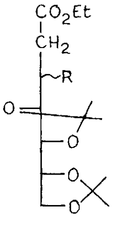
Scheme 7

A C-aryl substituted amino sugar is mentioned in Chapter 9, and branched-chain alditols are covered in Chapter 18.

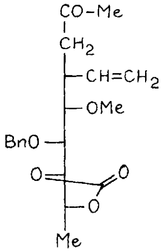
2 Compounds Containing an R-C-H or R^1-C-R^2 Branch

Copper salts promote the Michael addition of Grignard reagents to αβ-unsaturated esters derived from L-arabinose, leading to the

3-C-substituted sugar derivatives (26), the stereoselectivity varying with the reagent.[20] Likewise vinyl cuprate reagents add with high stereoselectivity to carbohydrate enones, leading, for example, to the tetradeoxy C-vinyl ketone (27).[21]

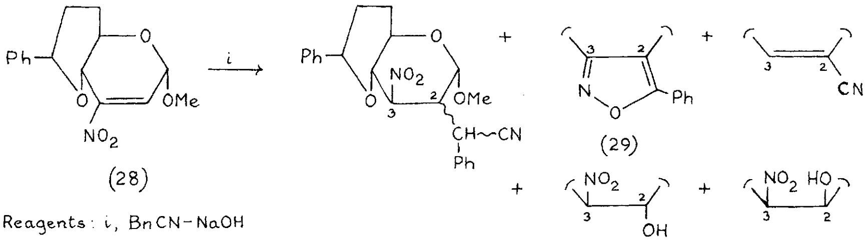


(26)



(27)

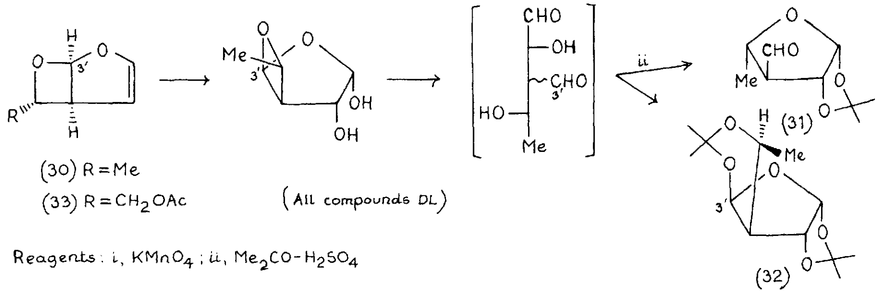
The unsaturated nitro-sugar (28) reacted with alkaline benzyl cyanide to yield a mixture of branched-chain sugar derivatives as shown in Scheme 8; a mechanism is proposed to account for the oxazole (29). The β-anomer of (28) behaved similarly.[22] The reaction of glycals with organometallic reagents leading, inter alia, to branched-chain sugars, is mentioned in Chapter 13, which includes other references to unsaturated, branched-chain sugars.



Reagents: i, BnCN-NaOH

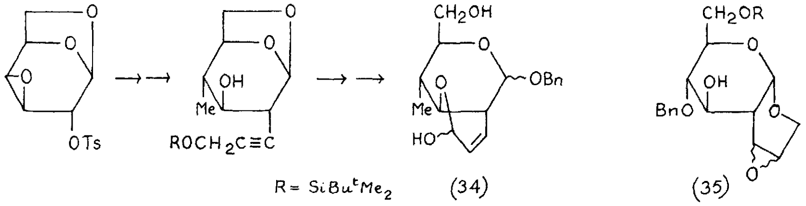
Scheme 8

An interesting synthesis of 3-deoxy-DL-streptose utilized the dioxabicycloheptene (30) obtained by cycloaddition of furan and ethanal; stereospecific exo-cis-hydroxylation was accompanied by C-3 epimerization, giving a mixture resolved into the deoxystreptose derivatives (31) and its 3-lyxo-epimer (32) by acetonation (Scheme 9).[23] The acetoxymethyl analogue (33) in an alternative hydroxylation procedure using MCPBA only gave lyxo-product, epimerization being discouraged by hemiacetal formation between the C-3' formyl and C-5-hydroxy groups.



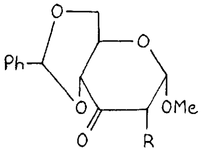
Scheme 9

Methyl 4,6-*O*-benzylidene-2,3-anhydro-α-D-allopyranoside reacts with 2-propenylmagnesium chloride to afford the 2-deoxy-2-*C*-(2-propenyl)altroside exclusively, and diethylmagnesium gives mainly the 2-deoxy-2-*C*-ethyl analogue. The C-4-epimeric 2,3-anhydroguloside reacts similarly with the propenyl reagent to give 2-C-substituted (ido) product, but fails to react with diethylmagnesium. Regioselectivity is lost with flexible anhydro sugar analogues.[24] 1,6;3,4-Dianhydro-D-galactopyranose has been used as a precursor for the preparation of the double-branched-chain sugar (34) by the sequence traced in Scheme 10. A related sequence likewise yielded the novel dianhydro-branched-chain sugars (35), the stereochemistry of epoxidation, using the Sharpless reagent, depending on whether the C-3 hydroxy group is free or acetylated.[25]



Scheme 10

Reaction of methyl 2,3;4,6-di-*O*-benzylidene-α-D-mannopyranoside with butyllithium generated the enolate anion of the corresponding 2-deoxy-glycosid-3-ulose, which reacted with alkylating reagents to give a series of 2-deoxy-2-*C*-alkylated D-*ribo*-hexopyranosid-3-uloses (36). These could be further alkylated, via an enolate anion, to the gem-dialkyl sugars (37). Attempted alkylation using 2-bromoethyl acetate only gave the ethylene acetal of the glycosidulose (38).[26] Other *gem*-disubstituted derivatives prepared have included the 3-deoxy-3-carbamoyl-3-cyanopyranosides (39)



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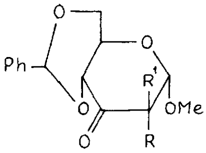

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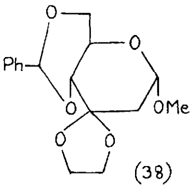
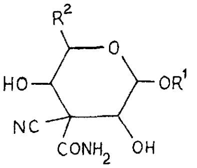


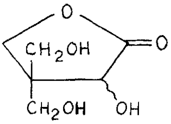
(38)

R,R^1 = Me, Bn, Allyl, Prop-2-ynyl, -CH$_2$CO$_2$Et

obtained by cyclization of a dialdehyde with cyanoacetamide,[27] and the 3-deoxy-3,3-di-(hydroxymethyl)-lactone (40) which was formed selectively in a formose reaction using D-fructose in



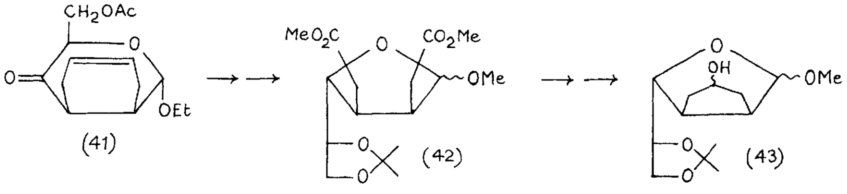
(39) R^1 = Me, Bn
R^2 = H, CH$_2$OH



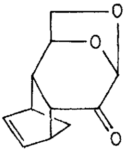
(40)

methanolic sodium hydroxide solution.[28]

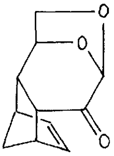
Diels-Alder additions to conjugated unsaturated glycosuloses have yielded the bicyclic pyranoside (41), which was further transformed to the diester (42) and the pentanols (43), and the



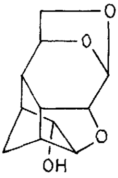
tetracyclic derivatives (44) and (45), prepared from levoglucosenone and cyclopentadiene.[10,30]



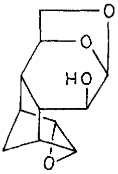
(44)
(minor)



(45)
(major)



(46)



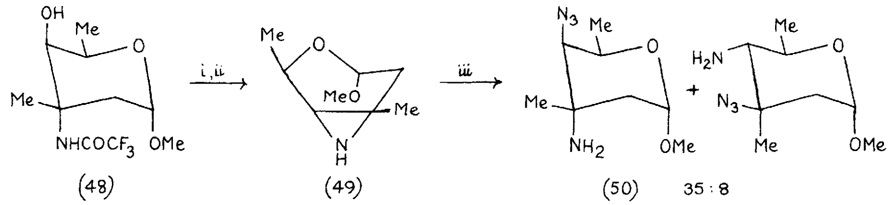
(47)

Borohydride reduction of these ketones yielded isomeric mixtures of the corresponding alcohols, the pair from (45) on MCPBA oxidation yielding the further derivatives (46) and (47) respectively.[30]

Deoxy-branched chain sugars are also referred to as precursors for alkaloid and polyketide synthesis in Chapter 24, and branched-chain sugar nucleosides are mentioned in Chapter 20.

3 Sugars Containing an R-C-N Branch

An improved synthesis of D-kijanose utilizes the trifluoroacetamido branched-chain sugar (48) to produce the aziridino-intermediate (49), which on azidolysis gives mainly the required D-*xylo* derivative (50), a known precursor for kijanose (Scheme 11).[31] Brimacombe's group have also reported the synthesis of the antibiotic sugar 3-amino-2,3,6-trideoxy-3-C-methyl-L-*xylo*-hexose using the ulose-cyanhydrin procedure.[32] Their synthesis of rubanitrose analogues is mentioned in Chapter 9, which also includes other syntheses of 2,3,6-trideoxy-3-*C*-methyl-3-amino-L-hexoses.



Reagents: i, MsCl-Py; ii, NaBH$_4$-EtOH; iii, NaN$_3$-NH$_4$Cl

Scheme 11

The occurrence of 2,3,6-trideoxy-3-*C*-methyl-3-nitro-L-hexose in the anthracycline antibiotic decilorubicin is covered in Chapter 19.

4 General

A ^{13}C n.m.r. study of a variety of 3-C-methyl, -cyano, and -nitromethyl branched-chain sugars derived from 1,2-5,6-di-*O*-isopropylidene-D-gluco-furanose is mentioned in Chapter 21.

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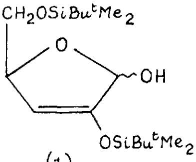
15
Aldosuloses, Dialdoses, and Diuloses

1 Aldosuloses

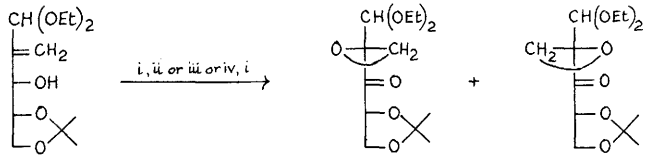
A simple and convenient enzymic conversion of D-glucose into D-*arabino*-hexos-2-ulose (D-glucosone) involves the use of a pyranose 2-oxidase from *Polyporus obtusis* which was purified and immobilized.[1] In related work the same group have described an extension of this reaction which leads via glucosone and with a D-glucose 1-oxidase, to D-*arabino*-2-hexulosonic acid.[2] D-Glucosone is the only product derived by oxidation of D-glucose with sodium 2-anthraquinone sulphonate in alkaline conditions.[3]

3-Deoxy-D-*glycero*-pentos-2-ulose has been produced enzymically from an (ADP-ribosyl)histone and also synthesized from D-ribono-γ-lactone via the silyl ether (1). It was identified by mass spectral examination of labelled reduction products.[4]



(1)

Catalytic hydrogenation of D-glucosone over palladium on charcoal gives D-fructose with over 90% selectivity. In conjunction with the above-mentioned enzymic oxidation of D-glucose to D-glucosone, this represents a practical conversion of D-glucose into D-fructose.[5]



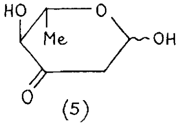
(2) (3) (4)

Reagents: i, $(COCl)_2$-DMSO-NEt_3; ii, H_2O_2; iii, cytochrome P450-O_2-NADPH; iv, Bu^tO_2H-$VO(acac)_2$

Scheme 1

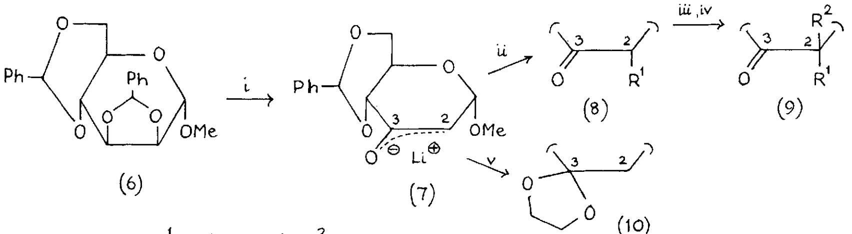
The epoxides (3) and (4) can be made by oxidation and epoxidation (or the reverse) of the alkene (2) (Scheme 1).[6]

As always, several reports have appeared on the chemistry of aldosiduloses. The 2,6-dideoxy-L-erythro-hexopyranos-3-ulose (5) has been found for the first time in Nature as a component of a polyenic macrolide.[7]



(5)

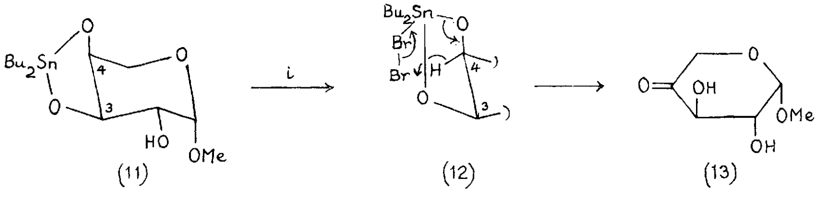
Reactions of methyl 2,3:4,6-di-O-benzylidene-α-D-mannoside (6) with butyl lithium gave the enolate (7) which, with alkylating reagents, afforded firstly the 2-alkyl-3-ulosides (8) and thence the gem-dialkyl compounds (9). Reaction of the enolate with 2-bromoethyl acetate gave only the acetal (10) (Scheme 2).[8]



Reagents: i, BuLi; ii, R^1Br; iii, LDA; iv, R^2Br; v, $AcOCH_2CH_2Br$

Scheme 2

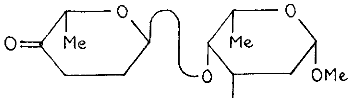
A further method of making ulosides involves brominolysis of stannylene derivatives. Thus the methyl β-L-arabinoside derivative (11) gave the ketone (13) by way of the illustrated intermediate (12) (Scheme 3), the axial oxy group being oxidized.[9]



Reagent: i, Br_2

Scheme 3

The disaccharide ketone (14), which occurs in the trisaccharides of some anthracyclinones, has been synthesized from a glycal,[10] and related procedures were used to obtain the trisaccharide derivative (15).[11]



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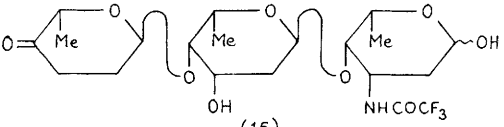
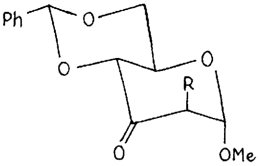


(15)

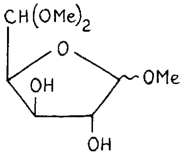
Photobromination reactions utilizing uloside derivatives are referred to in Chapter 8.

The axial proton at C-2 in the glycosid-3-ulose (16) surprisingly undergoes deuterium exchange 1000 times faster than does the axial proton at C-2 in 4-t-butylcyclohexanone;[12] the use of the 2-deuterio derivative (17) for the synthesis of labelled citric acid is mentioned in Chapter 14.



(16) R = H

(17) R = ^{2}H

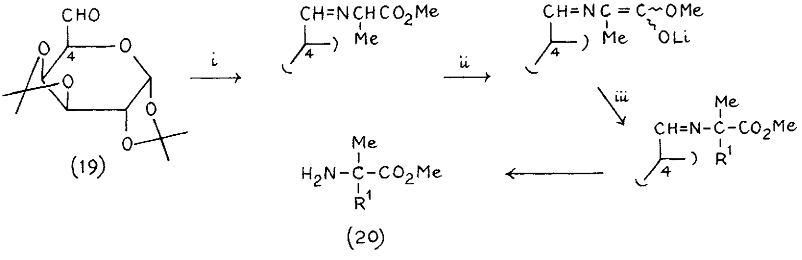


(18)

2 Dialdoses

Photolysis of D-glucose in methanol containing titanium(IV) chloride gave the D-xylose dialdose glycoside acetal (18) in 60% yield; D-galactose behaved similarly.[13]

The D-galacto-dialdose derivative (19) has been used as a chiral



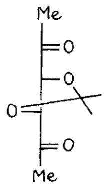
Reagents: i, $H_2NCH(Me)CO_2Me$; ii, LDA ; iii, R^1Br ; iv, H_3O^+

Scheme 4

auxiliary to obtain (S)-α-methyl-α-aminoacid methyl esters (20) as illustrated in Scheme 4.[14]

3 Diuloses

Attempted deisopropylidenation of the L-threo-hex-2,5-diulose (21) led to the tricyclic acetal (22) which was structurally characterized by X-ray analysis.[15] 1-Deoxy-D-erythro-2,3-hexodiulose (23),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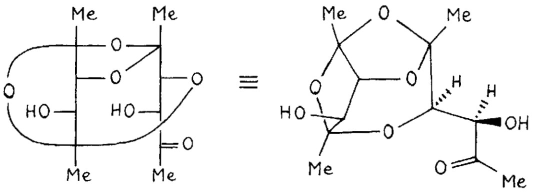
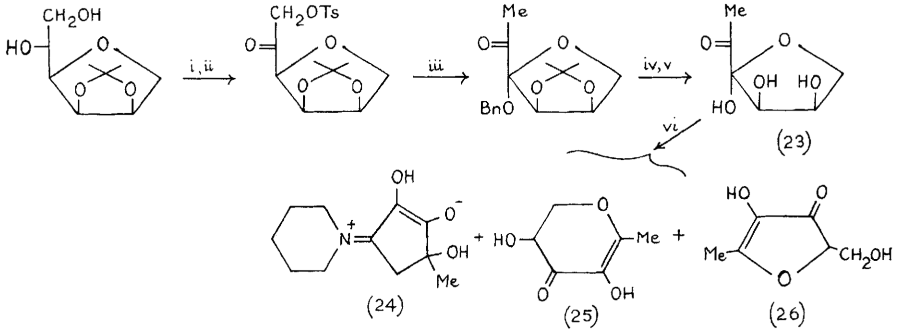

(22)

a postulated major intermediate in non-enzymic browning reactions, has been made as outlined in Scheme 5. The unusual rearrangement process occurring in the third step (c.f. A. Dmytraczenko, W.A.Szarek, and J.K.N.Jones, Carbohydr. Res., 1973, 26, 297) conceivably proceeded by way of the 4,5-enol and an allylic rearrangement process. The diulose (23), with piperidine acetate, gave several products, including compounds (24)-(26).[16]



Reagents: i, TsCl-Py; ii, RuO_2-KIO_4; iii, BnOH-TsOH-Et_3N; iv, H_2-Pd/C; v, H_3O^+; vi, $\overset{+}{N}H_2\overset{-}{O}Ac$

Scheme 5

Enol derivatives of diuloses are referred to in Chapter 13, and branched-chain diulose compounds having antiviral activity are noted in Chapter 19.

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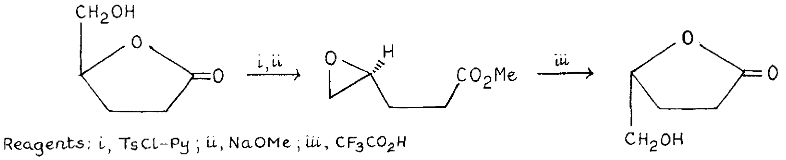
16
Sugar Acids and Lactones

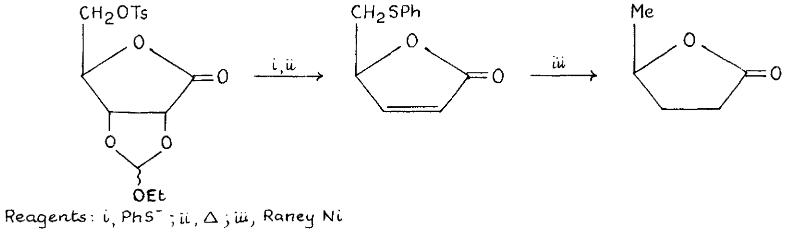
1 Aldonic Acids

Several studies have focussed on different methods of oxidizing D-glucose to D-gluconic acid or its lactone. These include observations on the use of hexachloroiridate and tetrachloroaurate (radical procedures),[1] immobilized glucose oxidase-catalase,[2] and a membrane reactor of a new type which depended on the use of these same two enzymes.[3] The dehydrogenation of sugars and alditols by use of tris(triphenylphosphinyl)ruthenium dichloride with cyclohexanone as hydrogen acceptor to give aldonolactones (in some cases with epimerizations) has been examined.[4]

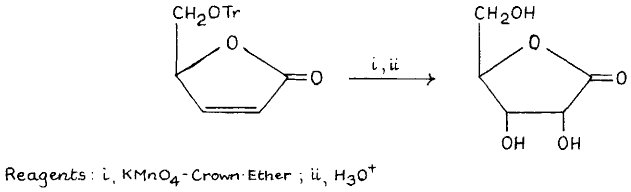
Specific syntheses have been reported of (R)-γ-hydroxymethyl-γ-butyrolactone from the cheap (S)-enantiomer (Scheme 1),[5] of (R)-β-angelica lactone from D-ribono-γ-lactone (Scheme 2)[6] and of the latter compound (racemic) from γ-butenolide (Scheme 3).[7] Six


Reagents: i, TsCl-Py ; ii, NaOMe ; iii, CF_3CO_2H

Scheme 1


Reagents: i, PhS⁻ ; ii, Δ ; iii, Raney Ni

Scheme 2

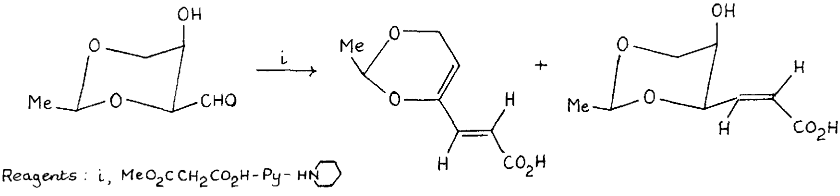


Scheme 3

2-amino-2-deoxyheptonic acids have been synthesized from the 2-(benzylamino)2-deoxyheptononitriles with the D-glycero-L-gulo-, D-glycero-D-ido-, and D-glycero-D-talo-configurations by hydrolysis (which caused partial epimerization at C-2) followed by hydrogenolysis.[8]

Reactions of aldonic acids described include electrochemical oxidation to D-arabinose in the presence of cerium sulphate,[9] and partial benzoylation of L-rhamnono-1,4-lactone (mainly to the 2,5-dibenzoate) and D-mannono-1,4-lactone (mainly to the 2,5,6-triester; also 3,6-diester and tetraester).[10] The ^{13}C n.m.r. spectra of various rhamnono-lactone benzoates and related compounds have been reported.[11] Some acyclic heterocyclic aldonic acid derivatives are referred to in Chapter 10.

Knoevenagel-Doebner condensations of 2,4-O-ethylidene-D-erythrose and -D-threose with malonic acid or its mono-methyl ester furnishes the corresponding unsaturated acids, illustrated in Scheme 4.[11a]

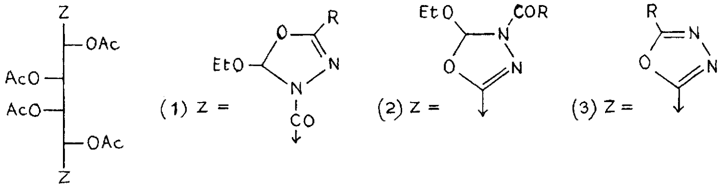


Scheme 4

Other unsaturated aldonic acid derivatives are noted in Chapter 13. Orthoesters derived from the lactone carbonyl groups of D-glucono-D-galactono- and L-glycero-D-gluco-heptono-1,5-lactones and the 2,3-diol of methyl 4,6-substituted-α-D-mannopyranoside were made by way of the trimethylsilyl ethers and with trimethylsilyl trifluoromethanesulphonate as catalyst.[12]

2 Aldaric Acids

Tetra-*O*-acetylgalactaric acid bis(aroylhydrazides) have been converted into compounds (1)-(3)[13] and bis(2-chloroethyl)amides of aldaric acids have been reported.[14]

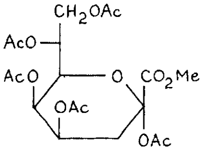


3 Ulosonic Acids

Further reports on the oxidation of 2,3:4,6-di-*O*-isopropylidene-L-sorbose to the ulosonic acid acetal have dealt with the kinetics of the reaction carried out with palladium on charcoal in alkaline solution at elevated temperatures[15] and with the electrochemical oxidation carried out in a "Swiss-roll" cell.[16]

A pyranose-2-oxidase has been used to make D-*arabino*-2-hexulosonic acid from D-glucose via D-glucosone,[17] and similar oxidation of 3-deoxy-D-*erythro*-hexos-2-ulose gave the analogous 3-deoxy acid.[18] On the other hand, 3-deoxy-D-*arabino*-2-heptulose was produced (as were isomers) as its glycoside by reduction of methyl (methyl 3-deoxy-D-*arabino*-2-heptulosid)onate.[19]

3-Deoxy-D-*manno*-2-octulosonic acid (KDO) has been identified (m.s.-g.l.c. of the peracetylated methyl glycosides) from the lipopolysaccharides of the *Vibrionaceae* which previously have been believed not to contain this acid.[20] The KDO derivative (4) with catalytic trimethylsilyl triflate gives the alkene (5) in high



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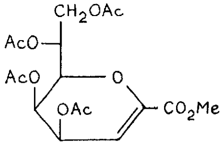
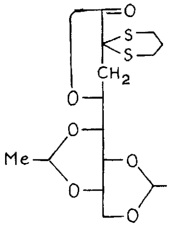


(5)

yield, and a similar elimination was carried out on an analogous 3-deoxynonulosonic acid derivative.[21] The 3-deoxy-2-octulosonic acid derivative (6) was obtained by treatment of 1,2-anhydro-3,5:4,6-di-*O*-ethylidene-L-gulitol with ethyl 1,3-dithiane-2-carboxylate,[22] and KDO itself has been prepared from 1,2-anhydro-3,4:5,6-di-*O*-isopropylidene-D-mannitol by treatment with malonate anion.[22a]

4 Uronic Acids

Reviews have appeared on the conversion of D-glucose into D-glucuronic acid[23] and of D-glucose derivatives into those of D-glucuronic acid.[24]



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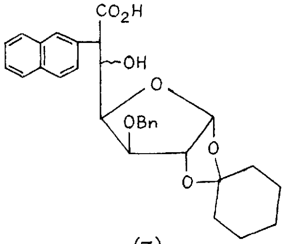

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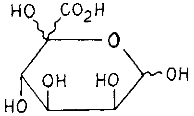


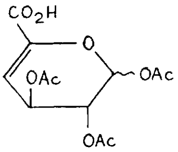
(8)

Application of the Ivanov reaction led to the production of compound (7)[25] and chain extension methods applied to 5'-aldehydes have been used to produce modified uronic acid nucleosidic compounds (Chapter 20).

Selective cleavage of β-D-glucosiduronic acid or amide linkages in oligo- or poly-saccharides can be achieved by conversion to the 5-isocyanates (acids treated with diphenylphosphoroazidate, amides with lead tetra-acetate) and hence, with benzyl alcohol, into 5-benzyloxycarbonylaminopentopyranosides which, on mild hydrolysis, cleave to give the pentodialdoses.[26] A related oxidation has been used to cleave selectively a glucose residue from a compound containing this sugar and D-xylose by initial tritylation, methylation, detritylation, oxidation to the uronic acid and finally cleavage with lead tetra-acetate.[27] The D-*lyxo*-5-hexulopyranuronic acid (8) has been identified as a component of *Sphagnum* moss holocellulose and forms a point of cross-linkage between cellulosic, hemicellulosic and pectin like chains. It apparently is not formed during the chlorite delignification step.[28]

On selective tosylation, D-glucurono-6,3-lactone gave the 5-tosylate and 2,5-ditosylate as main products; anomeric configurations were not assigned to these crystalline compounds.[29] Selective glycosylation, acylation and tritylation of methyl 1,2-O-cyanoethylidene-α-D-glucopyranuronate gave the 3- and 4-substituted products which were required as monomers for the preparation of polyuronides.[30]

Treatment of D-galacturonic acid with acetic anhydride and (dimethylamino)pyridine gave the unsaturated acid (9) in high yield, whereas reaction of tetra-O-acetyl-D-galacturonic acid with acetic anhydride and triethylamine gave this same product together with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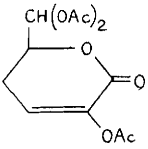
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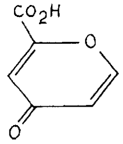
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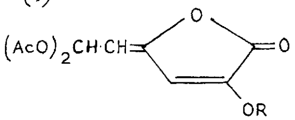
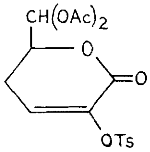

(12) R=OAc
(14) R=OTs


(13)

similar amounts of the enone (10) and the γ-pyrone (11).[31] In related work it was shown that with potassium acetate in acetic anhydride in the presence of crown ether 5-O-tosyl-D-glucuronolactone gives similar amounts of compounds (12) and (13) as main products, whereas the 2,5-ditosylate gives the γ-lactone (14).[32]

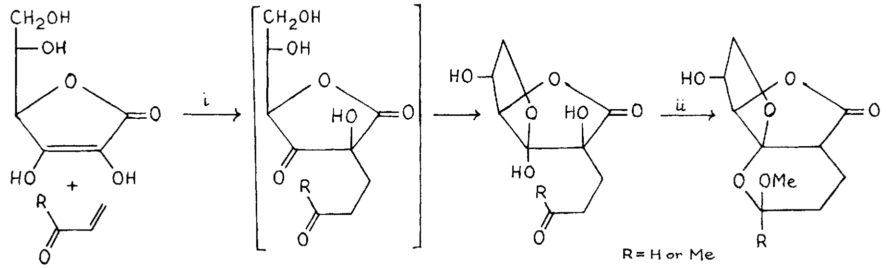
5 Ascorbic Acids

Oxidation reactions used in the preparation of vitamin C are mentioned in section 3 above.

The oxidation of ascorbic acid still commands much attention. The kinetics of the oxidation with nickel(III) tetraazamacrocycles have been examined[33] and the rate of oxidation by oxygen in the presence of iron(II) sulphate has been shown to be increased by the addition of amino acids such as glycine or histidine.[34] Likewise the oxidation by oxygen in the presence of Cu(II) salts has been found to be accelerated by ligands which stabilise Cu(I) and decelerated by those which stabilise Cu(II).[35] A more comprehensive analysis deals with the physical properties (absorption spectra, pK_1, pK_2 and redox values at various pH values) of L-ascorbic acid, D-isoascorbic acid, D-gluco-ascorbic acid and D-galacto-ascorbic acid. Their oxidation by oxygen in the presence of heavy metals was also investigated.[36] The preparation of dehydro-L-ascorbic acid by use of oxygen and activated charcoal as catalyst has been modified to give a pure product by way of the methanol adduct.[37]

E.s.r. spectra of a γ-irradiated single crystal of L-ascorbic acid have been reported.[38] The acid has been shown to act as a radical scavenger in the autoxidation of methyl linoleate, and to exert a synergistic effect when used with Vitamin E.[39]

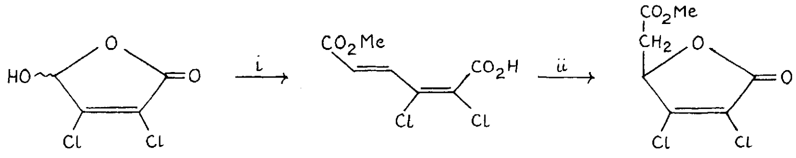
The levels of vitamin C in leaves of 213 angiosperm species have been assayed.[40]



Reagents: i, H_2O, pH 4; ii, $MeOH-H^+$

Scheme 5

L-Ascorbic acid reacts as a Michael donor with acrolein or methyl vinyl ketone; the products can be converted to cyclic acetals as shown in Scheme 5.[41] The analogue (15) of ascorbic acid has been made as indicated in Scheme 6; the halogen at C-3 can be displaced by nucleophiles by addition, elimination procedures.[42]

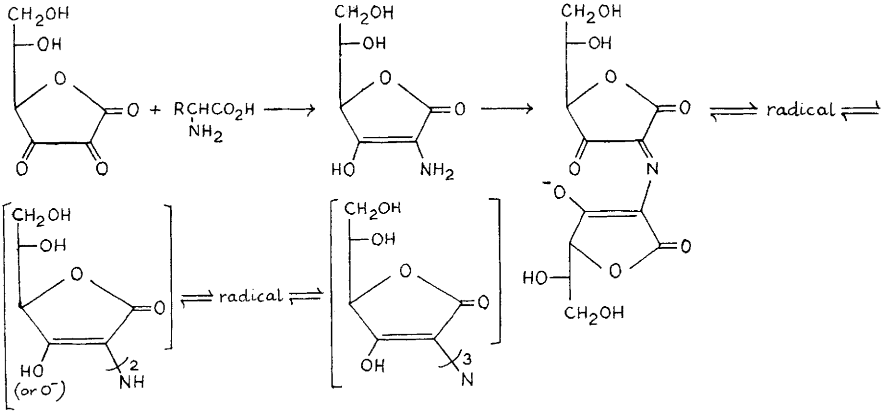


(15)

Reagents: i, Methyl diethylphosphonoacetate; ii, Δ

Scheme 6

Treatment of dehydro-L-ascorbic acid with o-phenylenediamine gives a product which shows 3 polarographic reduction waves. The reactions involved were discussed.[43] A study of the reaction of the same acid with α-aminoacids has shown that a complex set of species are formed (Scheme 7).[44]



Scheme 7

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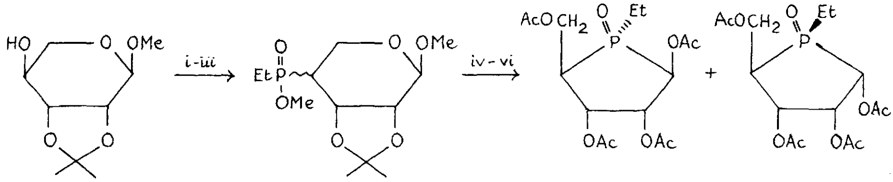
17

Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

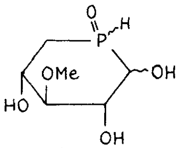
Considerable attention has again been paid to compounds with phosphorus as the heterocyclic atom, the first such D-ribofuranose compounds having been produced as indicated in Scheme 1.[1]



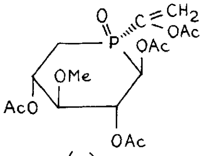
Reagents: i, DMSO-$(COCl)_2$-Et_3N ; ii, EtPH(O)OMe ; iii, $NaBH_4$; iv, $NaAlH_2(OMe)OEt$; v, H^+ ; vi, Ac_2O-Py

Scheme 1

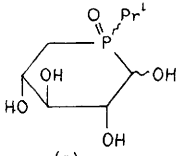
Most work has related to six-membered cyclic compounds such as the phosphinyl derivatives (1) which were synthesized from 1,2-O-isopropylidene-3-O-methyl-5-O-tosyl-α-D-xylofuranose by an improved established procedure.[2] A peracetate derived from this product was previously wrongly characterized; it is now formulated as the enolacetate derivative (2).[3] Related studies produced compounds (3) from 3-O-acetyl-5-deoxy-5-iodo-1,2-O-isopropylidene-α-D-xylose,[4]



(1)



(2)



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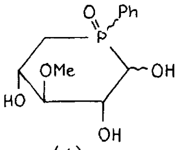

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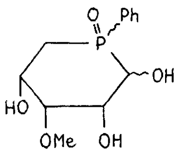

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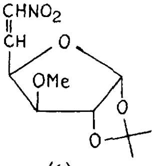

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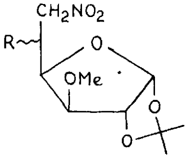
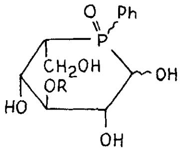


(7) R = $POPh_2$

(8) R = PHPh



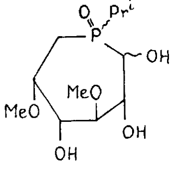
(9) R = H

(10) R = Me

(4) from 1,2-O-isopropylidene-3-O-methyl-D-xylo-pentodialdose[5] and the related D-ribo-compound (5) from the isomeric D-ribo-pentodialdose derivative.[6]

The nitroalkene (6) allowed access to compounds (7)[7] and (8),[8] and from the latter and closely related compounds, the L-ido-products (9)[9] and (10)[8] were derived. Related studies have provided 6-deoxy analogues of compounds (9).[10]

Mass spectral studies have been reported on peracetylated derivatives of pyranoid and furanoid compounds with phosphorus in the ring. Molecular ions are more stable than those of analogues with oxygen in the ring.[11] A new procedure has produced a septanose analogue (11) from the precursor (12) which was made from 6-deoxy-6-iodo-1,2-O-isopropylidene-3-O-methyl-α-D-glucofuranose.[12]



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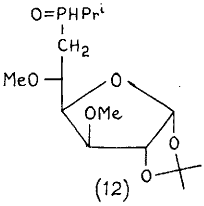

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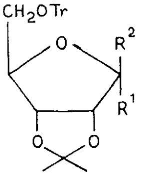
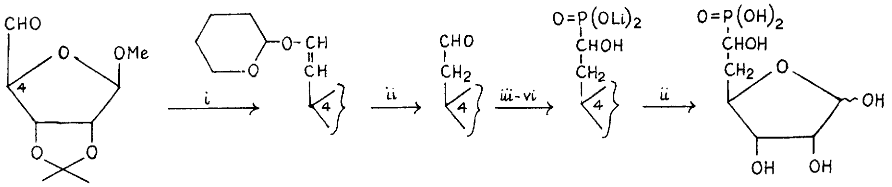


(13) $R^1 = CH_2P(O)(OPh)_2$, $R^2 = H$

(14) $R^1 = H$, $R^2 = CH_2P(O)(OPh)_2$

Compounds (13) and (14), which are derivatives of phosphonate analogues of α- and β-D-ribofuranosyl phosphate, have been made by use of an appropriate Wittig reagent applied to 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose,[13] and the related phosphonate (15) has been prepared by the procedures outlined in Scheme 2.[14]

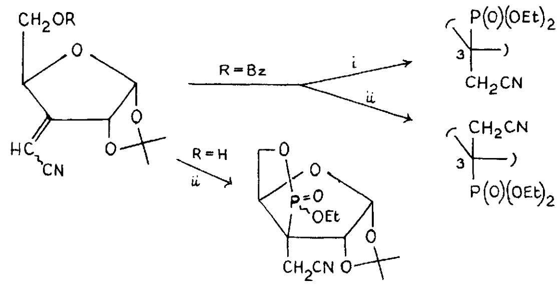


Reagents: i, $\bigcirc$-OCH$_2\overset{+}{P}$Ph$_3$Cl$^-$-BuLi; ii, H$^+$; iii, (MeO)$_2$PHO-MeONa; iv, Et$_3$N-Me$_3$SiBr; v, H$_2$O; vi, LiOH

(15)

Scheme 2

Two sets of branched-chain sugar phosphonates, having the phosphonate attached to the C-3 branch carbon, have been synthesized, one such set being illustrated in Scheme 3,[15] and a variety of compounds of this type and related phosphinates and phosphine oxides were studied by ^1H, ^{13}C and ^{31}P n.m.r. spectroscopy, which allowed determination of configuration at C-3 as well as at the asymmetric phosphorus atoms.[16]

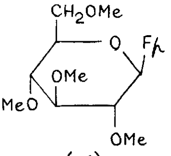


Reagents: i, $(EtO)_2PHO$-NaH; ii, $(EtO)_3P$-EtOH

Scheme 3

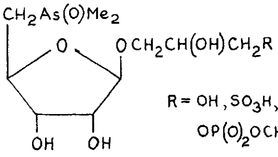
2 Other Carbon-bonded Compounds

Reaction of tetra-O-methyl-α-D-glucopyranosyl bromide with sodium (η^5-cyclopentadienyl)dicarbonylferrate gave compound (16) as a stable, crystalline solid together with minor proportions of the α-anomer.[17] The unusual arsenic-containing β-D-ribofuranosyl derivatives (17) have been isolated from brown kelp.[18]



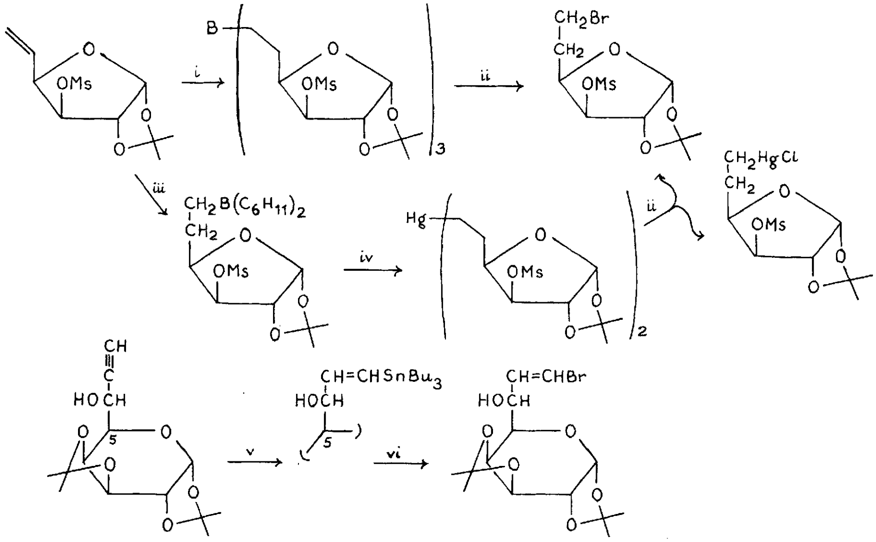
$F\lambda = (\eta^5\text{-}C_5H_5)Fe(CO)_2$

(16)



R = OH, SO_3H, OSO_3H, $OP(O)_2OCH_2CH(OH)CH_2OH$

(17)



Reagents: i, BH_3; ii, BrCl; iii, $(C_6H_{11})_2BH$; iv, $Hg(OAc)_2$; v, Bu_3SnH; vi, NaBr-chloramine T-HCl

Scheme 4

A set of sugar derivatives containing C-B, C-Hg and C-Sn bonds have been used as new means of preparing C-Br containing sugars (Scheme 4).[19]

3 Oxygen-bonded Compounds

An interesting paper on selective monobenzoylation of pento- and hexo-pyranosides before and after treatment with di- or tributyltin oxide is referred to in Chapter 7, as is the use of 3,4-_O_-stannylene derivatives of α-L-arabinopyranosides in the preparation of 3-coumaroyl esters. The brominolysis of such a derivative gave a glycosid-4 ulose from which a 4-amino-4-deoxyarabinoside was produced (Chapter 9). The X-ray crystal structure of methyl 4,6-_O_-benzylidene-2,3-_O_-dibutylstannylene-α-D-mannoside has been reported (see Chapter 22).

The regioselective enhancement of the nucleophilicity of the hydroxy groups of methyl α-L-rhamnopyranoside on complexing with tin(II) chloride has been assessed, and a tentative model for the complex formed has been proposed following analysis of the methyl ethers produced on treatment with diazomethane and catalytic tin(II) chloride.[20]

Sucrose treated with 1,3-bis(2,2-dimethylpropanoyloxy)-1,3-diethyldiborane affords the 4,6-ethylboronate and hence a route to 2,3,1',3',4',6'-hexa-_O_-acyl derivatives.[21]

A D-fructose-iron(III) complex is implicated as being the photoreactive species in the oxidative degradation of the sugar to D-_erythrose_ on photolysis in aqueous solution in the presence of iron(III) chloride.[22] A polarographic and spectrophotometric study of complexes of mannose and arabinose with Fe(III), In(III), and Hg(II) ions has been reported.[23] The X-ray crystal structure of a nickel-rhamnose complex is noted in Chapter 22, and palladium complexes of sugar phosphites are referred to in Chapter 7.

Studies of the following ionic complexes have also been recorded: Ca^{2+} with D-glucuronic acid,[24] Ca^{2+} with carbohydrates generally (geometric features),[25] Na^+, K^+, Li^+ and Ca^{2+} with sucrose,[26] H^+, Zn^{2+}, Mg^{2+} with D-fructose 1,6-diphosphate[27] and Gd^{3+} with a tetrasaccharide of glycophorin,[28] with a trigalactosyl hexapeptide,[29] and with various glycolipids.[30] Ion-specific electrodes and metallochromic indicator methods were used in an investigation of the bonding of Cd^{2+} and Cu^{2+} to oligogalacturonic acids (DP 1 → 9).[31]

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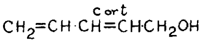
18
Alditols and Cyclitols

1 Alditols

The accumulation of sorbitol and consequent uptake of water leads to opacification of the lens, *i.e.* diabetic cataract. In diabetic rabbit lens, formation of fructose and sorbitol was enhanced, while that of *myo*-inositol decreased, relative to normal lens.[1] The following polyols have been identified in human urine for the first time: 4-deoxythreitol, 4-deoxyerythritol, 5-deoxyxylitol, 5-deoxyarabitol, 2-deoxyribitol, 6-deoxymannitol, 6-deoxygalactitol, *neo*-inositol, and *chiro*-inositol.[2] Riboflavin has been shown to be biosynthesized from two molecules of a corresponding deoxyribityl-pteridine precursor by disproportionation.[3]

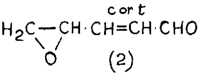
The hydrogenation of D-glucose in weakly alkaline aqueous ethanol over ruthenium on alumina,[4] and of L-arabinose and D-glucose over Raney nickel,[5] has been studied.

Approaches to the synthesis of pentitols from the pentadienols (1) or epoxypentenals (2) have been reported which depend on



$CH_2{=}CH\cdot\overset{c\ or\ t}{CH{=}CH}CH_2OH$

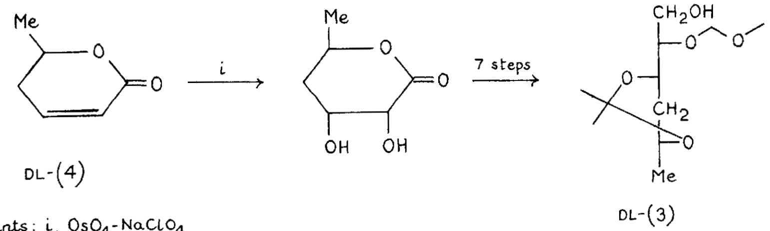
(1)



(2)

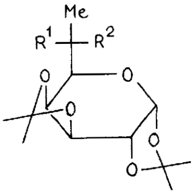
a) epoxidation of allylic double bonds followed by selective ring opening or b) *syn*-hydroxylation of these double bonds.[6] The synthesis of alditol acetate derivatives for g.c. analysis is covered in Chapter 23.

2,3,4,5-Tetra-*O*-acetyl-1-bromo-1,6-dideoxy-L-glucitol, a precursor for the side chain of (+)-anamarin, has been synthesized by conventional methods from D-gulono-1,4-lactone, *via* 2,3,5,6-tetrakis-*O*-(trimethylsilyl)-D-gulofuranose.[7] 1-Amino-1-deoxy-hexitol derivatives have been prepared by reductive amination ($NaBH_3CN$) of D-glucose, D-galactose, and D-mannose with lysine and hydroxylysine, the products being connected through the 6- rather than the 2-amino-group of the amino-acid.[8] *N*-Ethyl-1-amino-1-deoxy-D-glucitol has been obtained by reductive amination of D-glucose and ethylamine over Raney nickel.[9] 1-Amino-1-deoxy-D-glycero-L-manno-heptitol resulted from ferrous hydroxide reduction of the corresponding 1-nitro-heptitol.[10] 4,6-Dideoxy-3,5-O-isopropylidene-2-O-(methoxymethyl)-DL-glucitol (3) has been synthesized from (±)-parasorbic acid (4) (Scheme 1), and the enantiomers resolved by h.p.l.c. of their benzoates on a column packed with (+)-poly(triphenylmethylmethacrylate) on silica gel; the D-enantiomer was desired for the synthesis of the antibiotic griseusin A.[11] The C-5 epimeric 7-deoxyheptose derivatives (5) and (6), obtained in a 4:1 ratio from addition of methylmagnesium bromide to a 6-aldehydo-D-galactose precursor, have been used to prepare the deoxyheptitol (7), and the 3- and 4-carbon molecules (8) and (9) of value in the synthesis of chiral compounds.[12] The synthesis of 2-O-alkyl-D-glyceric acid derivatives from 1,3:4,6-di-O-benzylidene-D-mannitol is covered in Chapter 24.



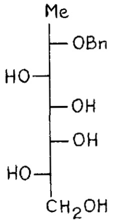
Reagents: i, OsO_4-$NaClO_4$

Scheme 1

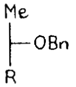


(5) $R^1 = H, R^2 = OBn$

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

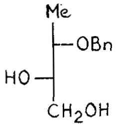


(7)



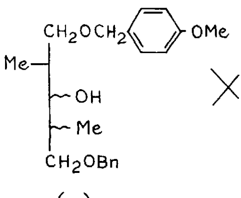
(8)

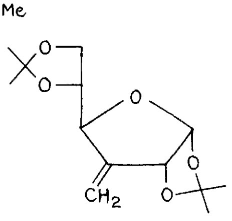
$R = CH_2OH, CHO, CO_2H$

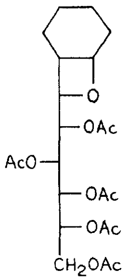


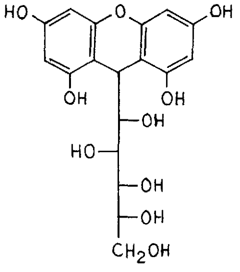
(9)

Branched-chain di-C-methylpentitol derivatives (10) with the L-xylo-, L-ribo, D-lyxo, and D-arabino-configuration, required for the synthesis of polyketide-derived natural products, have all been synthesized from the exo-methylene derivative (11).[13] Photochemical addition of cyclohexene to aldehydo-D-glucose pentaacetate gave the 8-(pentitol-1-yl)-7-oxabicyclo[4.2.0]octane derivative (12) in 65% yield.[14] The 1,1-di-C-substituted-1-deoxy-D-glucitol derivative (13) was the major product from acid-catalysed

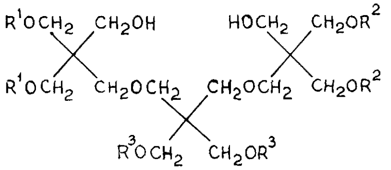

(10)


(11)


(12)


(13)

condensation of D-glucose with phloroglucinol in DMSO at 100°C, a similar derivative being obtained with phloroacetophenone.[15] The formose reaction has been modified to yield 2-hydroxymethylglycerol, 3-hydroxymethylpentitol, and 2,4-bis(hydroxymethyl)pentitol, by continuous addition of paraformaldehyde to an aqueous solution of paraformaldehyde and calcium hydroxide at pH 11.0 and 6°C.[16] Acid-catalyzed condensation of tripentaerythritol with formaldehyde led to the mono-, di- and tri-O-methylidene acetals (14), (15), and (16) in 36, 34, and 17% isolated yields.[17]



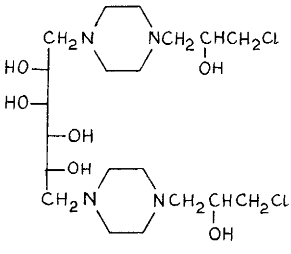
(14) $R^1,R^1 = CH_2<$, $R^2 = R^3 = H$
(15) $R^1,R^1 = R^2,R^2 = CH_2<$, $R^3 = H$
(16) $R^1,R^1 = R^2,R^2 = R^3,R^3 = CH_2<$

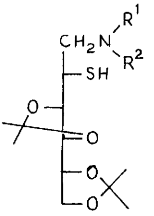
Kinetic studies on the oxidation of D-mannitol with vanadium(V) species,[18] and of D-mannitol, D-glucitol, and galactitol with cerium(VI) ions[19] and with manganese(III) pyrophosphate[20] have been reported.

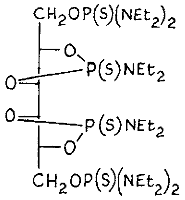
A much improved yield (92%) of the 1,2:5,6-di-O-isopropylidene acetal derivative can be obtained from D-mannitol by reaction with 2-methoxypropene/p-toluenesulphonic acid in DMF containing anhydrous calcium sulphate. The 1,2-acetal could be obtained in ca. 70% yield with the same reagents under modified conditions.[21] Cleavage of a glycosyl-alditol linkage under acetonation conditions is covered in Chapter 4.

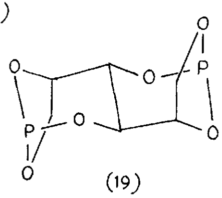
1,5-Dideoxy-1,5-dibromo-, 1,5-dideoxy-1,5-diiodo-, and 1,2:4,5-dianhydroxylitols have been synthesized by standard procedures from xylitol and used to prepare 3-O-alkyl and -acyl derivatives, required as analogues of galactose derivatives which are anti-tumour compounds.[22] Cytostatically active piperazine-containing carbohydrate derivatives have been reported, the most active derivative (17) being prepared from 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol, piperazine, and epichlorohydrin.[23]

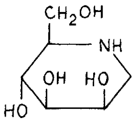
The 1-amino-2-thio-D-glucitol derivatives (18) have been obtained in moderate yields by amination of the corresponding 1,2-epithio-derivative.[24] The unusual phosphite ester (19) has been obtained from the reaction of galactitol with phosphorous trichloride (in dry dioxane at 55-60°C); further treatment with diethylamine and sulphur yielded the phosphorylated derivative (20).[25]


(17)


(18) $R^1 = H, R^2 = Bu^i$; $R^1 = R^2 = Et$


(20)


(19)

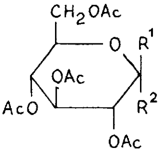

(21)

Conversion of a chiral tetritol 2,3-epoxide into a β-lactam intermediate is covered in Chapter 24.

1,5-Anhydro-D-glucitol has been isolated in 3-4% yield (dry weight basis) from leaves of *Protea* species as the major metabolite,[26] while 1,5-dideoxy-1,5-imino-D-mannitol (21) has been shown to be a potent glycosidase inhibitor.[27]

The cyclization of tetritols, pentitols, and their peracetates in hot acetic acid, both with an without protonic acid catalysts, has been investigated. On prolonged treatment, an equilibrium mixture containing all the possible 1,4- and 1,5-anhydrides was formed, and a mechanism involving acyloxonium ions has been postulated to account for the required configurational inversions.[28] Similar complex mixtures of 1,4- and 1,5-anhydrides, accompanied by mono- and di-chlorodeoxypentitols and their 1,4-anhydrides, resulted from the treatment of pentitols with concentrated hydrochloric acid at 100°C.[29] 1,4-Anhydro-erythritol and -threitol, prepared from the corresponding tetritols by acid-catalyzed dehydration, have been studied by variable temperature ^{13}C-n.m.r. methods and shown to undergo significant molecular association with water.[30]

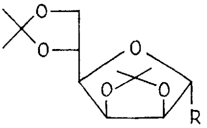
The free-radical reduction (Bu_3SnH or Bu_3SnD, initiated with azobisisobutyronitrile) of glycosyl halides is highly selective in favour of α-attack. Thus both anomers of the glycosyl chloride and bromide (22) gave a 9:1-mixture of the α- and β-deuterated derivatives (23) and (24), while the α-chloride (25) gave the α-deuterated derivative (26) exclusively.[31] Reduction of C-β-D-galacto- and -gluco-pyranosyl nitromethanes with ferrous hydroxide led to 1-amino-2,6-anhydro-1-deoxy-heptitols.[10]



(22) R^1,R^2 = H,Cl or H,Br

(23) R^1 = H, R^2 = D

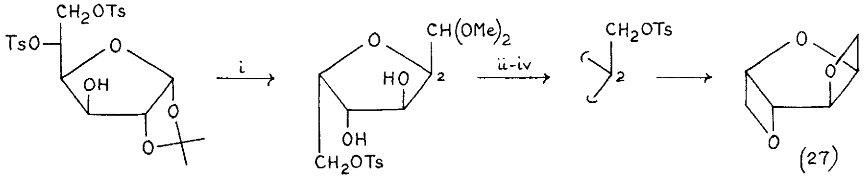
(24) R^1 = D, R^2 = H



(25) R = Cl

(26) R = D

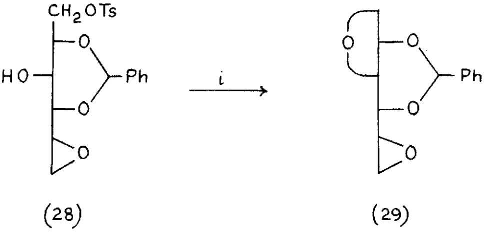
1,3:2,5:4,6-Trianhydro-L-iditol (27), the second known tri-anhydrohexitol, has been synthesized by two routes, one being shown in Scheme 2.[32]



Reagents: i, MeOH-H^+; ii, H_3O^+; iii, reduction; iv, TsCl-Py; v, MeONa-MeOH

Scheme 2

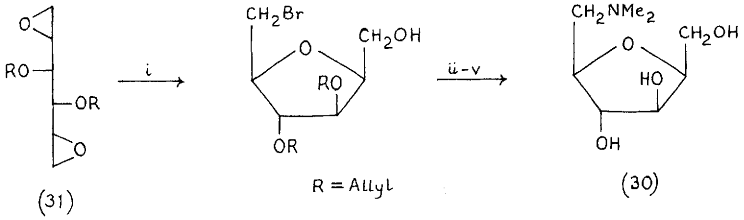
An attempt to synthesize 2,4-O-benzylidene-1-O-tosyl-D-glucitol by monitored hydrolysis of epoxide (28) led instead to products



Reagent: i, H_3O^+

Scheme 3

with a 1,3-anhydro-ring by way of the dianhydride (29) (Scheme 3). 3,5-Di-*O*-acetyl-6-*O*-benzoyl 2,4-*O*-benzylidene-1-*O*-tosyl-D-glucitol was obtained along with other products by reaction of 3,5-di-*O*-acetyl-2,4-*O*-benzylidene-1,6-di-*O*-tosyl-D-glucitol with lithium benzoate in DMF.[33] D-Mannitol has been used to prepare 1- and/or 6-amino-deoxy derivatives of 2,5-anhydro-D-glucitol. Thus, the 6-dimethylamino derivative (30) was obtained from the dianhydride (31) as shown in Scheme 4.[34]



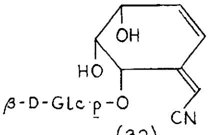
Reagents: i, HBr; ii, NaN$_3$; iii, H$_2$S-Py; iv, HCHO-HCO$_2$H; v, Pd/C

Scheme 4

References to acylated and nitro-containing anhydrohexitols are made in Chapters 7 and 10 respectively.

2 Cyclitols

Ciceritol, a new α-digalactoside of pinitol, isolated from chick pea cotyledons, has been identified as α-D-galactopyranosyl-(1 → 6)-α-D-galactopyranosyl-(1 → 2)-1D-4-*O*-methyl-*chiro*-inositol; the same structure is proposed for the component previously thought to be "manninotriose" [α-D-Gal-(1 → 6)-α-D-Gal-(1 → 6)-D-Glc].[35] α-*N*-Acetylneuraminosyl-(2 → 3)-β-D-galactopyranosyl-(1 → 1L)-*myo*-inositol has been isolated from pregnancy urine of a single donor.[36] The glucosylated cyanomethylene cyclohexenetriol (32)

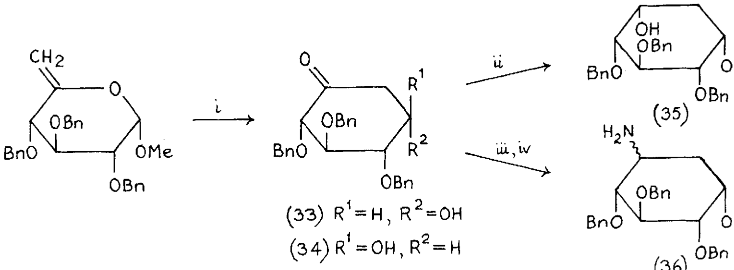


(32)

has been isolated from *Ilex warburgii* fruit;[37] lithospermoside, the C-5 epimer of (32), has been reported previously (K.Takahashi *et al.* *Chem. Pharm. Bull.*, 1978, **26**, 1677).

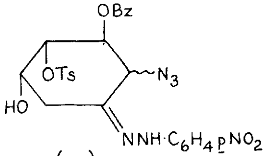
Pseudo-β-DL-glucose and pseudo-α-DL-galactose, in which a methylene group replaces the ring oxygen atom of the parent sugar, are half as sweet as sucrose, and as sweet as D-glucose.[38] The excess thermodynamic properties of aqueous myo-inositol solutions have been determined and differ remarkably from those of pyranosides.[39]

Ferrier's mercury(II) ion induced carbocyclization of hex-5-enopyranosides has been used to obtain a 3:1-mixture of the epimeric cyclohexanes (33) and (34) in 80% yield, both of which were converted into cyclitols and aminocyclitols (Scheme 5). Thus borohydride reduction of (33) led almost exclusively to diol (35), while formation and reduction of the oxime of (33) led to a 2:1-mixture of epimeric inosamines (36).[40] The epimeric 2-azido-inosose hydrazone derivatives (37) have been synthesized from a tetrahydroxycyclohexanone derivative, made available by a Ferrier carbocyclization reaction.[41]



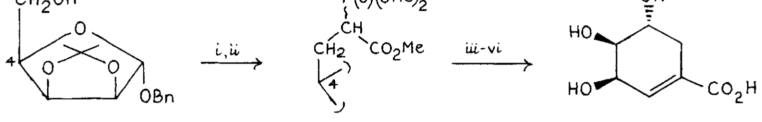
Reagents: i, $HgCl_2$; ii, $NaBH_4$; iii, NH_2OH; iv, LAH

Scheme 5



(37)

(3R,4S,5R)-Shikimic acid (38) has been synthesized from D-mannose in 25% overall yield, via the known lyxofuranoside (39) (Scheme 6); carbocyclization was effected by intramolecular Wadsworth-Emmons olefination.[42]

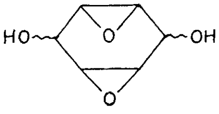


(39) (38)

Reagents: i, Tf_2O-Py; ii, $(MeO)_3P(O)\bar{C}HCO_2Me.\overset{+}{Na}$-18-crown-6; iii, H_2-Pd/C; iv, MeONa; v, Resin(H^+); vi, OH^-

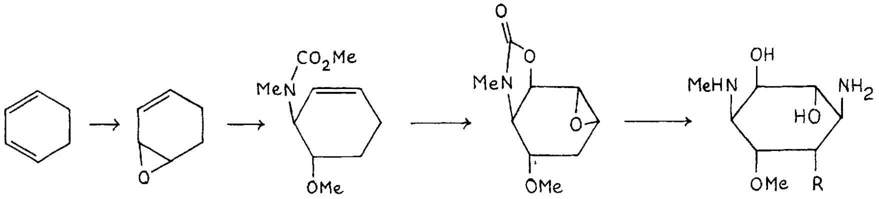
Scheme 6

Prinzbach and co-workers have synthesized the series of meso-diepoxides (40) from benzene, and have obtained from them a variety



(40)

of cis-1,4- and cis-1,3-disubstituted cyclohexanetetraols, including the meso-inosadiamines 2- and 5-epistreptamine and actinamine, by epoxide ring opening.[43] Racemic fortamine (41) and 2-deoxyfortamine (42) have been synthesized from cyclohexa-1,3-diene by multistep procedures outlined in Scheme 7.[44]

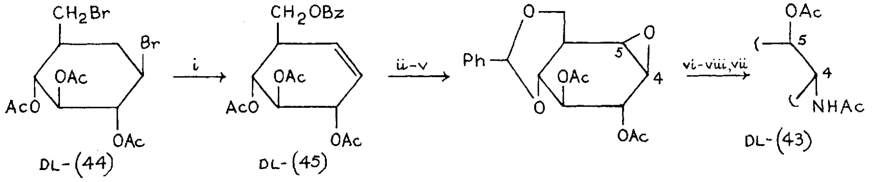


DL-(41) R = OH

DL-(42) R = H

Scheme 7

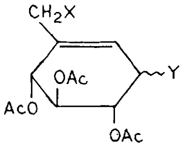
Ogawa and co-workers have continued to develop syntheses of a large number of racemic branched-chain cyclitols, many related to natural products, from a common original starting material - the Diels-Alder adduct of acrylic acid and furan (see Vol.11, p.150 and Vol.13, p.154). The structure of hydroxyvalidamine, a component of validamycin B, has been confirmed by the synthesis of its racemic hexaacetate; the racemic derivative (43) could be synthesized more efficiently, using the dibromide (44) and the cyclohexene (45) (Scheme 8).[45] Syntheses of racemic valienamine



Reagents: i, NaOBz-LiBr ; ii, MeONa ; iii, PhCH(OMe)$_2$-TsOH ; iv, Ac$_2$O-Py ; v, MCPBA ; vi, NaN$_3$-NH$_4$Cl
vii, Ac$_2$O-Py ; viii, H$_2$S-Py

Scheme 8

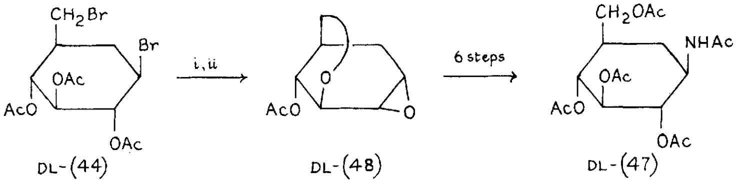
and related branched-chain aminocyclitols (Vol.14, p.148) have been published in full,[46] as have those of a large range of related unsaturated cyclitol derivatives [general structure (46)].[47]



e.g., X = Br, OAc
Y = Br, OR, OAc

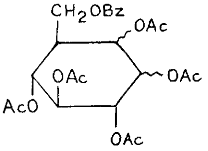
(46)

Racemic 1-epivalidamine (47) has been prepared by standard reactions by way of the dianhydride (48) (Scheme 9).[48] The racemic (hydroxymethyl)cyclohexanepentaol derivatives (49), related to chiro- and myo-inositol, have been obtained by epoxidation (MCPBA) or cis-hydroxylation (OsO_4) of alkene (45).[49] Another paper reports the conversion of the bromomethylcyclohexene (50) to epoxy [e.g., (51)] and diepoxy analogues, which are related to natural products.[50] Syntheses of racemic 2-deoxy-hydroxyvalidamine (52) and 2-deoxyvalienamine (53) have employed similar strategies start-

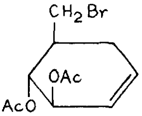


Reagents: i, MeONa; ii, Ac_2O-Py

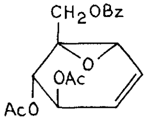
Scheme 9



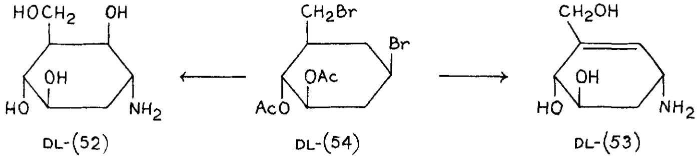
DL-(49)

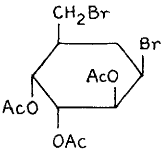


DL-(50)

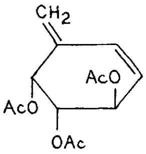


DL-(51)

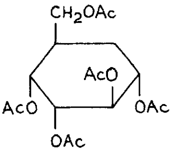




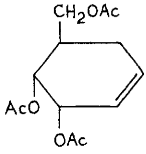
DL-(55)



DL-(56)



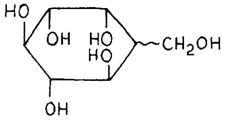
DL-(57)



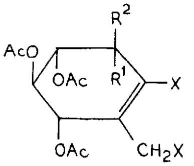
DL-(58)

ing from the dibromide (54).[51] Analogously, the dibromide (55) furnishes a range of deoxy and unsaturated inositol derivatives such as (56)-(58).[52]

The epimeric 1L-1-deoxy-1-*C*-hydroxymethyl-*myo*- and *chiro*-inositols (59) have been synthesized from an inosose derivative using a standard Wittig-hydroboration sequence to introduce the hydroxymethyl group.[53] The cyclohexenones (60) and cyclohexenes (61) have been prepared by conventional dehydration of the corresponding tertiary alcohols.[54] In elucidating the structure of the saponin 3-*O*-β-D-xylopyranosyl-6-*O*-β-D-glucopyranosylcycloastragenol, selective cleavage of glucoside was effected by conversion to glucuronoside and lead tetraacetate-induced oxidative cleavage of the permethylated derivative (see, *e.g.*, Vol.12, p.31); the cleavage product was converted to a known nitrocyclitol mixture for characterization.[55]



(59)



(60) R^1,R^2 = O, X = Cl, or OAc
(61) R^1 = OAc, R^2 = H, X = Cl, or N$_3$

The Raney nickel catalysed H-D exchange at the carbon atoms of four inositols and various *O*-methylated derivatives has been studied using ^{1}H-n.m.r. methods. The rate of exchange could be correlated with the configuration, conformation, and site of methylation of these compounds; equatorial hydrogens exchanged rapidly (<10 min at 60°), axial hydrogens more slowly (<30 min), and hydrogens *syn*-axial to a bulky substituent within *ca*. 300 min. Methylation of an adjacent hydroxy group also lowered the rate of exchange.[56]

Carbocyclic nucleoside analogues with substituted cyclopentane moieties are covered in Chapters 19 and 20.

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19
Antibiotics

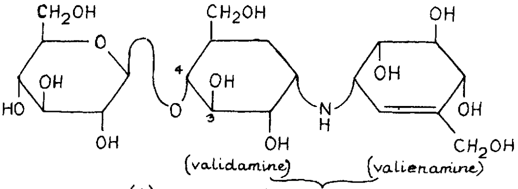
Recent developments in the synthesis of sugar-containing antibiotics have been reviewed (in Japanese).[1]

1 Amino-Glycoside Antibiotics

Reviews have appeared on the total synthesis and chemical modification of aminoglycoside antibiotics,[2] and on 1,4-diamino-cyclitol containing antibiotics (in Japanese).[3]

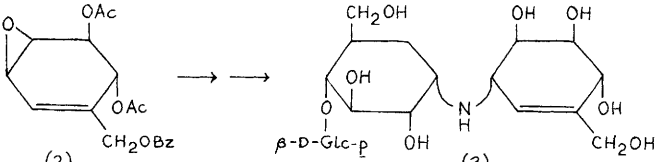
3-*O*-Demethyl-3-*O*-methanesulphonyl-fortimicin derivatives have been used to prepare 3-*O*-demethyl-2,3-di-*epi*-fortimicins A and B and 3-*O*-demethyl-3-*epi*-fortimicins A and B,[4] and also 3-amino-3-demethoxy-fortimicin A and 2-amino-3-*O*-demethyl-2-deoxy-fortimicin A,[5] using standard methods. Similarly the fortimicin analogue istamycin B has been converted to 3-*O*-demethyl and 3-demethoxy derivatives, including 5-epimers, some being more effective antibiotics than the parent.[6] Other papers describe the synthesis of 3-fluoro and 3,3-difluoro derivatives of 3-demethoxysporaricin A,[7] and of 5-deoxy-5-fluorosporaricin A,[8] by direct fluorination procedures using diethylaminosulphurtrifluoride (DAST).

Further studies by Ogawa and Suami's group have confirmed that validamycin A (1) has the D-glucopyranose residue 4-β-linked to validoxylamine A, and is not 3-linked as originally proposed. (See Vol. 14, p. 153). (±)Validamine was glucosylated at O-3[9] and O-4,[10] the latter yielding a diastereoisomer identical to a derivative from validamycin A. Validoxylamine A derived from validamycin was also reconverted to validamycin A by Koenings Knorr β-glucosylation at O-4,[11] completing the total synthesis of this



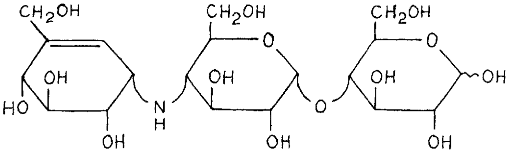
(1)

antibiotic following the synthesis of validoxylamine A reported last year. (See Vol. 16, p.190). Racemic stereo- and regio-isomers of validoxylamine A have been synthesized from validamine and appropriate brominated cyclohexene precursors.[12] Condensation of a β-D-glucosylvalidamine derivative with the racemic cyclohexene oxide (2) in an oxiran cleavage procedure has been used to prepare 6"-epivalidamycin A (3) together with its expected regioisomer.[13] The oxiran (2) has similarly been used to prepare DL-6'-epivalidoxylamine from a protected validamine derivative.[14] In another



(2) (3)

synthesis, the Japanese workers have condensed O-protected (±)valienamine with 1,6;3',4'-dianhydro-D-maltose to prepare adiposin-1 (4), a component of the adiposin α-glucosidase inhibitor complex.[15] Another paper describes the synthesis of DL-2-deoxyvalidoxylamine B (5) from (±) monomers.[16]



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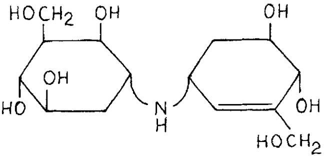
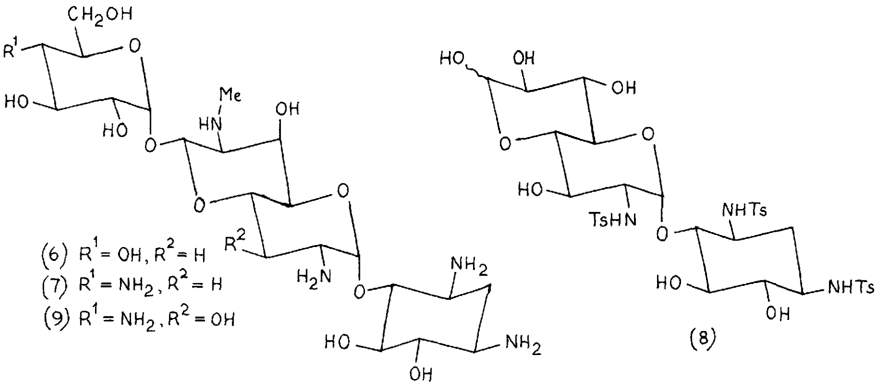


(5)

New amino-glycoside antibiotics saccharocin[17] and KA-5685,[18] isolated from strains of Saccharopolyspora, have been shown to be 4"-deamino-4"-hydroxyapramycin (6). A total synthesis of apramycin (7) has been described (26 steps, overall yield 0.08%!), starting from neamine.[19] The 4-O-(aminooctodiosyl)-2-deoxystreptamine (8), a close analogue of a component of oxyapramycin (9), has been synthesized from paromamine, elongating the glucosamine unit stereoselectively as outlined in Scheme 1.[20]

The discovery and chemical aspects of dibekacin have been reviewed.[21] The new aminoglycoside antibiotic, G-367S, produced by a strain of Dactylosporangium, has been shown to be 2'-N-formylsisomicin.

Synthetic transformations on kanamycins have included selective 2"-O-benzoylation of a partially-blocked kanamycin A under phase

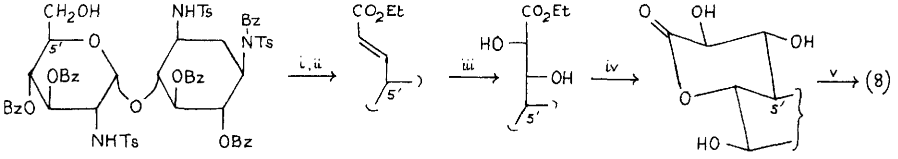


(6) $R^1 = OH, R^2 = H$

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

(9) $R^1 = NH_2, R^2 = OH$

(8)



Reagents: i, DMSO-DCC-Py-CF_3CO_2H ; ii, $Ph_3P{=}CHCO_2Et$; iii, OsO_4-Py ; iv, NaOMe ; v, LAH

Scheme 1

transfer conditions, leading to 3'-deoxy-2'-epikanamycin A;[23] the synthesis of 1-N-(2-aminoethanesulphonyl) derivatives of kanamycin, ribostamycin, and dibekacin, which show potent antibacterial activity;[24] the synthesis of 5- and 6"-monofluoro and 5,6"-difluoro-kanamycin A (using DAST);[25] the synthesis of 5-deoxy-, 5,4'-dideoxy-, 5-deoxy-5-epichloro-, and 5,4'-dideoxy-5,4'-diepichloro-kanamycin using sulphuryl chloride, the chloro-compounds being reduced ($Na-NH_3$) to give the deoxy analogues;[26] the synthesis of hexa- and hepta-deoxy (5,2',3',4',(2"),4",6") derivatives of kanamycin and amikecin, starting from 3',4'-dideoxykanamycin B, leading to antibacterial studies suggesting that the amino groups play a predominant role in kanamycin activity, and that the 2"-hydroxy group and (S)-4-amino-2-hydroxybutanoyl moiety attached at the 1-amino group markedly augment activity;[27] the synthesis of 3'-deoxykanamycin B (tobramycin);[28] the synthesis of 4"-epi-kanamycin A derivatives by sulphonate displacement reactions, with concomitant formation of 4",5"-unsaturated and 3",4"-cyclic urethane by-products;[29] and the synthesis of 1-epikanamycin A, the inversion being carried out by peroxide-tungstate oxidation of the amino-group to the corresponding oxime with subsequent catalytic hydrogenation of this intermediate.[30] Kanamycin A has also been converted biologically to amikacin by a mutant strain of butirosin-producing Bacillus circulans (amidation using L-α-hydroxy-γ-aminobutyric acid).[31]

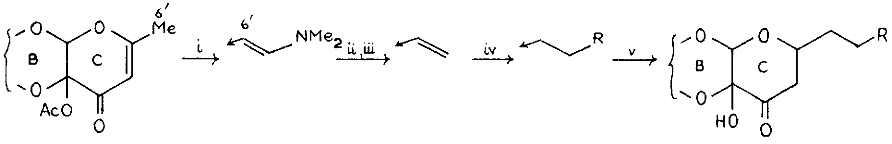
Gentamicin C_2 has been converted to 1-deaminogentamicin C_2 (by the sequence R-NH$_2$→R-NHCHO→R-N≡C→RH), and shown to be a less effective antibiotic than the parent compound.[32]

The conversion of the 6'- and 6'''-amino groups in neomycin B to hydroxy groups has been reported (by diazotization);[33,34] again, some loss of antibacterial activity results.

Studies using ^{1}H and ^{14}C-labelled D-glucose have shown that in the biosynthesis of neomycins by S. fradiae, both the C-6 hydrogens were retained at C-2 in the 2-deoxystreptamine moiety, thereby eliminating myo-inositol-1-phosphate as a possible intermediate; an alternative mechanism was proposed.[35] Similar studies have indicated that the 6-amino group in the neosamine C moiety is introduced by an oxidation-transamination sequence,[36] and a stereochemical study of this process in the formation of neosamine C in ribostamycin indicates that the retained proton at C-6 is inverted in the product.[37] A study of the conversion of neamine to the corresponding 3',4'-dideoxy-3'-unsaturated pseudo-disaccharide suggested that radical elimination of its 3',4'-bis(methylxanthate) diester was the best method; the product was then used to prepare gentamine C_{1a}.[38] The synthesis of a 2,4,2',6'-tetraamino-isomaltoside related to neamine is mentioned in Chapters 3 and 9.

5''-Deoxy-5''-fluoro-lividomycin has been prepared using the DAST reagent as a lividomycin derivative.[39]

A series of 6'-alkylated spectinomycin analogues have been prepared as indicated in the sequence shown in Scheme 2; increasing lipophilicity of the 6'-substituent increased bacterial potency.[40]



Reagents: i, Me$_2$NCH(OMe)$_2$-DMF; ii, NaBH$_3$CN; iii, MeI-KHCO$_3$; iv, RMgX-Cu$_2$Br$_2$; v, H$_2$-PtO$_2$-Pr^{i}OH-NEt$_3$

R = C_1, C_2, C_4, C_7 and C_{10}

Scheme 2

A one-pot tritiation procedure for aminoglycoside antibiotics has been reported, involving hypochlorite oxidation of the amino groups and sodium borotritiide reduction of the resulting imino groups.[41]

A study of the conformations of fortimicins from n.m.r. and X-ray data has been reported, which indicates that the chair form of the fortamine ring in fortimicin A is inverted in the fortimicin B free base; the relative orientation about the glycosidic bond was also investigated, and the implications of the results for the three-dimensional structure-activity relationships of amino-glycoside antibiotics were discussed.[42]

The FAB mass spectrum of gentamycin sulphate has been reported,[43] and the FD mass spectra of eleven aminoglycosides, including neamine and kanamycin A.[44] H.p.l.c. analyses have been reported for sisomicin[45] and amikacin.[46]

2 Macrolide Antibiotics

Takacidin and antibiotic U-0142 have been shown to be identical with monazo-mycin, a 48-membered lactone ring macrolide with α-D-mannose attached.[47] A further study on desertomycin (originally reported in 1958) has shown that this antibiotic also contains mannose linked to a large-ring macrolide.[48] Candidoin, a component of the candiden antibiotic complex produced by S. viridoflavus, has been shown to be a macrolide with mycosamine and 2,6-dideoxy L-erythro-hexopyranos-3-ulose separately attached, (the first reported occurrence of the latter sugar).[49] The structures of mycinamycin VI and VII, minor components of the mycinamycin complex (see Vol. 14, p. 157), have been determined; the 6-deoxy-2,3-di-O-methyl-D-allose (mycinose) residue is unmethylated in mycinamycin VI, and is lacking altogether in mycinamycin VII.[50]

The isolation of methyl β-D-cymaroside from the methanolysis of cytovaricin has served to assign the absolute configuration of this antibiotic.[51] Chimeramycins, new macrolide antibiotics, have been synthesized by the new technique of hybrid biosynthesis, which utilizes enzyme inhibitors; this allows the conversion of the aglycone protylonolide to chimeramycin A and B, (containing forosamine and mycarosyl-mycaminose as carbohydrate sidechains) by a spiramycin producing strain of S. ambofaciens, which is prevented from synthesizing aglycone de novo.[52] Use of ^{13}C- and ^{14}C-labelled L-methionine has demonstrated that this amino-acid is the source of the N-methyl groups in forosamine and mycaminose and the C-methyl group in mycarose in the biosynthesis of Spiramycin I.[53] Neospiramycin I, the de-mycarose derivative of spiramycin, forms the expected O-3 and O-4' acetals with dihydrofuran and dihydropyran.[54]

A pathway has been proposed for the biosynthetic hydroxylation and glycosylation of tylactone to give the antibiotic tylosin (contains mycinose and mycarosyl-mycaminose carbohydrate units).[55]

Amadori rearrangement in the reaction of D-glucose with polyene macrolide antibiotics containing mycosamine, e.g. nystatin, yield N-(1-deoxy-D-fructos-1-yl) derivatives, which on acid hydrolysis yield the fructosyl-mycosamine disaccharide.[56]

3 Anthracycline Antibiotics

The papers given at a symposium devoted to anthracycline antibiotics have been published.[57]

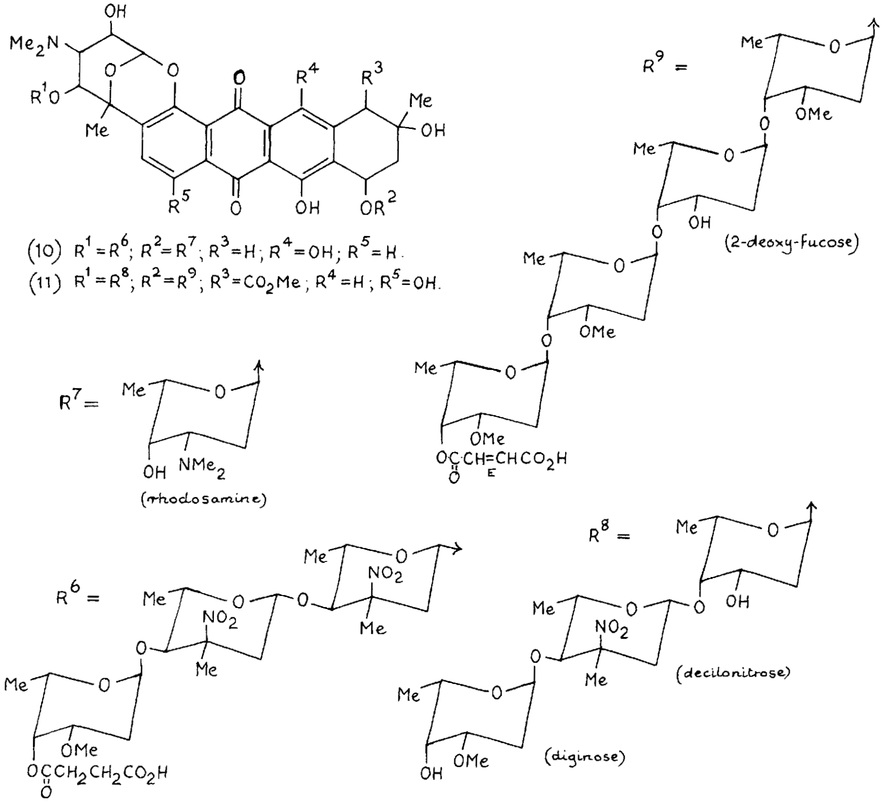
More anthracycline antibiotics containing complex oligosaccharide structures have been discovered. Decilorubicin (10), has been isolated from a strain of S. virginiae;[58] the constituent decilonitrose, (the 4-O-demethyl, 3-epi analogue of evernitrose) and 4-O-succinoyl-L-diginose units have been characterized, and the former synthesized from a 2,6-dideoxy sugar prepared from L-rhamnose, using the aziridine route described for evernitrose by Yoshimura's group. (See Vol. 13, p. 127).[59] Arugomycin (11), obtained from a strain of S. violochromogenes, contains two oligosaccharide chains.[60]

The ditrisarubicins A, B, and C, contain two trisaccharide chains, each linked by rhodosamine to β-rhodomycinone; all contain the cinerulose B-2-deoxyfucose terminal disaccharide unit (12); the other unit is either the same (B form) or the variants (13) (A form) or (14) (C form), which also occur in aclacinomycin.[61]

N-formyl daunosamine occurs in the new antibiotic, N-formyl-13-dihydrocarminomycin, obtained from Actinomadura roseoviolacea.[62]

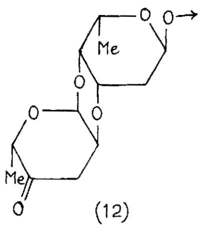
2-Hydroxyaclacinomycin A has been prepared by chemical glycosidation of 2-hydroxyaklavinone using a trisaccharide precursor in a Koenings-Knorr procedure.[63] Carminomycine analogues containing aminodeoxy L-lyxo-hexofuranosyl units of daunosamine have been synthesized. Standard procedures were used to prepare 3-azido-2,3,6-trideoxy and 3,5-diamino-2,3,5,6-tetradeoxy sugar derivatives, the latter showing a better therapeutic index than carminomycine.[64]

Anthracycline analogues have been prepared by coupling dauno-



(10) $R^1 = R^6$; $R^2 = R^7$; $R^3 = H$; $R^4 = OH$; $R^5 = H$.

(11) $R^1 = R^8$; $R^2 = R^9$; $R^3 = CO_2Me$; $R^4 = H$; $R^5 = OH$.



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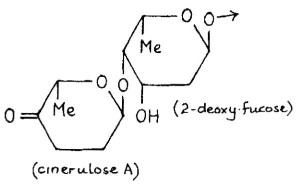

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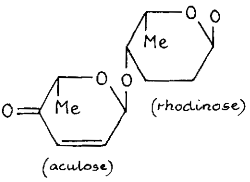


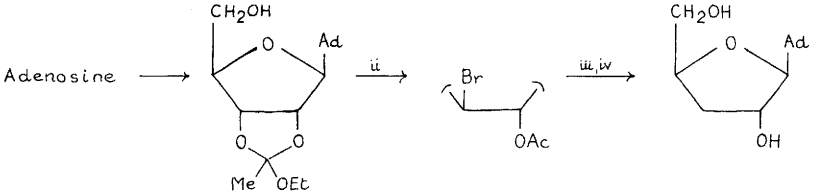
(14)

mycinone with 1-chloro-4-C-methyl-daunosamine[65] or 4-O-methyl or 4-deoxydaunosamine[66] derivatives, leading to doxorubicin analogues, showing useful, and in some cases, improved cytotoxic activity. Carminomycinone has also been coupled with 3-azido-3-deoxy- and 3,5-diazido-3,5-dideoxy-glycosyl chlorides.[67]

4 Nucleoside Antibiotics

An extensive review on the chemistry of nucleoside antibiotics has been published.[68]

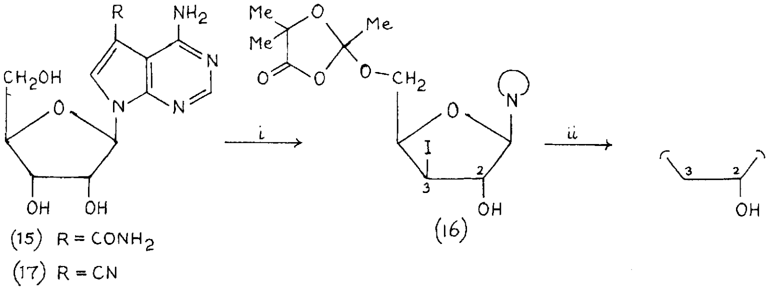
An improved 4-stage synthesis of 3'-deoxyadenosine (cordycepin) from adenosine has been described, giving a 38% overall yield. (Scheme 3).[69]



Reagents: i, $MeC(OEt)_3$-H^+; ii, AcBr ; iii, Bu^n_3SnH – 2,2'-azobis[2-methylpropionitrile]; iv, NH_3-MeOH

Scheme 3

A different approach has been used to convert sangivamycin (15) to 3'-deoxysangivamycin via the intermediate (16) (Scheme 44); toyocamycin (17) was also converted to 2'-deoxysangivamycin via 6,2'-S-cyclo-2'-thiosangivamycin and the 5'-deoxy analogue prepared from sangivamycin via 5'-phenylthio-5'-deoxysangivamycin. Of these

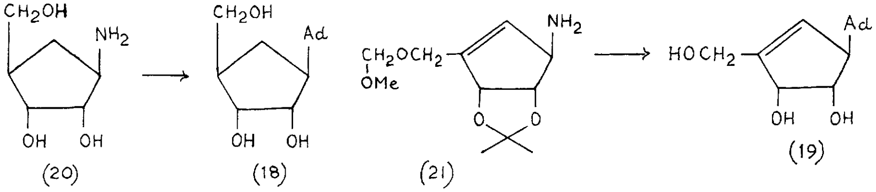


Reagents: i, NaI-α-acetoxyisobutyryl chloride ; ii, H_2-Pd

Scheme 4

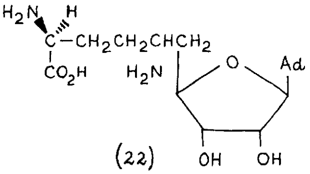
analogues, only the 3'-deoxy compound showed any anti-leukaemic activity.[70] Tubercidin (15, R = H) has been converted to toyocamycin using standard reactions.[71]

The carbocyclic nucleoside analogues (-) aristeromycin (18) and neplanocin A (19) have been synthesized from the Diels-Alder adduct of cyclopentadiene and dimethyl acetylene dicarboxylate using a combined chemical and enzymatic strategy. Pig liver esterase enantioselectively hydrolysed a diester intermediate to give the acid-ester in good optical yield, leading to the intermediates (20) and (21).[72]

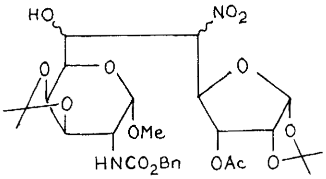

(20) (18) (21) (19)

2'-Deoxyneplanocin A has been synthesized from either 2'-bromo-2'-deoxy or 2'-imidazolylthiocarbonyl precursors using tributylstannane. Similar treatment of a 2',3'-cyclicthiocarbonate precursor led to 3'-deoxyneplanocin A regiospecifically, the allylic ester oxygen being displaced.[73] Full details of the synthesis of 2'-substituted-2'-epimers of neplanocin A and arabinofuranosyladenine analogues have been published. (See Vol. 15, p. 188).[74]

A synthesis of sinefungin (22) proceeded from a condensation of N^6-benzoyl-2',3'-*O*-isopropylidene-adenosine 5'-aldehyde with nitromethane, the nitroaldol then being reduced to the corresponding 5',6'-dideoxy-6'-nitro derivative, which was further condensed with an L-aspartic acid derivative leading to (22) and its 6'-epimer.[75] The synthesis of pyrazofurin and related compounds from ribosyl β-keto acid derivatives has been reported,[76] and a promising approach to the synthesis of sinefungin involves the transglycosylation of a precursor prepared from uridine, using 6-*N*-acyladenine as the transfer base.[77] The final steps in the biosynthesis of herbicidins (analogues of nucleoside antibiotics) have been investigated.[78]


(22)

Condensation of appropriately substituted 2-amino-2-deoxy-D-galactodialdose with 5-deoxy-5-nitro-D-xylofuranose gave the intermediate (23), which was then transformed to the tunicamine derivative (24).[79]



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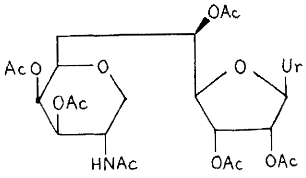
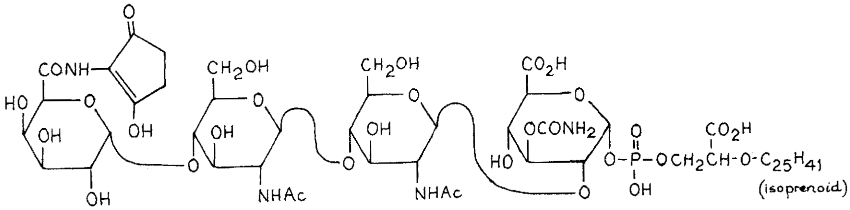


(24)

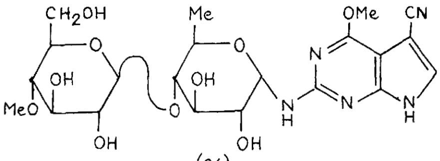
5 Miscellaneous Antibiotics

The structure of moenomycin A (see Vol. 15, p. 191) has been confirmed by ^{13}C n.m.r. and FAB-m.s.[80] A structural analogue of the glucuronyl phospholipid unit of moenomycin A has been synthesized by linking a D-glucosyl phosphate derivative to 2-O-(lipid substituted)glyceric acid, the last step involving catalytic oxidation to the uronic aicd.[81] Pholipomycin, a new phosphoglycolipid antibiotic closely related to moenomycin, has been assigned the structure (25).[82]



(25)

A new pseudo-nucleoside antibiotic, dapiramicin A, has been characterized as the disaccharide derivative (26).[83] Miharamycins A and B have the pseudo-nucleoside structure (27).[84] Spicamycin, which induces differentiation in human promyelocytic leukaemia cells, has the structure (28);[85] it was shown to be the 2'-epimer



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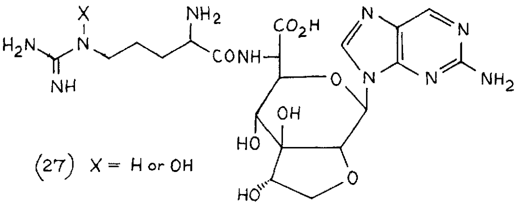
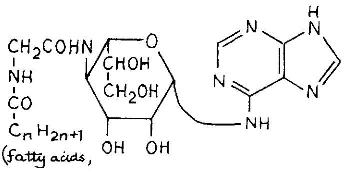


(27) X = H or OH



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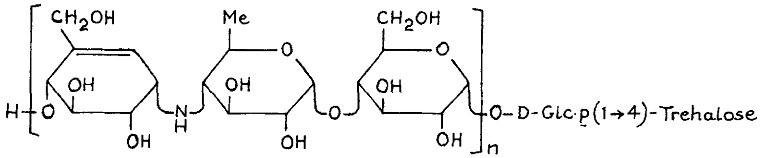
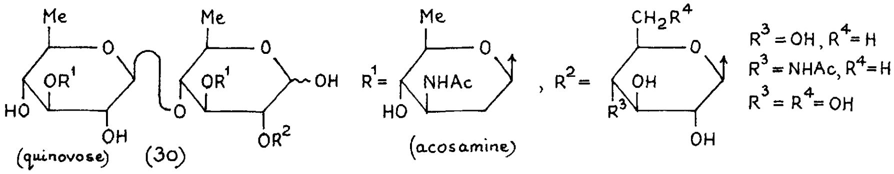


(29) n = 1-3

of the sugar characterized as a component of septacidin (H. Agahigian et al., J. Org. Chem., 1965, 30, 1085).

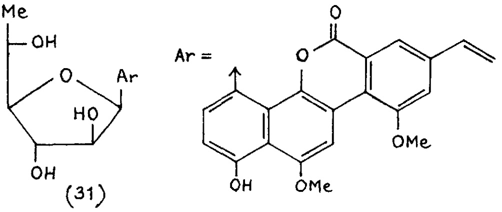
Trestatins A, B, and C, new α-amylase inhibitors, are basic oligosaccharides (29) containing 1-3 units of a trisaccharide linked to trehalose through glucose.[86]

Aqueous ammonium hydrolysis of N-acetyl-sporaviridin released three pentasaccharides, summarized in structure (30).[87]



(30)

An antibiotic (31) isolated from a Streptomyces sp. has been shown to be identical with toromycin and gilvocarcin V, (see Vol. 15, p. 192). On acid-catalysed isomerization, a mixture of C-α and β-fucofuranosides and C-β-fucopyranoside was obtained, which



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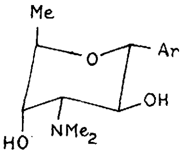
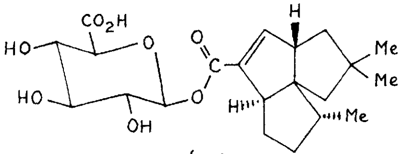


(32)

was analysed by quantitative proton n.O.e. and T_1 n.m.r. measurements on their per-acetates.[88] There has been another report on the closely related *C*-glycoside antibiotic, ravidomycin (32) (obtained from *S. ravidus*), which contains the novel amino sugar ravidosamine (3,6-dideoxy-3-dimethylamino-D-altropyranose) linked to the same aglycone present in toromycin and gilvocarcin.[89] (See also Vol. 15, p. 45). Simple derivatives of this antibiotic have also been described.[90]

Degradation of the avoparcin complex, a glycopeptide antibiotic mixture related to vancomycin and ristocetin, has yielded a variety of carbohydrate derivatives, including oligosaccharides containing β-D-glucose, α-L-ristosamine, α-D-mannose, and α-L-rhamnose.[91]

Lipiarmycin, a chlorine-containing antibiotic from *Actinoplanes deccanensis*, shows spectral evidence for 2-*O*-methyl- and 5-*O*-methylrhamnopyranose units, and methanolysis yielded methyl 2-*O*-methyl-4-*O*-homodichloro-orsellinyl-β-rhamnopyranoside.[92] In a study on the biosynthesis of pentalenolactone in *S*. strains, deoxypentalenylglucuron (33) was isolated, showing some antitumour activity.[93] A new glycopeptide antibiotic from an *S. hygroscopicus* subspecies has been shown to contain glucose.[94]



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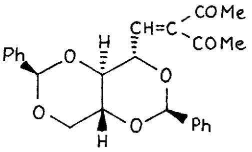

(34)

The formation of the disaccharide glycoside in a first step has led to an improved synthesis of bleomycin.[95]

Condensation of 2,3;4,5-di-*O*-benzylidene-D-ribose or related *aldehydo*-D-ribose or -D-glucose derivatives with a number of active methylene compounds, *e.g.*, pentane-2,4-dione, gave the expected Knoevenagel condensation products, which all showed antiviral activity and cytotoxicity; the most effective against herpes simplex virus was the ribose-2,4-pentanedione derivative (34); titanium tetrachloride was an efficient catalyst for the condensation step (Lehnert's conditions).[96]

The biosynthesis of streptonigrin has been shown to incorporate twelve carbon atoms from three molecules of D-erythrose (1-^{13}C labelled).[97]

The structure determination of sakyomicin containing

2,3,6-trideoxy-D-*threo*-hexose is mentioned in Chapters 12 and 22; n.m.r. spectral studies of pentasaccharide fragments from N-acetylsporaviridin are referred to in Chapter 21, and C.I.m.s. studies on permethylated viridapentaoses is covered in Chapter 22.

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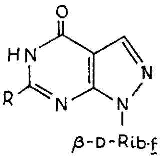
20
Nucleosides

1 General

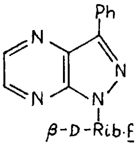
Theophylline-9-β-D-glucopyranosyl 6'-monophosphate has been isolated from Cicer arietinum; this is the first example of a naturally occurring theophylline nucleoside derivative.[1] $\underline{N}^6$-(2-hydroxyethyl)adenosine has been isolated from the mycelia of Cordyceps and Isaria fungi, and identified as a calcium antagonist and an inotropic agent.[2] 5-Ribosyluracil (pseudouridine) accumulates in germinating seeds and seedlings of Phaseolus vulgaris.[3] The growth inhibition of E. coli by nucleoside analogues has been studied. Very high antibacterial activity was observed with most derivatives of 5-fluorouridine, including 2'- and 5'-deoxy analogues and the arabinosyl equivalents; by contrast, similar derivatives of cytosine or adenosine show little or no activity.[4]

2 Synthesis

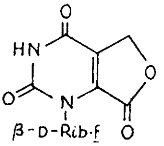
Standard condensation procedures have been used to synthesize β-D-ribofuranosyl derivatives of 5-fluorocytosine,[5] a variety of substituted pyridazines,[6] pyrazolo[3,4-d]pyrimidines (8-aza-7-deazapurines),[7,8] e.g. the guanosine analogues (1), 8-aza-2-fluoroadenine,[9] N-(3-methyl-but-2-enyl)-7-deaza-adenine,[10] 7-deazaguanine,[11] 6,7-disubstitutedbenzimidazoles,[12] the pyrazolo-pyrazine (2), including the β-D-glucopyranosyl analogue;[13] and the furo[3,4-d] pyrimidine derivative (3).[14] The α-nucleoside of 5,6-dimethylbenzimidazole has also been reported.[15] The imidazole nucleoside (4) has been elaborated from a ribosylimino-acetate precursor.[16] Arabinofuranosyl derivatives have also been described for 7-deazaguan-



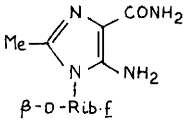
(1) R=H or NH$_2$



(2)



(3)



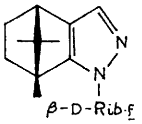
(4)

ine (both α,β forms),[17] guanine,[18] substituted-pyrazoles and -1,2,4-triazoles (α anomers) including an analogue of virazole,[19] 7-deaza-6-thiomethylpurine,[20] and 2-nitroimidazole.[21] This last paper also reports the preparation of α and β forms of D-*erythro*-hexenosyl nucleosides and 2-tetrahydrofuranyl derivatives of this base, using several methods. Ribo-nucleosides have also been converted to corresponding arabino nucleosides by sequential oxidation reduction at C-2 or 3',5'-*O*-1,1,3,3-tetraisopropyl-disiloxy derivatives.[22] *N*-D-Glycopyranosyl-3-methyl-pyrazol-5-ones have been prepared from L-arabinose, D-xylose, and D-galactose,[23] and an *N*-β-D-glucopyranosyl derivative of imidazole-3,4-dicarboxamide.[24] Glycosyl isothiocyanates prepared from standard disaccharides have been cyclized with acylhydrazines to give the corresponding 1,2,4-triazol-3-thione derivatives; other heterocyles were elaborated by condensation of these isothiocyanates with 6-amino-1,3-dimethyluracil and chloromethylammonium chloride.[25] (β-D-Ribofuranosyl)-4,7-methano-imidazoles have been prepared by condensation of a ribosylhydrazine derivative with an enone derived from camphor, leading to the analogue (5).[26]

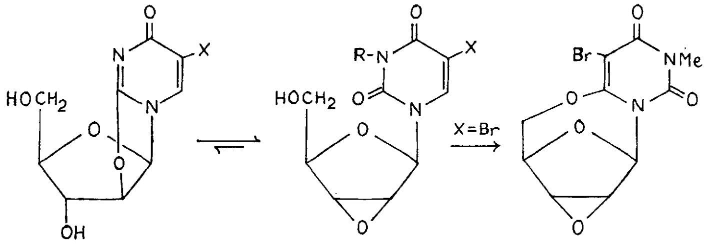
3 Anhydro-and Cyclo-Nucleosides

The base-induced equilibrium between the 2,2'- and the 2',3'-anhydronucleosides (6) and (7) (R=H) respectively is upset by N-methylation, which yields the latter derivative (7) (R=Me); under more vigorous methylating conditions, the 5-bromo analogue yielded the 2',3':5',6-dianhydride (8). Under acidic conditions, O-2 participation occurs in the cleavage of oxiran (7), leading either to arabino-nucleosides or to 2'-substituted-ribo-nucleosides, depending on the reagent.[27]

Reaction of 6,2'-*O*-cyclo-uridine with fluorine in acetic acid yielded the difluoro-2',5'-acetal (9); the corresponding 6,3'-*O*-

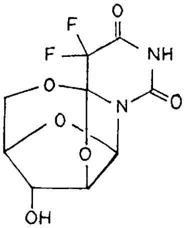


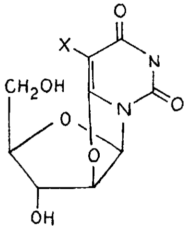
(5)



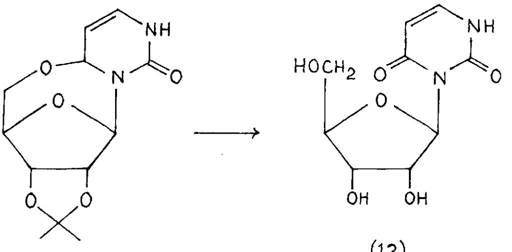
(6) X=H,Br (7) (8)

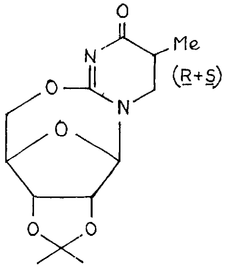
cyclo-uridine yielded the isomeric difluoro-3',5'-acetal.[28] Other halogens or *N*-halo-succinimides yielded a mixture of analogous dihalo-acetals together with 5-halogeno-6,2'-*O*-cyclouridines (10),


(9)

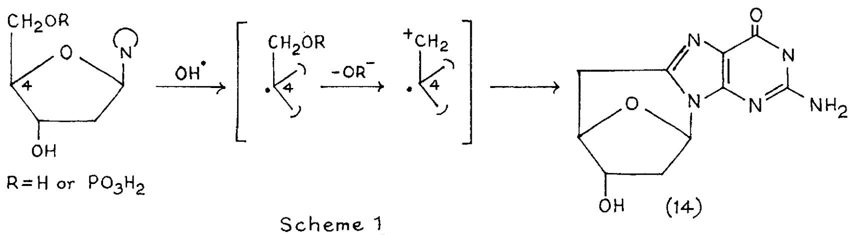

(10) X = Cl, Br, I

and corresponding mixtures resulted from 6,3'-*O*- and 6,5'-*O*-cyclo-uridines.[29] Derivatives of the bridged nucleosides 6,5'-cyclo-5'-deoxyuridine, 6,5'-cyclouridine, 6,3'-methylene-cyclo-2',3'-dideoxyuridine, and 6,2'-ethylene-cyclo-2'-deoxyuridine, have been reported. These all have the pyrimidine ring locked in the *anti*-conformation.[30] The ribo-nucleoside obtained from 1,2-dihydro-pyrimidin-2-one gives a 6,5'-anhydro-isouridine derivative (11) in aprotic solvents, which could be selectively oxidized *o*-chloro-anil), leading to 3-*O*-β-D-ribofuranosyluracil (isouridine) (12).[31] 2,5'-Anhydro-2',3'-*O*-isopropylidene-5-methyl-uridine on hydrogenation over a rhodium catalyst yielded a mixture of 5,6-dihydro, 5(R and S)methyl derivatives, separated as 5-*O*-benzoyl derivatives, which were converted to the corresponding 6,5'-anhydro derivatives (13) by a standard 5'-OTs→5'-I→(13) sequence.[32] γ-Irradiation of 2'-deoxyguanosine or its 5'-monophosphate in deoxygenated aqueous


(11) (12)


(13)

solution gave 8,5'-cyclo-2',5'-dideoxyguanosine (14); initial hydrogen abstraction from C-4' was proposed (Scheme 1), leading to (14) amongst a complex mixture of products.[33]

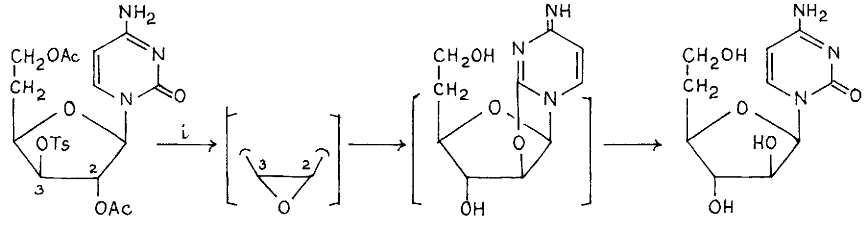


(14)

Scheme 1

4 Deoxy-nucleosides

Standard condensation procedures have been used to prepare 7- and 9-(6'-deoxy-α-L-talofuranosyl) derivatives of hypoxanthine, guanine, and 6-thio-purine,[34,35] the derivatives of the last purine showing marked antitumour activity. 2-Deoxy-D-ribofuranosyl chloride condensed with N-trimethylsilyl-4-carboxymethyl-5-cyanomethylimidazole in presence of stannic chloride (best catalyst tried) gave α- and β-forms of the N-1 and N-3 substituted nucleosides, which were converted to corresponding derivatives of 3-deazaguanine.[36] Likewise 2'-deoxytubercidin has been prepared from a 7-deazaadenine derivative.[37] Two routes to 4'-homoara-C (15) have been examined, using conventional procedures from either a 3,5,6-tri-O-tosyl-D-allofuranose derivative or a 5-deoxy-D-xylo-hexofuranose derivative, the latter providing the efficient epimerization sequence in one step shown in Scheme 2.[38] 2,6-Dideoxy-L-lyxo-hexofuranose has been converted to 7- and 9-substituted hypoxanthine nucleosides.[39] 3'-Deoxyadenosine, an antibiotic, has been prepared by an improved four-

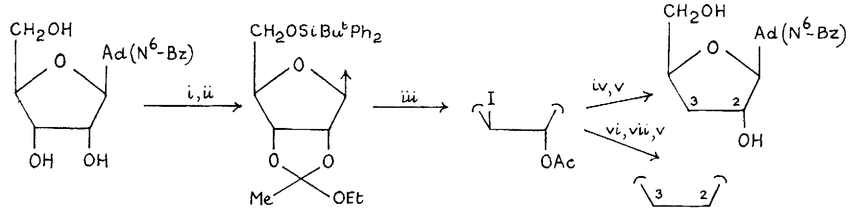


Reagents: i, NaOH-MeOH

(15)

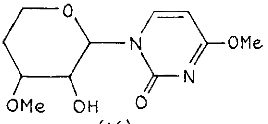
Scheme 2

step procedure in 38% overall yield from adenosine (see Chaper 19, ref. 69); the sequence modifies an ethyl orthoacetate procedure described earlier by J.Engels outlined in Scheme 3, which yielded 3'-deoxy and 2',3'-dideoxy derivatives of N-benzoyladenosine.[40] 4-Deoxy-β-DL-erythro- and threo-pentopyranosyl pyrimidine nucleosides (16) have been synthesized using the appropriate sugar 1,2-



Reagents: i, Bu^tPh_2SiCl-Py; ii, $(EtO)_3CMe$-H^+; iii, NaI-$BF_3 \cdot Et_2O$; iv, Bu_3SnH; v, Bu_4NF; vi, e^--Hg; vii, H_2-Pd(SiO_2)

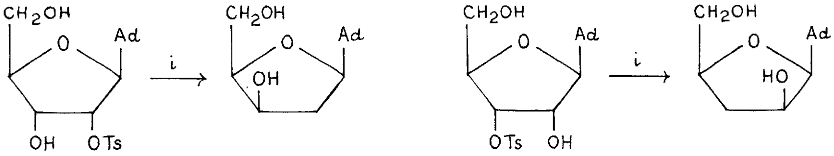
Scheme 3



(16)

anhydride with 2,4-dimethoxypyrimidine.[41] The disiloxy-protected nucleosides mentioned above have also been used to prepare corresponding 2'-deoxy derivatives by conventional deoxygenation procedures.[22] 2',3'-Dideoxy analogues of standard nucleosides have been obtained by C-3' deoxygenation of 2'-deoxy-5'-O-methoxytrityl nucleosides by treatment of their methylxanthate esters with tributyl stannane.[42] Likewise phenyl-thiono-carbonate ester intermediates of nucleosides have been reduced by tributylstannane to yield 3'-deoxy nucleoside analogues.[43]

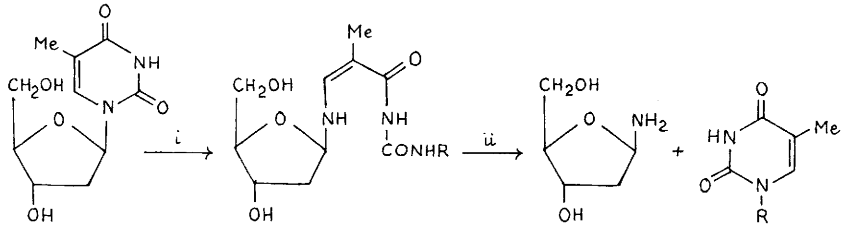
Efficient deoxygenation of 2'- or 3'-O-tosyl-adenosine with concomitant adjacent epimerization to yield threo-deoxypentose derivatives on treatment with lithium triethylborohydride (Scheme 4); stereospecific reduction of keto-sugar intermediates explains the observed epimerization.[44]



Reagents: i, $LiBHEt_3$-DMSO

Scheme 4

Thymidine undergoes heterocyclic ring cleavage on photolysis in presence of primary amines and sodium bicarbonate, yielding a substituted glycosylamine which fragments on heating to give 2-deoxy-D-erythro-pentosylamine (Scheme 5).[45] The conversion of the nucleoside antibiotic sangivamycin to its 3'-deoxy analogue is mentioned in Chapter 19.



Scheme 5

5 Halo-Nucleosides

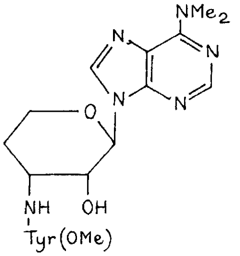
2',5'-Dibromo- and 2',5'-dichloro-2',5'-dideoxy derivatives of uridine and 5-substituted uridines have been obtained by treatment of the nucleosides with the appropriate Vilsmeier reagent; a 2,2'-anhydronucleoside intermediate was postulated to account for the observed retention of configuration at C-2'.[46] 5'-Bromo-5'-deoxy derivatives of ara-uridine and ara-cytidine have been obtained by cleavage of 2',5'-anhydro-nucleoside precursors with hydrogen bromide in DMF.[47]

2-Deoxy-2-halogeno-arabinosyl bromides have been used to prepare halo-nucleosides from 5-substituted-uracil or -cytosine bases leading to 2'-bromo, 2'-chloro, and 2'-fluoro-arabino-nucleoside analogues; the 2'-fluoro analogues were most effective as anti-viral agents.[48] These last analogues have also been prepared by an improved condensation procedure.[49]

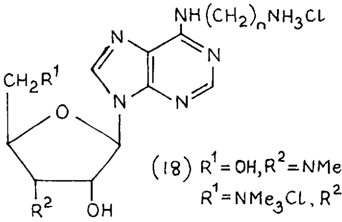
6 Amino- and Nitrogen-substituted Nucleosides

3'-Azido and 3'-amino analogues of 2'-deoxy-5-substituted uridine and cytidine, together with 3'-amino-5'-fluoro-thymidine, have been prepared by standard procedures using 3'-O-mesyl ester intermediates; the most active anti-cancer compounds were the 3'-amino-5-fluoro analogues of 2'-deoxyuridine and 2'-deoxycytidine and the 3'-amino analogue of 2'-deoxycytidine.[50,51] An alternative double-inversion sequence at C-3' using a 3'-chloro-3'-deoxyxylo-nucleoside intermediate has been described for the preparation of 3'-amino analogues of thymidine, 2'-deoxyuridine, and 2'-deoxy-5-iodouridine.[52] Methyl 2,3-anhydro-4-deoxy-αβ-DL-*erythro*-pentopyranosides have been used to prepare the pyranose analogues (17) of puromycin; a better yield was obtained if the purine base was coupled to the sugar before the latter was animated rather than as a last step.[53] Bis-(trimethylammonio) analogues (18) of adenosine have been reported.[54] The 8,5'-N-cyclonucleosides (19) of 5'-amino-5'-deoxyadenosine have been prepared by a sequence from 8-bromo-adenosine as shown in Scheme 6.[55]

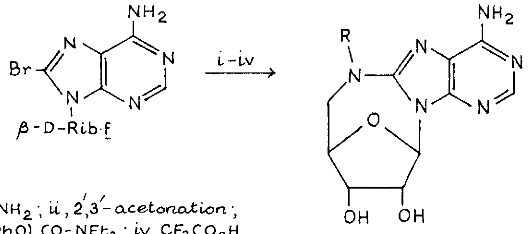
Nitromethane condensation with the dialdehyde obtained from periodate-oxidized uridine yields a crystalline 3-deoxy-3-nitro-β-D-glucopyranosyluracil contaminated by the D-galacto isomer; their 4',6'-O-benzylidene derivatives could be separated however.[56] 6'-Nitro derivatives of 5'-alkylated-adenosines are mentioned in Chapter 10.



(17)



(18) $R^1 = OH, R^2 = NMe_3Cl$, $n = 3$; $R^1 = NMe_3Cl, R^2 = OH$, $n = 2$

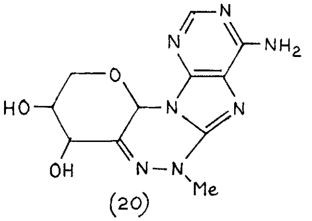


Reagents: i, RNH_2; ii, 2',3'-acetonation; iii, $(PhO)_2CO$-NEt_3; iv, CF_3CO_2H.

(19) R = Me, Bn (Also Bn → H)

Scheme 6

Purine 8,2'-N^{α}-methylhydrazino-cyclonucleosides have been isomerized to their pyranosyl analogues (20) and (21).[57]



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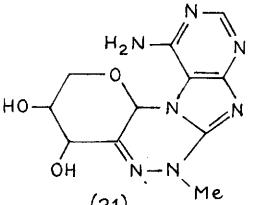


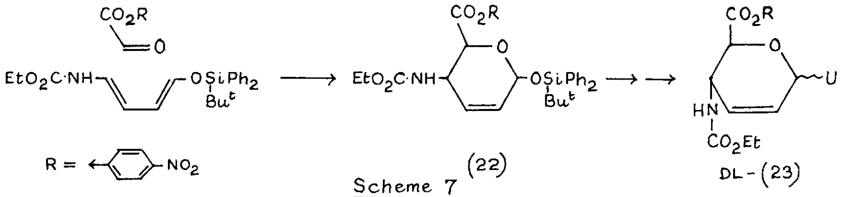
(21)

7 Thio-Nucleosides

A one-pot procedure for synthesizing 5'-thionucleosides has been described, which involves treating the nucleoside with dialkyldisulphide in presence of tributylphosphine.[58] Thiol displacement of a 2'-deoxy-adenosine 3'-tosylate led to a ~6:1 mixture of threo and erythro 2'-deoxy-3'-alkylthio-adenosine, the former being characterized by an X-ray crystal structure analysis of the 3'-ethylthio isomer.[59] Treatment of 5'-deoxy-5'-iodo-nucleosides with thiourea followed by hydrolysis gave 5'-thionucleosides, which were then converted to dimethylarsine derivatives using iododimethylarsine; these proved to be inactive as anti-cancer agents.[60] Treatment of 5'-chloro-5'-deoxyadenosine with N-methyl-3-indolylmethanethiol acetate in presence of base yielded S-3-indolylmethyl derivatives of 5'-thioadenosine, of interest as potential enzyme inhibitors.[61]

8 Unsaturated Nucleosides

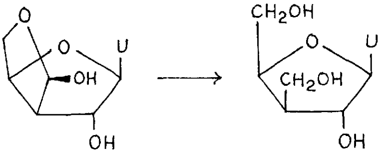
Full details of the synthesis of the 4',5'-unsaturated analogue of adenosine using a 5'-deoxy-5'-phenyl selenoxide intermediate have now been reported.[62] (See Vol. 12, p. 174, ref. 82). (See also a very similar approach reported in Vol. 15, p. 206, ref. 76). A hetero Diels-Alder reaction between a dienaminol and glyoxylic ester has led to the expected stereoisomers of the 4-amino-hex-2-enuronic ester (22) (Scheme 7), one diastereomer of which was converted to the uracil nucleoside analogue (23) (αβ ratio depends on R).[63] Unsaturated C-nucleosides and unsaturated ketonucleosides are mentioned below.



Scheme 7

9 Branched-Chain Nucleosides

3'-*C*-methyluridine and 3'-*C*-methylcytidine have been prepared by standard steps from 3-*C*-methyl-D-allose.[64] Nitrous-acid deamination of 3'-amino-3'-deoxy-D-glucopyranosyl-uracil led to the rearranged 3'-deoxy-3'-*C*-formylpentose analogue obtained as the hemiacetal (24). The 3'-amino-2',3'-dideoxy-D-glucopyranosyluracil analogue rearranged similarly to give a mixture of the 2',3'-di-deoxy-3'-*C*-formyl-ribose and -xylose isomers. The formyl compounds were also reduced to the corresponding hydroxymethyl branched-chain nucleosides.[65] 2- , 3'-, and 5'-*O*-phosphates of 3'-*C*-methyluridine have been prepared, including the 2',3'-cyclophosphate.[66]

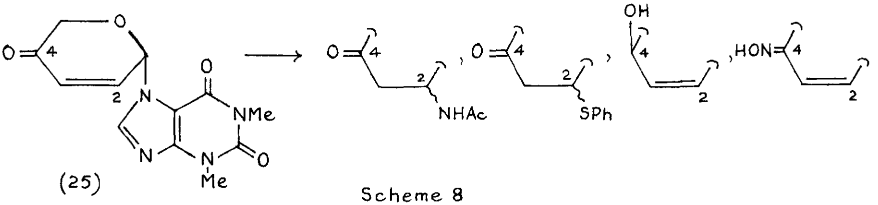


(24)

10 Keto- and Uronic Acid Nucleosides

Various suitably-protected nucleosides have been oxidized with chromic oxide-pyridine reagent in acetic anhydride to yield 2'-keto- and 3'-keto-nucleoside analogues, which on reduction yield the 2'- and 3'-epimers of the parent nucleosides.[67] (See also Section 2, ref. 22). 7-(3,4-*O*-isopropylidene-β-L-fucopyranosyl)-theophylline has been converted to the unsaturated keto nucleoside (25) by a standard sequence, and this was used to prepare the analogues indicated in Scheme 8 by conventional reactions.[68]

A standard condensation procedure has been used to prepare 1-*N* and 3-*N*-(β-D-glucopyranosyluronic acid)-5-fluoro-uracil deriv-

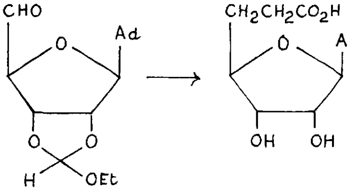


(25)

Scheme 8

atives.[69]

An improved synthesis of 5'-deoxy-5'-adenosine acetic acid (26) has been reported, utilizing the dialdose derivative (27) with a Wittig reagent.[70] Similarly a dialdose derivative of ara-adenosine has been used to make ara-5'-deoxy-5'-adenosine acetic acid via the ester (28), and also the corresponding acetamide and ethanol.



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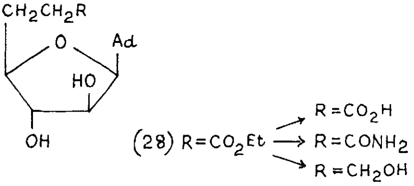
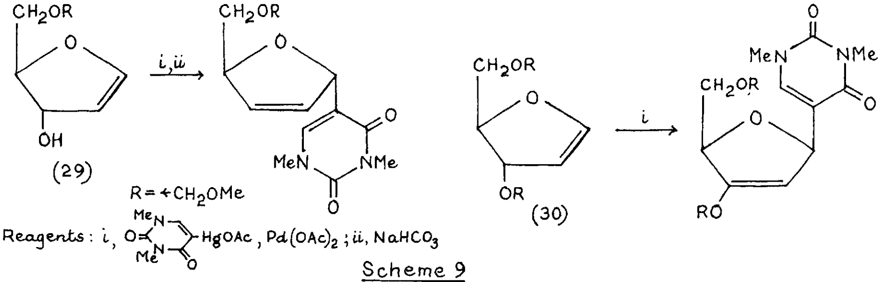


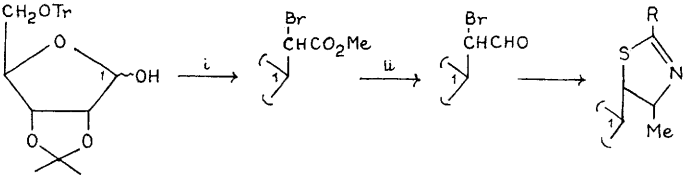
11 C-Nucleosides

Condensation of 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide with 2-chloromercuri-furan gave the 2-(α- and β-ribosyl)furan, the α form isomerizing to the β in presence of trifluoroacetic acid; sequential treatment of this furan derivative with bromine-methanol and hydrazine gave the corresponding 3-β-D-ribofuranosyl-diazine.[72] Pyrimidine-mercury complexes with palladium acetate react with furanoid glycals to give 2,3-unsaturated-C-nucleosides; whereas the erythro-glycal (29) gave the α-anomer, the threo-3-O-acetal (30) gave the β-form (Scheme 9), which was interpreted as indicating that the stereochemistry is governed by the relative steric bulkiness of the glycal substituents.[73]



Scheme 9

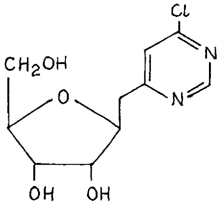
Wittig condensations on reducing sugar derivatives have also been used to make C-nucleosides; e.g., the synthesis of the thiazole nucleoside analogue shown in Scheme 10.[74] The homo-C-nucleoside (31) has been similarly synthesized,[75] and the α-keto ester



Reagents: i, Ph_3P $C(Br)CO_2Me$; ii, DIBAL ; iii, $RCSNH_2$

Scheme 10

C-glycoside (32), obtained as shown in Scheme 11, has been used to prepare showdomycin and the *C*-imidazole and *C*-pyrazole analogues (33) and (34) respectively.[76] Condensation of D-*glycero*-D-*gulo*-heptose with phenylhydrazine and *o*-phenylene diamine led to pyrazoloquinoxaline polyol derivatives, which were cyclized by dehydration to give the C-nucleoside (35).[77] A related cyclization of



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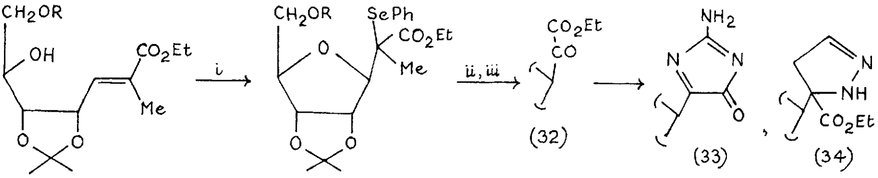
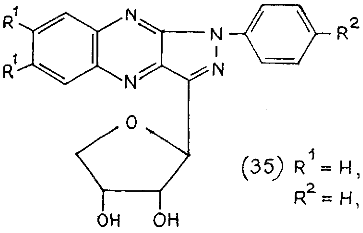


Reagents: i, PhSeCl ; ii, H_2O_2 ; iii, O_3

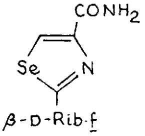
Scheme 11



(35) $R^1 = H, Me$
$R^2 = H, F$

dopamine and tryptamine 2,5-anhydro D-mannose leading to C-arabinosyl-β-carbolines is mentioned in Chapter 10.

Other syntheses have utilized C-glycoside precursors. Reaction of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl cyanide with hydrogen selenide gave the corresponding seleno-amide which could by cyclized to the selenazole (36), giving a nucleoside analogue showing anti-cancer activity.[78] A 1,3-dipolar cyclo-addition of a ribofuranosylacetylene carboxylate with diazo-camphor gave an adduct which underwent a [1,5]-sigmatropic rearrangement, leading to the pyrazole derivative (37).[26] The ethyl ester of this same acetylenecarboxylic acid has also been selectively reduced to the corresponding acetylenecarboxaldehyde, which on cyclization successively with diazomethane and methoxycarbonylhydrazine led to the inosine C-nucleoside analogue (38).[79] Other reports describe the conversion of a nitromethyl C-glycoside to an isoxazole C-nucleoside (Scheme 12),[80] and of a 2-amino-1-cyanoethenyl C-glycoside to 9-deazainosine and 9-deazaguanosine.[81] A ribosyl-acetic ester has been used to synthesize homo-C-nucleosides, *e.g.*, homo-ψ-uridine (39).[82] Other syntheses of C-nucleosides have included the αβ-DL-erythrose derivative (40) by hydroxylation of the corresponding dihydrofuran compound,[83] and a wide range of pyrimidine C-nucleosides with branched-chain sugars, *e.g.*, (±)-1'-methyl-ψ-uridine and (±)-4'-methyl-ψ-uridine (41), from bicyclic branched-chain precursors, *e.g.*, (42)→(41),[84] (See also Vol. 15, p. 210, for other



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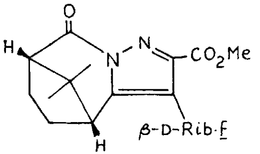

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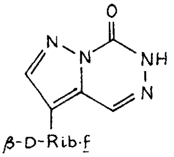

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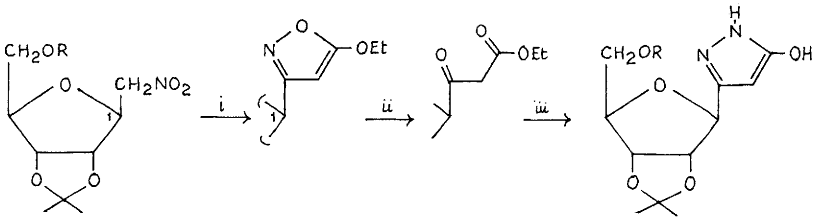
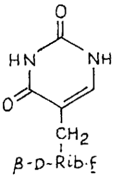


Reagents: i, EtOC≡CH, PhNCO, Et_3N; ii, H_2-Ni, BCl_3; iii, N_2H_4

Scheme 12

branched-chain sugar ψ-uridine derivatives). 5'-Deoxy-5'-substituted ψ-uridine derivatives have also been described, prepared by standard sulphonate displacement reactions.[85]



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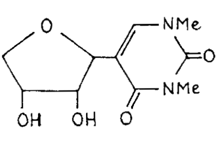

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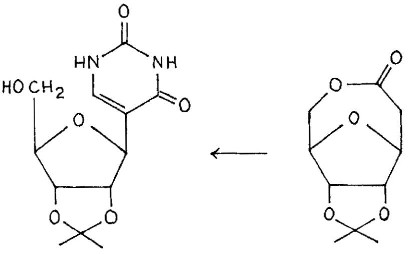
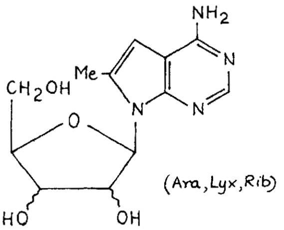


(41) (42)

12 Miscellaneous Nucleosides

Carbocyclic analogues (43) of 6-methyltubercidin have been reported, prepared by condensing 5-acetonyl-4,6-dichloropyrimidine with cyclopentylamines followed by C-6 amination.[86] Reaction of a pentosuronyl chloride with adenine followed by base-catalysed elimination of a 3'-sulphonate ester group has furnished the unsaturated nucleoside analogue (44).[87] Reaction of methylaminodeoxypentopyranosides and cyclohexanolamines with 4,6-dichloro-5-acetonylpyrimidine leads to novel analogues of tubercidin, e.g., compound (45), some showing antiviral activity.[87a]



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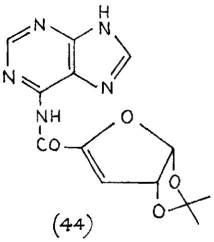

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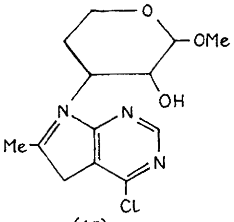


(45)

13 Ether Derivatives

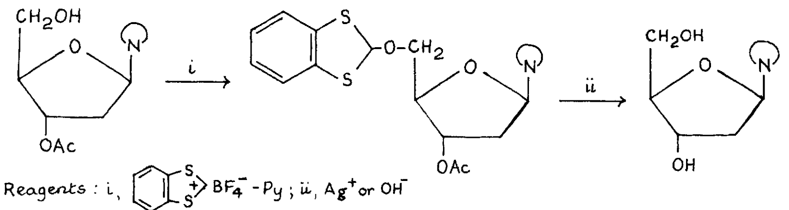
4,4',4"-Tris(benzoyloxy)trityl bromide selectively protects the primary hydroxy group in nucleosides. It is more stable than trityl under acid conditions, but is base-labile. It was applied to the synthesis of 3'-substituted thymidines carrying 3'-acid-labile groups.[88] 2-Oxymethyleneanthraquinone (MAQ) has been found to be a useful 3'-protecting group in nucleosides; being relatively base and acid-stable, it is easily removed in the presence of sodium dithionite in buffered solution. At the same time the 7-chloro-9-anisoyl-thioxanthen-9-yl group was used to protect the 2'-position, a group which is more acid-labile. Used in conjunction with the 5'-protecting group, FMOC, a new strategy for oligonucleotide synthesis is available.[89] A study of the protection of D-arabino-nucleosides has shown that, with O-5' blocked by mono- or di-methoxytrityl groups, O-2' or O-3' can be selectively protected by *tert*-butyldimethylsilylation by choice of appropriate basic catalysts.[90] The three mono-*tert*-butyldimethylsilyl ethers of tubercidin have been prepared.[91] Improved syntheses of 2'-O-tetrahydrofuranyl nucleosides *via* 3',5'-bis-*tert*-butyldimethylsilyl[92] or 3',5'-tetraisopropyldisiloxanyl[93] protected intermediates have been described, and another paper describes a similar method for preparing 2'-O-methyluridine.[94] Ribose has been alkylated with an oestrone 3-O-ω-hydroxy-alkyl ether at O-5, and then converted to the corresponding adenosine methylene-bridged oestrogen.[95]

14 Ester Derivatives

The 2-(4-chlorophenyl)sulphonylethyl carbonate ester group has been proposed as a convenient protecting group for primary hydroxy groups in nucleosides or nucleotides, being readily removed by β-elimination using triethylamine under conditions not affecting blocked phosphotriester groups at O-3'.[96]

The selective 2'-benzoylation of 5'-O-dimethoxytrityl-nucleosides has been studied, using either benzoyl or 3,4,5-trimethoxy benzoyl reagents, giving intermediates suitable for conversion to 3'-phosphate derivatives leading to oligonucleotide synthesis.[97]

Standard methods have been used to prepare 2'-O-nitro derivatives of arabino-nucleosides of cytosine[98] and of adenine and hypoxanthine,[99] and also 3'-O-formyl derivatives of 2'-deoxy-ribonucleosides.[100] Bis-3'-O-(2'-deoxy-5-ethyluridine)-sulphoxide has been prepared from the nucleoside by reaction of its 5'-O-trityl derivative with thionyl chloride.[101] 1,3-Benzodithiol-2-yl ortho-ester groups can be used to protect hydroxy groups in nucleosides in oligo-nucleotide synthesis, as illustrated in Scheme 13.[102,103]



Reagents : i, BF_4^- - Py ; ii, Ag^+ or OH^-

Scheme 13

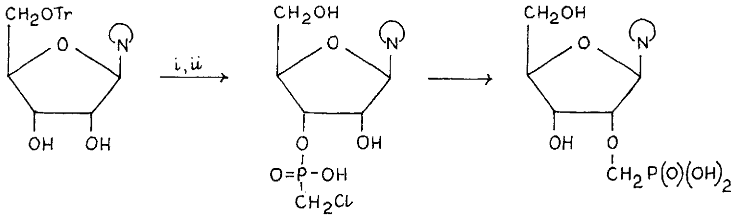
15 Phosphorus Derivatives

As usual, standard syntheses of nucleotides are not included.

A one-pot conversion of 2'-deoxycytidine to a fully protected 2'-deoxycytidine 3'-monophosphate has been described.[104]

Deoxynucleoside phosphorothiolates have been prepared from nucleoside 5'-O-phosphites by sulphurization, which were then used to prepare nucleoside α-thiotriphosphates.[105]

2'- and 3'-O-Phosphonylmethyl derivatives of nucleosides (which are methylene analogues of ribonucleoside 2'- and 3'-phosphates) have been synthesized by base-catalysed rearrangement of 3'- and 2'-O-(chloromethyl)phosphonyl derivatives, as outlined in Scheme 14.[106]



Reagents: i, $ClCH_2P(O)Cl_2$; ii, H^+ ; iii, NaH or NaOH.aq

Scheme 14

A mild phosphorylation procedure for nucleosides has been described, involving low temperature base catalysed treatment with diarylphosphorochloridates.[107] A study of the barium hydroxide catalysed hydrolysis of cyclic nucleotides using labelled oxygen compounds is mentioned in Chapter 7.

16 Reactions

Nucleosides can be oxidized in good yields using polymer-bound periodate; the reaction is slower in DMSO than in ethanol or water.[108]

17 Spectroscopic and Other Physical Measurements

The rules relating chemical shifts to anomeric configuration in nucleosides have been surveyed, and exceptions to the rules rationalized.[109]

^{1}H and ^{13}C n.m.r. spectra of *O*- and *N*-methylated 2'-deoxynucleosides have been recorded, and ^{1}H n.m.r. measurements together with U.V. data used to investigate the pH dependence of their stability.[110] ^{17}O n.m.r. data have been used to study hydration equilibria of nucleoside-water complexes; 2',3'-*O*-isopropylidene uridine enriched at either O-4 or O-2 with ^{17}O showed that hydration occurs more extensively with the 4-carbonyl group, and both mono- and di-hydrates are formed.[111]

Differences in reported ^{1}H n.m.r. data for 3-deazaadenosine have been attributed to preparations being either free nucleoside or the hydrochloride salt.[112]

Conformations of nucleotides have been studied using ^{13}C n.m.r., and ^{13}C-^{31}P J values,[113] and ^{1}H and ^{13}C n.m.r. data used for a detailed discussion of nucleoside 2',3'-cyclic phosphate conformations.[114] The effect of metal ions on the ^{1}H n.m.r. spectra of nucleoside 5'-diphosphates has been investigated,[115] and n.O.e. studies of adenosine 5'-phosphate in presence of lanthanide shift reagents have been reported.[116]

The solution conformation of imidazole, pyrazole and triazole nucleosides have been investigated using u.v. and c.d. data.[117] Negative ion m.s. of nucleosides and their ester or ether derivatives have been reported.[118] The ultrasonic relaxation of cytidine 2',3'-cyclic phosphate in the absence or presence of ethidium bromide has been used to study the syn-anti interconversion of the pyrimidine base.[119] pK_b Values of *O*-benzoylated *N*-glycosylimidazoles and -pyrazoles, and of related compounds, have been reported.[120]

A study of inosine using dipole moment and other dielectric properties suggests that a *syn* conformation predominates in solution.[121]

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21

N.M.R. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

A review of n.m.r. spectroscopy in the study of mono- and oligosaccharides covers the period 1973-80.[1] The ^{13}C-n.m.r. of monosaccharides has been reviewed.[2]

Detailed descriptions of an instrumental method for assigning ^{13}C n.m.r. resonances in carbohydrates in the solid state have been published.[3]

An improved procedure for determining the magnitude of the anomeric effect of substituents at C-1 of tetrahydropyrans has been demonstrated, and a value for _O_-alkyl substituents of 8.8 kJ mol^{-1} calculated, which is almost 50% larger than currently accepted values. Weakly positive anomeric effects for carboxymethyl, methylamino, and dimethylamino groups, previously considered to display reverse anomeric effects, were also deduced.[4] The exo-anomeric effect and its relationship to polysaccharide conformation has been the subject of a review.[5]

Theoretical studies on sugar conformations, as affected by hydration of the acetal portion of glycosides, have shown that the equilibrium between conformers should not be influenced by such hydration: the anomeric or exo-anomeric effects are largely unchanged. Monohydration of the glycosidic oxygen appears to be favoured over that of the ring and over dihydration.[6] A semi-empirical approach to optimizing the positions of carbon, oxygen, and hydrogen atoms in ribofuranoses has provided tables of optimized geometry for eight structures.[7] The Cremer-Pople ring puckering programme has been modified to include the standard deviations of the parameters calculated from the atomic positions, and to allow convenient input and output.[8] A new method for defining furanose ring conformation in nucleosides has been described: a set of pseudorotation co-ordinates, defined from the curvilinear displacement of C-1' and C-4' from the planar conformation, are used to characterize the ring pucker.[9]

The two-dimensional J-resolved ^{1}H-n.m.r. spectrum of α,β-D-glucose in D_2O at 500 MHz has been reported.[10] The considerable suppression of n.O.e. for carbons bearing deuterium has been confirmed in a study of the ^{13}C-n.m.r. of seven deuterated methyl α-D-glucopyranosides.[11] ^{13}C-n.m.r. spectra of glycosides, disaccharides, and β-cellodextrin with exchangeable protons partially deuterated have been obtained in DMSO-d_6. The signals appear as multiplets because two-bond and three-bond deuterium-induced shifts are observed. The magnitude of the shifts vary with configuration of the carbons and their substitution and with hydrogen bonding of the hydroxy group. The effects can be used in signal assignments and in the detection of specific inter-unit intramolecular hydrogen bonds in oligosaccharides.[12] The ^{13}C spin-lattice relaxation times of several [1-^{13}C]-enriched carbohydrates were found to bear an approximately linear relationship to their molecular weights, although both configuration and conformation had substantial effects on rates.[13]

Full analysis of seven O-methylated inositols has allowed a study of the effect of methylation on chemical shifts in the ^{1}H and ^{13}C n.m.r. spectra.[14] The ^{13}C-n.m.r. spectra of 1-thio-β-D-galactose, -glucose, -xylose, and of a number of their S-glycosides, as well as that of 5-thio-α-D-glucose, have been fully assigned.[15] N.m.r. has been used to determine the ring size, conformation, and configuration of flavonoid O-rhamnosides (rutinosides).[16] That the amounts of D-glucose and D-fructose increase sharply at the expense of L-malate and L-tartrate in unpicked grape berries has been deduced from ^{13}C-n.m.r. studies.[17]

^{13}C-N.m.r. has been used to study deuterium - hydrogen exchange using the Raney nickel - deuterium oxide technique. Partial epimerization was shown to occur after 24h with methyl α-L-arabino- and β-D-xylopyranosides. Methyl α-L-rhamnopyranoside was epimerized more slowly to yield methyl-L-quinovopyranoside. The best conditions for minimizing epimerization were found to be heating under reflux with Raney nickel W7 in 1:1 deuterium oxide-dioxan or 1:1 methanol-d_5-deuterium oxide for about 9h. Methyl β-sophoroside, methyl β-cellobioside, and the β-sophorosyl and β-gentiobiosyl units of ginsenoside-R_{61}, a ginseng saponin, were deuterated as expected under these conditions, while C-2 and C-4 of the inner β-glucopyranosyl moiety of methyl laminaribioside and C-4 of the inner β-glucopyranosyl moiety of methyl 2,3-di-O-β-D-glucopyranosyl-β-D-glucopyranoside remained almost undeuterated. Deuteration of an α-(1→6)-glucan proceeded slower than those of the mono- and oligosaccharide to obtain the expected deuteration after 24h. In the cases of *cis* and *dl*-

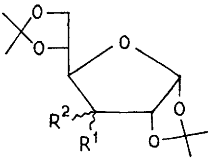
trans-1,2-cyclohexanediols, both deuteration and epimerization proceeded rapidly to give an equilibrated mixture. Some revisions to assignments in the published ^{13}C-n.m.r. spectra of these compounds were made.[18]

The ^{13}C-n.m.r. spectra of nine heptoses and all the heptuloses have been measured and most of the resonances assigned, and hence the furanose and pyranose compositions were determined. For the heptoses the compositions were similar in the main to those for the homomorphous hexoses, while the compositions of the heptuloses varied from 100% α-pyranose for the D-gluco isomer to mainly furanose, e.g., D-ido-heptulose exists as 11% α-furanose and 65% β-furanose.[19]

Proton-decoupled ^{13}C-n.m.r. spectra of partially hydroxy-deuterated carbohydrates show signals in which the multiplicities depend on the environment of the hydroxy group. Five types of multiplet were identified as being characteristic, e.g., C-6 of a hexopyranose gives a broad doublet, while C-1 of a glycoside gives a narrow doublet, etc.[20] The ring sizes of benzoylated L-rhamnonolactones as determined by ^{13}C-n.m.r. spectroscopy are discussed in Chapter 16.

2 Acyclic Sugar Derivatives

In a study of the biosynthesis of riboflavin from [U-^{13}C]glucose, application of ^{13}C-homonuclear J-spectroscopy and 2D-chemical shift correlation spectroscopy, as well as 2D-INADEQUATE techniques, were used to assess ^{13}C-enrichments in the tetraacetate of the vitamin.[21] Conformations of D-gluconic, D-mannonic, and D-galactonic acids in solution have been determined by 300 MHz ^{1}H- and ^{13}C-n.m.r. spectroscopy. For the gluco isomer there is a conformational equilibrium between the zig-zag and $_{3}G^{+}$-sickle form, while for the manno and galacto acids, the predominant form is the planar zig-zag.[22]



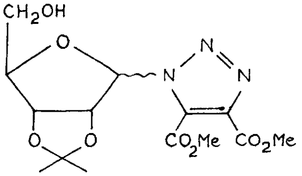
(1) R^1 = H, or OH, or R^2
R^2 = Me, CN, CH_2OH, CH_2NO_2, CH_2CN

3 Furanose Systems

The motional behaviour of 2,3:5,6-di-O-isopropylidene-α-D-manno-furanose has been studied by relaxation times in ^{1}H-n.m.r. spectra in DMSO; ring oscillation, ring puckering interconversions, methyl internal rotations were all recognised, superimposed on an overall isotropic reorientation.[23]

The anomeric configurations of the ribofuranosyl amines, obtained from various primary amines and 2,3-*O*-isopropylidene-D-ribose, have been assigned by using $\Delta\delta$ values for the isopropylidene methyl ^{13}C-n.m.r. signals.[24] A comprehensive ^{13}C-n.m.r. study of branched sugars of type (1) has been carried out.[25] ^{13}C-n.m.r. data in the benzoyl derivatives of methyl aldotetrofuranosides and conclusions on their conformations have been reported.[26]

The chemical shift rules used for determining the anomeric configuration in nucleosides have been surveyed (in French); exceptions to current rules were discussed and rationalized.[26] The ^{3}E conformation is adopted by the sugar rings in 3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) nucleosides, as evidenced by ^{1}H-n.m.r. spectroscopy; $J_{1',2'}$ values of ⩽ 1.5Hz allowed 1,2-*trans*-assignments to be made. An *X*-ray structure determination of the cytidine derivative confirmed the ^{3}E conformation.[28] Nucleosides (2) and (3) have been studied to examine the $\Delta\delta$ criterion for configurational assignment from n.m.r. spectra, and (2) was found to be an exception to the rule.[29] Discrepancies noted in the original Karplus equation applied to 2',5'-oligonucleotides for $^{3}J_{POCC}$ have been explained in terms of substituent electronegativities at C-1'. New Karplus parameters were devized for analysis of $^{3}J_{POCC}$ magnitudes in 3'- and 5'-nucleotides and 3',5'-oligonucleotides by examining ^{13}C-n.m.r. measurements. Suggestions were made for the analysis of J_{P-C1} in 2'-, 2',3'-cyclic, and 2',5'-oligonucleotides.[30] The pseudorotational disorder of the furanose rings of nucleic acids has been studied in detail, and the mobility of these rings compared by means of *X*-ray and solution data.[31]



(2) α-anomer

(3) β-anomer

4 Pyranose Systems

The additivity of ^{13}C- and ^{1}H-n.m.r. chemical shift increments for acetylated xylopyranosides propounded by T.McEwan et al (see Vol. 14, p.196, ref. 23) has been further investigated.[32-34] Deviations from the preducted chemical shift values have been ascribed to changes in conformation populations. In one ^{1}H-n.m.r. study, it was shown that while α-anomers of partially acetylated methyl D-xylopyranosides occur exclusively in the $^{4}C_{1}$ conformation, the β-forms occupy the $^{1}C_{4}$ conformation to varying extents ranging from 14-43%. Even so, predictability in the α-series is poor.[32] Besides the position of acyl groups, solvent interactions have been shown to influence conformer populations,[33] and similar effects have been demonstrated in the ^{13}C-n.m.r. spectra of various acylated methyl O-benzyl-β-D-xylopyranosides.[34] Attempts to improve chemical shift additivity through use of pertrimethylsilylation to create conformational homogeneity have been made. All possible mono-, di-, and tri-O-methyl, -benzyl, -benzoyl, and -acetyl derivatives of methyl β-D-xylopyranoside were examined; $J_{H,H}$ values varied little throughout the series in deuterochloroform, and it was concluded that the method could provide useful information by means of the additivity rules.[35]

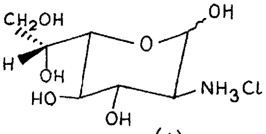
The ^{13}C-n.m.r. spectra of benzoylated methyl D-aldopentopyranosides have been reported,[26] as have those of the D-ribopyranosylamines.[24] The α-anomers of the latter take up the $^{1}C_{4}$ conformation, whereas the β-anomers assume the $^{4}C_{1}$ conformation.

Using known co-ordinates for carbon, oxygen, and hydrogen in hydroxymethine groups, the rotational states of hydroxy groups and the hydrogen bonding patterns in crystals of α- and β-D-gluco- and galactopyranose and of methyl α-D-altro- and β-D-galacto-pyranoside have been predicted from an atom-atom potential method. Good agreement was observed between theoretical and neutron-diffraction data.[36]

A critical study of the use of n.m.r. and o.r.d.-c.d. for determining conformation and anomeric configuration has been carried out. Anomeric pairs of glyco- and 1-thioglyco-pyranosides, for which the ring oxygen helicity rule was previously proposed (based on the sign and rotational strengths of the ring oxygen band), have been subjected to ^{1}H- and ^{13}C-n.m.r. spectroscopy. The ^{1}H chemical shifts and spin coupling data were analyzed by means of the conventional rules relating these data with structural parameters. The

^{1}H chemical shifts showed a linear relationship with the rotational strength of the ring oxygen band, suggesting that both methods can be applied. ^{13}C-N.m.r. shifts also showed this relationship. Exceptions were found for phenyl 1-thioglycopyranosides in the $\delta\beta > \delta\alpha$ rule for C-1 shifts. It was shown that the differences between $\delta\beta$ and $\delta\alpha$ decreased with the deshielding effect of the aglycone.[37] It has been shown that the anomeric configuration influences the effect of temperature on the chemical shifts of exchangable protons in pyranoid compounds. Thus, in DMSO, $\Delta\delta/\Delta T$ for C-2-OH and C-2-NHR is greater for the α- than for the β-anomers; the opposite was found for C-1-OH and C-1-NHR groups.[38]

Analysis of the ^{1}H-n.m.r. spectra of α- and β-D-glucopyranose, twelve proton spin systems, in DMSO-d_6 has been achieved at 400 MHz either by 2D-J resolved spectra or by rapid chemical exchange of hydroxy protons by trifluoroacetic acid. A complete set of chemical shifts and J_{CH-OH} values were obtained and the conformational analysis of the anomers inferred.[39] The ^{13}C-n.m.r. spectra of the α- and β-anomers of D-talo-, D-gulo-, and L-ido-pyranose and of 1,6-anhydro, 6-*O*-methyl, and 6-deoxy derivatives of L-idopyranose have been measured. Data was also obtained for α- and β-D-talofuranose.[40] Both ^{13}C- and ^{1}H-n.m.r. spectra have been obtained for the penta-*O*-benzoyl derivatives of α- and β-D-gluco-, α-D-galactopyranose and α-D-galactofuranose. Also reported were the ^{1}H-n.m.r. data for penta-*O*-benzoyl-α-D-mannopyranose and the ^{13}C-n.m.r. measurements for penta-*O*-benzoyl-β-D-galactofuranose.[41] In order to facilitate the analysis of *O*-carboxymethyl derivatives of cellulose by hydrolysis-^{13}C-n.m.r. procedures, the spectra of 2-, 3-, and 6-mono-, 2,3-, 2,6-, and 3,6-di-, and 2,3,6-tri-*O*-(carboxymethyl)-D-glucoses have been determined.[42] Full assignments of the ^{13}C-n.m.r. spectra of methyl 2-, 3-, 4-, and 6-deoxyfluoro-β-D-galactopyranosides and their peracetates have been made.[43]



(4)

A structural study of 2-amino-2-deoxy-D-*glycero*-L-*gluco*heptose (4) in solution using ^{1}H-n.m.r. data has shown that the α:β anomeric ratio is 66:34. Some acylated derivatives, including the peracetate, and the per-O-acetyl-N-acetyl,N-benzoyl derivative were also examined.[44]

Spin-lattice relaxation rates and n.O.e. or protons of exo- and endo-diastereoisomers of 1,2-O-(1-methoxyethylidene) and 1,2-O-(1-benzyloxyethylidene) derivatives of 3,4,6-tri-O-acetyl-β-D-mannopyranose and some specifically deuterated analogues have been used to verify the configurations of substituents on the quaternary carbon of the acetal groups.[45]

The extent to which the sulphur atom in the ring of the anomers of 5-thio-D-xylopyranose and 6-thio-D-fructopyranose distorts the chair conformation compared to the oxygen counterparts has been determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy. It was shown that the distortion is more pronounced in the α-anomers.[46]

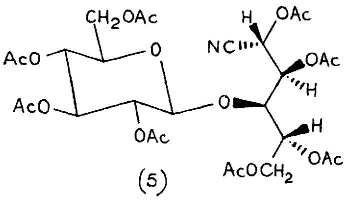
The conformation - reactivity relationships of 1,6-anhydro-β-D-glucopyranose derivatives are mentioned in Chapter 5.

5 Oligo- and Polysaccharides

The conformational relationship between chemical shifts of anomeric carbon atoms in oligo- and polysaccharides has been the subject of a review,[47] as has the ^{13}C-n.m.r. spectroscopy of xylans and related carbohydrates.[48]

Spin-lattice relaxation times, n.O.e. data, and chemical shifts have been applied to the conformational analysis of oligosaccharides by ^{1}H-n.m.r. spectroscopy. Differences in δ values for similar protons in different oligosaccharides can be conformationally significant where $\Delta\delta$ is $\geqslant$ 0.1 p.p.m., and may be attributed to specific inter-unit deshielding by oxygen atoms with which the proton is in a strong non-bonded interaction.[49] A new method for sugar sequence determination in linear oligosaccharides relies on measurements of relaxation time gradients in ^{13}C-n.m.r. when the centre of mass of the molecules is shifted by complexation with cyclodextrin. Quick and precise relaxation time measurements can be obtained in reasonable machine time because of the high solubility of simple methylated derivatives of cyclodextrin in water, and because of the host-guest ratio of unity.[50]

Specific structural assignments have been made for the O-acetyl group resonances in ^{1}H-n.m.r. of 1,2,3-tri-O-acetyl-4-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-β-D-xylopyranose. All six signals were separate at 200 MHz and identified by using specifically deuterated acetyl derivatives prepared from [^{2}H$_3$]acetic anhydride.[51] Complete and unambiguous assignments for cellobionitrile octaacetate (5) have been achieved by combined application of 2D-^{1}H and ^{13}C-n.m.r. spectroscopy.[52] Theoretical analysis of glycosyl (1→3)-galactosides, differing either in absolute configuration or in the configuration of the anomeric centre in the non-reducing residue, used calculations of changes in the values of the C-4 atom of the galactose residue in the ^{13}C-n.m.r. spectrum to predict the disaccharide conformation in solution.[53] The methods of measurement of multiplicities of signals under conditions of slow exchange (see Ref. 11, above) have been applied to cellobiose.[54] The 360 MHz ^{1}H-n.m.r. spectra of methyl 3-O- and 6-O-(α-D-mannopyranosyl)- and 3,6-di-O-(α-D-mannopyranosyl)-α-D-mannopyranoside, and methyl 3-O-(α-D-mannopyranosyl)-6-O-(3-O-α-D-mannopyranosyl-α-D-mannopyranosyl)-α-D-mannopyranoside, synthetic analogues of the mannose structures of N-linked glycopeptides in glycoproteins, have been fully assigned. Several chemical shift perturbations associated with changes in the (1→6)-linkage conformation were detected.[55] Solution conformations of synthetic methyl mannobiosides and a methyl mannotrioside containing α-D-(1→6)-linkages have been determined using ^{1}H-n.m.r., n.O.e. and T_1 measurements. The $^3J_{C,H}$ obtained from a compound enriched with carbon-13 was also used. The allowed conformations were in agreement with those predicted by potential energy calculations and crystal structures.[56] Five crystalline forms of lactose have been examined by cross-polarization - magic-angle sample spinning (CP-MAS) ^{13}C-spectroscopy. Anhydrous α-lactose has at least two molecules per unit cell, unlike the monohydrate, and β-lactose, which have been shown by X-ray data, and, in the present study, by CP-MAS, to have identical environments for each disaccharide molecule. Both mixed-crystal lactoses with α to β ratios of 5 to 3 and 4 to 1 have very similar environments for the disaccharides to that in anhydrous α-lactose.[57] Crystalline lactulose and maltulose monohydrates have also been examined by CP-MAS ^{13}C-n.m.r. spectroscopy.[58,59] In combination with a 360 MHz ^{1}H-n.m.r. study of their unmutarotated



(5)

solutions in DMSO, it was shown that lactulose consisted of a mixture in the solid state of a 75:15:10 ratio of β-furanose to β-pyranose to α-furanose isomers of the reducing fructose moiety,[58,59] while only the β-pyranose form was present in maltulose.[59] The CP-MAS spectra of the two disaccharides each displayed three quaternary carbon resonances, underlining the complexity of solid state spectra where multiplicity can arise from either structural differences or from crystal effects.[59]

PCILO calculations on N-acetylgalactosamine and O-(2-acetamido-2-deoxy-α-D-galactosyl)-(1→3)-2-acetamido-2-deoxy-D-galactose have been carried out to determine the favoured orientations of their side groups and the mutual orientations of the two pyranose rings in the disaccharides.[60] The results were compared with determinations from X-ray crystallography and hard-sphere *exo*-anomeric calculations, carried out by the same group of workers.[61] A pulse sequence has been described to take advantage of the considerably shorter T_1 relaxation times of the anomeric protons compared to those of ring protons linked to the acetoxylated carbons in p-trifluoroacetamidophenyl 2-acetamido-2-deoxy-4-O-α-D-glucopyranosyl-β-D-glucopyranoside peracetate; a simplified spectrum was obtained in which the anomeric protons were readily identified.[62] The application of ^{1}H-n.m.r. spectroscopy for detecting 2-acetamido-2-deoxy-D-mannose and -D-mannuronate residues in oligosaccharides has been discussed. Detection is possible due to the fact that H-2 in mannose derivatives lies well downfield of the remaining envelope protons.[63]

Proton and carbon chemical shift data for several rhamnobioses and their acetylated derivatives have been used to compute the effect of substitution on the anomeric carbon atoms and glycosidically linked carbon atoms. The results were used to assign the structure of xanthorhamnin.[64]

Three oligosaccharides from human urine, α-NeuAc-(2→3)-β-D-Gal-(1→4)-D-Glc, α-NeuAc-(2→3)-β-D-Gal-(1→4)-D-GlcNAc (a new finding), and α-NeuAc-(2→6)-β-D-Gal-(1→4)-D-GlcNAc, have been investigated by 60 MHz ^{13}C-n.m.r. spectroscopy. The latter showed unusual chemical shifts due to intramolecular interactions between NeuAc and GlcNAc residues, which allowed additional conformational information to be obtained.[65] Two-dimensional J-resolved and J-correlated ^{1}H-n.m.r. spectroscopy has confirmed the structures of three peracetylated reduced oligosaccharides from human milk.[66] Further ^{1}H-n.m.r. studies on ten structurally related oligosaccharides from human milk made use of δ shifts on acetylation, which allowed all the signals to be observed without overlap, and, in addition, the high-field positions of the protons attached to the sites of glycosidic linkage. The carbohydrate sequence was established from n.O.e. studies of the anomeric and aglycone protons.[67] Two branched oligosaccharides from marsupial milk have been characterized from ^{13}C-n.m.r. data.[68]

Solid state ^{13}C-n.m.r. spectroscopy using CP-MAS methods on cellulose oligomers up to cellohexaose has been reported.[69]

The ^{13}C-n.m.r. spectra of the three pentasaccharides released by aqueous ammonia treatment of N-acetylsporaviridin have been examined; the glycosidation shift was successfully applied to characterize the glycosidic linkages in the constituent mono-, di-, tri-, and tetrasaccharides, but anomalous behaviour was found in the pentasaccharides.[70] (See also Chapter 19).

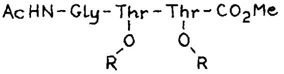
6 Glycopeptides

Ring sizes, anomeric configurations, and conformational equilibria in deuterium oxide of various D-gluco-, D-manno-, D-allo-, and D-gulo-N-acetylmuramoyl-L-alanyl-D-isoglutamine analogues have been studied by 400 MHz ^{1}H-n.m.r. spectroscopy.[71] High field ^{1}H- and ^{13}C-n.m.r. spectra of fourteen mutarotated N-(1-deoxy-D-fructos-1-yl)-L-aminoacids in deuterium oxide have been reported. From ^{13}C-n.m.r. spectra they were shown to be 64:15:15:6 mixtures of the β-pyranose, α-furanose, β-furanose, and α-pyranose forms respectively, and this ratio was found to be independent of acidity. On prolonged storage in deuterium oxide, H-1 in these compounds undergoes deuterium exchange, presumably *via* an enamine form.[72] Examination of the ^{13}C-n.m.r. spectra of two O-α-D-galactopyranosylated tripeptides showed that glycosylation of the peptides resulted in little structural perturbation.[73] Two papers on the solution conformation of asparagine linked saccharides, studied by high resolution ^{1}H-n.m.r. in conjunction with potential energy calculations, show that the linkage conformation of a mannose α-(1→3) residue is not affected by substitution either at O-2 by α-mannose or β-N-acetylglucosamine, or at O-4 by β-N-acetylglucosamine, or by the presence of a bisecting N-acetylglucosamine on the adjacent β-mannose residue.[74,75]

7 Inorganic Complexes

Complexation with boron(III) oxide as shift reagent has been applied to D-arabinose,[76] and to D-glucose and D-mannose.[77] Significant shifts in ring proton resonances in DMSO or DMF were noted, while those of hydroxy protons broadened when two molar equivalents of boron(III) oxide were used; further addition of the complexing agent caused downfield shifts and sharpening of hydroxy protons. Dilution shifts suggested that there was no covalent bonding between the sugar and the boron(III) oxide; however, a large hydroxy proton peak on addition of three molar equivalents of boric acid to glucose in DMSO suggested the formation of an ester linkage.[77]

The mode of interaction of gadolinium(III) and manganese(II) ions with two vicinally di-O-D-galactosylated tripeptides, (6) and (7), has been studied by ^{13}C-n.m.r. spectroscopy. The interaction appears to occur at O-2', O-6', and at the O-3 of threonine for the α-linked sugar tripeptides, and at O-3', O-6', and threonine O-3 for the β-isomers.[78]



$\mathrm{AcHN\text{-}Gly\text{-}\underset{\underset{R}{O}}{Thr}\text{-}\underset{\underset{R}{O}}{Thr}\text{-}CO_2Me}$

(6) R = α-D-Gal*p*

(7) R = β-D-Gal*p*

8 N.m.r. Spectroscopy of Other Nuclei

A review of the mechanisms for change in chemical shifts of phosphorus nuclei in ^{31}P-n.m.r. spectra of nucleotide derivatives has appeared.[79]

The ^{29}Si chemical shifts of TMS derivatives of methyl α- and β-D-galactopyranosides,[80] and of 1,6-anhydro-β-D-glucopyranose derivatives have been reported.[81] In the former, the 6-substituent was readily assigned while the 2-substituent was assigned by studying the effect of the anomeric configuration. The 3- and 4-O-TMS derivatives were not unequivocally assigned.[80] For the 1,6-anhydroglucose derivatives, the δ value was found to correlate well with the sum of the Taft polar constants, σ^*, for substituents at C-2 and C-4; this allowed assignment of the silyl group at O-3 when other TMS groups are present.[81]

Reference to sugar conformations determined by X-ray structure analysis will be found in Chapter 22.

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22

Other Physical Methods

1 I.r. Spectroscopy

Anomerization of D-glucose in aqueous solution has been monitored by F.t.i.r., many bands being identified specifically with the α- or β-anomer.[1] D-Ribose and 2-deoxy-D-ribose have been examined by both F.t.i.r. and laser-Raman methods, both in solution and in the crystalline form, as a prelude to nucleoside and nucleotide studies.[2] A method for calculating conformations and vibrational spectra of crystalline monosaccharides based on an additive model of interatomic interactions and including intermolecular hydrogen-bonding has been applied to α- and β-D-glucose, and β-D-galactose, the results comparing satisfactorily with experimental values.[3-5] The nitrile band is often absent from the i.r. spectra of per-acetylated aldohexopyranosyl cyanides, but it can be seen by laser-Raman spectroscopy, axial cyano-substituents absorbing lower frequencies than those of their equatorial counterparts.[6]

2 Mass Spectrometry

A review on new mass-spectral approaches to the analysis of complex carbohydrate structures has appeared,[7] and several carbohydrate examples, including gangliosides, glucose 6-sulphate, and glucuronides, are referred to in a review on liquid phase ionization techniques for obtaining spectra on molecules in the 10^3 -10^4 Dalton range.[8]

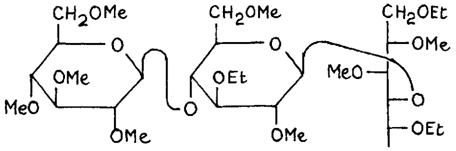
Fast atom bombardment mass spectra have been reported for (i) representative unmodified, permethylated, and peracetylated oligosaccharides;[9] (ii) glycosphingolipids, carbohydrates excreted by gangliosidosis patients, glucans from Rhizobium species, and a variety of cell wall oligosaccharides, with spectra up to 6620 Daltons for permethylated glucans;[10] (iii) 30 glucuronides, including 7 different glycosidic linkages, and employing both positive and negative ionization;[11] (iv) glucosinolates and desulphoglucosinolates, and crude plant extracts containing mixtures of glucosinolates;[12] (v) fructose, sucrose and melezitose as test samples on a new spectrometer.[13]

Time of flight mass spectra of cations obtained from sucrose particles containing sodium chloride on either a piotoform foil, or a self supporting silver film, have been reported.[14]

Field desorption - collision induced dissociation mass spectra of seven disaccharides, involving alkali metal-cationized molecular ions,[15] and negative ion field desorption mass spectra of sugars and nucleotides, in which $(M-H)^-$ ions were generated by ion-molecule reactions,[16] have been reported.

Supermolecular ion species, with an anhydrohexose attachment leading to (M + n.162) ions where n = 1-6, have been identified in repetitive laser desorption mass spectra of carbohydrates, and appear to result from thermally induced processes prior to desorption.[17] The kinetics of volatilization in rapid heating chemical ionization mass spectroscopy of some hydrogen bonded compounds including mannose, glucose, maltose and sucrose, has been examined, activation energies for the production of protonated or cationized molecular ions resembling experimental heats of volatilization, with _ca_. 4.4 kcal. mol^{-1} per CHOH group.[18] Desorption mass spectra of some mono- and di-saccharides from a gold support contained mainly $[M+1]^+$ and/or $[M-1]^+$ ions, the intensities of which depended upon the temperature and residence time of the sample in the ionization chamber.[19,20]

Chemical ionization mass spectra (iso-C_4H_9 and NH_3) of permethylated viridopentaoses and their constituent mono- to tetra-saccharides analogues have been studied, and the general approach was considered to be useful for sequencing unknown oligosaccharides.[21] McNeil, however, has demonstrated with a number of compounds that internal glycosyl residues can be eliminated during chemical ionization mass spectral fragmentation of per-_O_-alkylated oligosaccharide-alditols. Thus the central glycosyl moiety in the trisaccharide derivative (1) was lost from its (M+1) ion to form a



(1)

glucosyl alditol fragment ion.[22] In the ammonia chemical ionization mass spectra of seven glucuronides, the dominant ion was found to be the NH_4^+-adduct of the glucuronic acid portion resulting from glycosidic cleavage.[23]

In an e.i.-m.s. study on some labda-7,14-dien-13(R)-ol glycosides, O-isopropylidenation was used to distinguish between rhamnose, fucose and 6-deoxy-idose derivatives.[24] From an e.i.-m.s. study on all possible mono-benzyl ethers of methyl pento-, hexo- and 6-deoxy-hexo-pyranosides, criteria have been established that permit simple and unambiguous localization of the benzyl group.[25] Similarly the position of the methyl ether group on methyl (methyl O-methyl-α-D-mannopyranosid)uronate can be determined from its e.i.-m.s.[26]

The e.i.-m.s. fragmentation patterns of the following compounds have been examined in detail: pertrimethylsilylated methyl glycosides of monosaccharides and galacturonic acids found in pectin;[27] peracetates of 3,6-dideoxyhexoses in the pyranose and furanose form;[28] per-acetylated and -propanoylated aldopyranosylamines[29] and aldofuranosylamines;[30] and perbenzoylated aldononitriles and 5-[poly(benzoyloxy)alkyl]tetrazoles.[31]

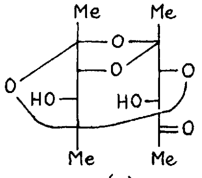
3 X-Ray and Neutron Diffraction Crystallography

Jeffrey and Mitra have concluded from a general analysis of hydrogen-bonding in crystals of pyranoid compounds that: i) the hydrogen-bonding energy is maximized by including all hydroxy groups and as many ring and glycosidic oxygens as possible; ii) co-operative hydrogen-bonding occurs where possible; and iii) the anomeric effect leads to the anomeric hydroxy groups behaving as strong donors and weak acceptors.[32] Westhof and Sundaralingham have published a detailed paper on the pseudorotational disorder of furanose rings, and have compared the mobility of furanose rings in nucleic acids by means of X-ray and solution data.[33]

Specific crystal structures have been reported as follows, neutron diffraction studies being identified by the letters 'n.d.'.

Free Sugars and Simple Derivatives Thereof.- 3-O-Methyl-α-D-glucopyranose,[34] 1,2,3,4,6-penta-O-acetyl-α- and -β-D-glucopyranose,[35,36] 5-O-acetyl-1,2:3,4-di-O-isopropylidene-α-D-glucoseptanose (both X-ray and n.d.),[37] and the tricyclic acetal (2) from attempted de-isopropylidenation of L-*threo*-2,5-diulose.[38]

Glycosides and Derivatives Thereof.- Phenyl α-D-glucopyranoside,[39] phenyl β-D-glucopyranoside dihydrate,[39a] 2-nitrophenyl β-D-glucopyranoside,[40] 4-nitrophenyl α-D-glucopyranoside,[41] 3,4-dinitrophenyl β-D-glucopyranoside[42] and its tetraacetate,[43] methyl β-D-glucoseptanoside,[44] methyl α-L-idoseptanoside[45] and its 2,3,4,5-tetra-*O*-acetate,[46] 2(*R*)-hydroxy-1(*R*)-cyclohexyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside,[47] 3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4-methyl-2(5*H*)-furanone,[48] the natural product glaucogenin-C mono-D-thevetoside as its di-*O*-acetate,[49] and the 1,2-acetal (3).[50]



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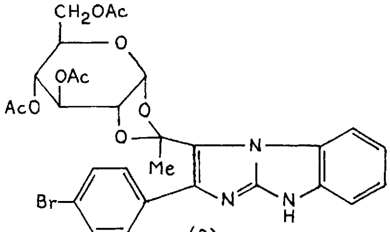
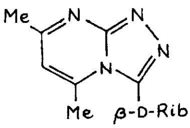


(3)

C-Glycosides and -nucleoside analogues reported were: 1-deoxy-1-methyl-α-D-glucopyranose,[51] 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*talo*-heptonamide (an α-*C*-glycoside),[52] ethyl 4-(α-D-erythrofuranosyl)-1,2-dimethyl-3-pyrrolecarboxylate,[53] 4-(α-D-erythrofuranosyl)-3-methyl-1-(*p*-tolyl)-4-imidazoline-2-thione monohydrate,[54] and the *C*-ribosides (4) and (5).[55]

Di- and Tri-saccharides and Derivatives Thereof.- A single-crystal sample of lactulose (4-*O*-β-D-galactopyranosyl-D-fructose) containing the β-furanose, α-furanose and β-pyranose forms in a 0.776: 0.111:0.125 mixture,[56] β-maltose octaacetate,[57] 2-acetamido-3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-1,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranose,[58] methyl 3,4-*O*-isopropylidene-2,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranoside,[59] and the unsaturated disaccharide (6).[60]



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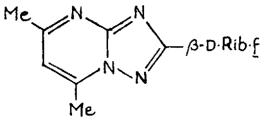

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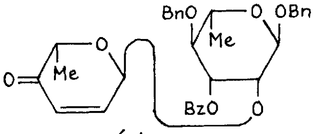

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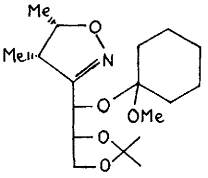
Halogen-, Nitrogen-, and Phosphorus-containing Compounds.- Methyl (2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate,[61] *tert*-butyl 2-azido-2-deoxy-β-D-galactopyranoside,[62] 2-amino-2-deoxy-D-arabinono-1,4-lactone,[63] the isoxazoline (7),[64] the bicyclic amino-sugar glycosylamine derivative (8),[65] methyl 2,3,4,6-tetradeoxy-4-(methoxycarbonylamino)-3-*C*-methyl-3-nitro-D-*xylo*-hexopryanoside (methyl tetronitroside),[66] (Z)-1,3,4,5,6-penta-O-acetyl-keto-D-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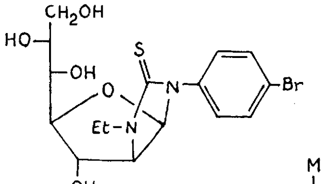
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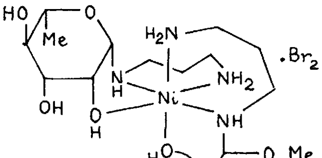
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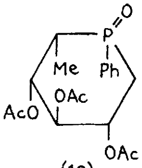
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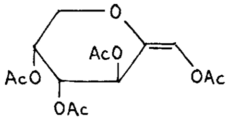
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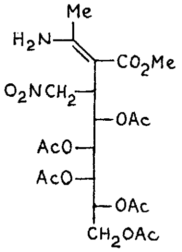
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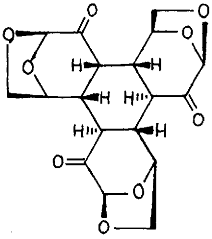
fructose (2,4-dinitrophenyl)hydrazone,[67] the octahedral nickel(II) complex (9),[68] and the 1,5-anhydro-5-C-phosphinyl-L-iditol derivative (10).[69]

Unsaturated Compounds.- (E)-1,3,4,5-tetra-O-acetyl-2,6-anhydro-D-arabino-hex-1-enitol (11),[70] and the nonenitol derivative (12).[71]

Anhydro-compounds.- Methyl 2,6-anhydro-α-D-mannofuranoside,[72] and the nonalkenic cyclic trimer (13) of levoglucosenone.[73]

Acid Derivatives.- D-Gluconic acid monohydrate,[74] 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone,[75] 5-C-hydroxy-1,2-O-isopropylidene-α-D-xylo-hexofuranurono-6,3-lactone (the hydrate of a 5-ulose),[76] methyl(ethyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)-uronate,[61] and the tricyclic derivative (14) derived from condensation of L-ascorbic acid with acrolein.[77]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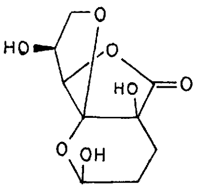
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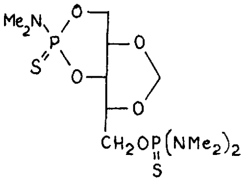
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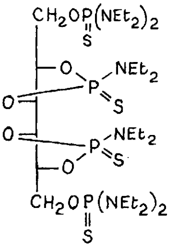
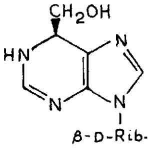

(16)

Alditols and Cyclitols.- 2,5-Anhydro-D-mannitol,[78] 1,5-anhydro-D-glucitol,[79] 1,2:4,5-dianhydro-3-*O*-(4-phenylbenzoyl)-xylitol,[80] and the phosphorylated xylitol and galactitol derivatives (15)[81] and (16).[82]

Nucleosides, Nucleotides, Derivatives and Related Compounds.- 5-Methyl-β-D-arabinofuranosylcytosine,[83] 5-methoxyuridine (a more precise determination),[84] 1-(6-deoxy-β-D-allofuranosyl)cytosine,[85] 1-(3'-*C*-methyl-β-D-ribofuranosyl)cytosine,[86] 1-(2-β-D-psicofuranosyl)cytosine,[87] *S*-adenosyl-L-homocysteine,[88] (5'-deoxyadenosin-5'-yl)acetic acid,[89] 3',5'-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)cytidine,[90] 5-bromo-2',3'-*O*-isopropylideneuridine,[91] 2',3'-*O*-isopropylidene-5'-*O*-tosyluridine,[92] 3',5'-di-*O*-acetyl-5-bromo-[93] and -5-iodo-2'-deoxyuridine,[94] and 1-(5'-*O*-acetyl-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-5-ditosylaminoimidazole-4-carbonitrile.[95]

The nebularine-methanol photoadduct (17),[96] the nucleoside analogue (18),[97] and the palladium(II) complex (19) containing glycine-L-tyrosine and cytidine.[98]



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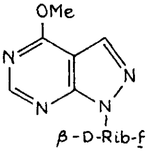

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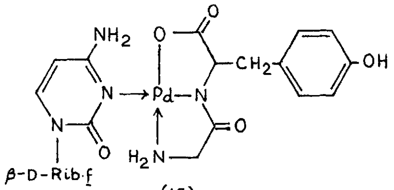

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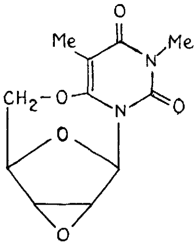
5'-Deoxy-5'-phenylselenoxyadenosine (one of the two diastereoisomers due to chirality at selenium),[99] 5'-deoxy-5',6-epithio-5,6-dihydro-2',3'-*O*-isopropylideneuridine,[100] 2',3'-anhydro-3-*N*-methyluridine and the 2',3'-*O*^{6},5'-dianhydride (20),[101] 8,5'-anhydro-8-hydroxy-9-β-D-ribofuranosyladenine (*i.e.*, 8,5'-*O*-cycloadenosine),[102] and 6,5'-anhydro-6-hydroxy-1-β-D-ribofuranosylcytosine (*i.e.*, 6,5'-*O*-cyclocytidine).[103]



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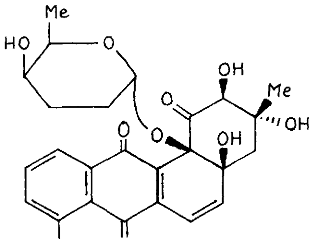

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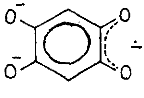

(22)

2'-Deoxy-5-fluorouridine 3',5'-cyclic phosphate,[104] and deoxycytidine 5'-phosphate disodium salt.[105]

Antibiotic.- The antibiotic metabolite of a Norcardia sp., sakyomycin A (21).[106]

4 E.s.r. Spectroscopy

An e.s.r. study on the alkaline, oxidative degradation of mono- and polysaccharides has revealed the common dominant radical (22) from 2,5-hydroxy-p-benzosemiquinone, which was considered to arise from air oxidation of phenolics from alkali catalyzed fragmentation-aldol condensation of sugars.[107] A trapped electron and a hydroxyalkyl and an alkoxy radical have been identified by e.s.r. in X-ray irradiated single crystals of trehalose at 3 K, a primary reaction mechanism being proposed.[108] A trapped hydrogen atom and both O-3' and O-2' radicals have been observed on similar irradiation of 6-methylmercaptopurine riboside at 20 K.[109] An e.s.r. and u.v. study of the radicals generated by ultrasound irradiation of D-glucose solutions and spin-trapped by 2,4,6-tri-tert-butylnitrosobenzene, suggested the intermediacy of reductones.[110] Mixed monoesters prepared by esterification of methyl-α-D-glucopyranoside with the nitroxide spin label 3-chloroformyl-2,2,5,5-tetramethylpyrroline-1-oxide, have been examined by e.s.r. as part of a study on a simple method for spin labelling polysaccharides.[111]

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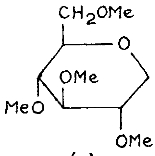
23

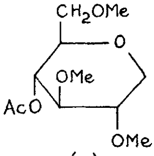
Separatory and Analytical Methods

1 Chromatographic Methods

General.- Several new techniques for sequencing oligosaccharides have been demonstrated on maltotriose and β-cyclodextrin and involve: i) conversion of reducing moieties into 1-deoxy-1-pyridinylamino-alditol moieties by reductive amination; ii) total or partial ionic hydrogenation (Et_3SiH-$BF_3{\cdot}Et_2O$) of permethylated substrates; iii) conversion of liberated free hydroxy groups to their naphthoyl ester derivatives; and iv) direct c.i.-m.s. or g.c.-m.s. analysis of products. Procedures i) and iii) render the components suitable for sensitive fluorescence detection on h.p.l.c. analysis. Maltotriose was thus reductively aminated, permethylated, reductively cleaved, and acetylated to give compounds (1)-(3).[1]



(1)



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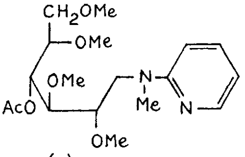


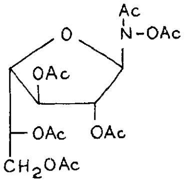
(3)

Gas-Liquid Chromatography.- The conditions required for methanolysis of polysaccharides prior to g.c. analysis of the constituent sugars have been examined, and the decrease in the acid concentration on heating methanolic hydrochloric acid at 80° has again been observed.[2]

A new method for preparing alditol acetate derivatives has been detailed which avoids the need to remove borate prior to acetylation, performing both the reduction ($NaBH_4$) and the acetylation (catalyzed by 1-methylimidazole) in DMSO;[3] it was applied to the capillary g.l.c. analysis of plant cell-wall constituents,[3] to neutral and amino-sugars released from glycoproteins and polysaccharides, and to the nitrous acid-deaminated products of amino-sugars.[4] It can be noted, however, that reduction of D-glucose under these conditions appeared to be only 87% complete.[3] A number of small but carefully considered changes to the traditional preparation and capillary g.l.c. analysis of neutral and amino-sugars as their alditol acetate derivatives have been described, and combined to provide an improved analysis procedure.[5] Retention data for a wide range of plasticizers have been reported under conditions suitable for capillary g.l.c. analysis of alditol acetates and their partially methylated analogues, and ways of minimizing contamination by these widespread compounds suggested.[6] A wide range of partially methylated pentitol and hexitol acetates have been examined on heat stable, weakly polar packed columns prepared by mixing two different phases (SE-30 and Silar 10C) in varying ratios.[7] A procedure for analysing the constituted sugars of cellulose and hemicelluloses in recent sediments, involving selected hydrolyses and g.l.c. analysis of alditol acetate derivatives, has been detailed.[8]

Sugar enantiomers have been separated as their diastereoisomeric α-methylbenzylaminoalditols (produced by reductive amination with a chiral amine) by capillary g.l.c. of either the peracetate or per-TMS derivatives. Twenty of twenty-four monosaccharides, including ketoses and N-acetylamino-sugars, were resolved as the above TMS-derivatives.[9]

The procedure employed for the preparation of aldononitrile peracetate derivatives, involving oximation (py-$NH_2OH.HCl$) and acetylation (py-Ac_2O), previously considered to give a quantitative conversion of monosaccharides to nitriles, has now been shown to provide significant amounts of N-hydroxy-D-glycosylamine hexa-acetates in the case of D-galactose and D-glucose. Thus D-galactose yielded the β-furanose (4), β-pyranose, and α-furanose isomers in 16, 2, and 1% isolated yields.[10] Some improvements in the g.l.c. analysis of acetylated aldononitriles have been described.[11]



(4)

Complementary procedures for capillary g.l.c. separation of enantiomeric sugars as either their trifluoroacetylated O-(-)-

menthyloxime[12] or O-(-)-bornyloxime[13] derivatives have been described, the former being applied to tetruloses and pentuloses with selected ion- c.i. (isobutane) -m.s. data being presented. Arabinitol, fucitol, and mannitol enantiomers have been resolved by capillary g.l.c. of their per-O-trifluoroacetates on a chiral stationary phase (a polysiloxane with L-valine-(R) or (S)-α-phenylethylamide substituents).[14]

Isosorbide (1,4:3,6-dianhydro-D-glucitol), a metabolite of isosorbide dinitrate, has been determined in urine by capillary g.l.c. of its heptafluorobutyrate derivative with electron-capture detection.[15]

Trimethylsilylation - capillary g.l.c. analysis has been used for the complete estimation of seventeen disaccharides,[16] for analysis of the common diluents (glucose, mannitol, lactose, sucrose, and fructose) in street samples of narcotics,[17] and, when coupled to an m.s., to identify polyols present in human urine and serum, several deoxyalditols and cyclitols being identified for the first time in urine.[18] Hydroxy acids (including gluconic, mannonic, arabinonic, and ribonic) such as those obtained by oxidation of glucose with oxygen, could also be analysed in this way, provided they were first converted to their ammonium salts using cation exchange techniques prior to silylation to avoid lactone formation; the ammonium salts were more soluble in the silylating medium than the corresponding sodium salts.[19] The low molecular weight carbohydrates in the seeds of seven commercially important legumes, namely cyclitols, cyclitol-derived oligosaccharides, and sucrose α-D-galactosides, were analysed as TMS-ethers on a packed column.[20]

In connection with the analysis of proteoglycans, sugars and amino-sugars have been analysed by capillary g.l.c. as their N-acetylated O-trimethylsilylated methyl glycosides.[21] O-Hydroxyethyl-D-glucoses released on acid hydrolysis of hydroxyethyl starch have been analyzed as TMS-oxime derivatives.[22] Free and bound sialic acid moieties have been analyzed by enzymic digestion (neuraminidase, N-acetylneuraminate lyase) and g.l.c. determination of the released N,O-acylmannosamines and pyruvic acid as their trimethylsilylated diethyldithioacetal derivatives; N-acetyl, N-glycolyl-, and N,O-diacetyl-neuraminic acid moieties have been detected, and preliminary analyses on urinary sialic acids have indicated significantly higher levels of N-acetylneuraminic acid in cancerous compared to normal subjects.[23]

O-Isopropylidene derivatives of seven naturally occurring mono-O-methylaldoses have been characterized by g.l.c.-m.s.[24]

Thin Layer Chromatography.- Applications of two-dimensional t.l.c. to carbohydrates have been covered in a general review of the method.[25] The thermal-u.v. method for detecting sugars on silica gel t.l.c. plates, in which the plates are heated to produce tiny amounts of strongly u.v.-detectable (366 nm) compounds, has been further studied. Temperatures for onset of u.v.-detection varied from 60° for glucosamine to 260° for trehalose, characteristic colours were seen for some compounds, and high sample recoveries could be achieved.[26] Fluorimetric detection of carbohydrates in t.l.c. or h.p.l.c. has been achieved using a taurine-borate buffer (pH 8.7) reagent, with detection down to 0.1-0.2 nmol for t.l.c.[27] Reducing mono- and oligo-saccharides (0.1-1 nmol) have been analyzed by reductive amination ($NaBH_3CN$-4-N,N-dimethylamino-4'-aminoazobenzene), two-dimensional t.l.c. separation on polyamide sheets, and detection as coloured spots on exposure to hydrogen chloride gas.[28] A silica gel-t.l.c. separation of dolichol (a generic name for polyprenols of 14-21 isoprene units) monophosphate mannose from dolichol monophosphate glucose has been reported which is dependent upon the saccharide unit, but independent of the size of the lipid moiety.[29] myo-Inositol has been determined quantitatively by silica gel-h.p.t.l.c. separation, lead tetraacetate-sodium fluorescein treatment, and fluorimetric detection.[30] Reversed-phase t.l.c. (dodecyltrichlorosilyl silica gel) separations of the main DNA nucleobases, nucleosides, and related 5'-nucleotides, and of the radiation induced degradation products of 2'-deoxyguanosine, have been reported.[31] In the separation of nucleosides and nucleobases on cellulose with water or aqueous salt solutions as eluant, increasing concentrations of ammonium sulphate have been shown to first increase then decrease R_F values, the latter salting-out effect permitting a large variation in retention in a very simple system.[32]

High Pressure Liquid Chromatography.- A review on the use of h.p.l.c. for the separation of sugars, covering the period 1970-80, has appeared.[33] A triple-pulse amperometric method for detecting sugars, using a platinum wire electrode, has been demonstrated for analysis of carbohydrate mixtures on two cation exchange resins, results being given for glucose and fructose levels in three wines.[34] A novel post-column photoreduction detector, which relies upon the dramatic increase in fluorescence quantum yield accompanying the photoreduction of anthraquinone-2,6-disulphonate to 9,10-dihydroxyanthracene-2,6-disulphonate that occurs only in the presence of hydrogen atom donating substances (e.g. alcohols, aldehydes, ethers, amines etc., but not water or acetonitrile), has been demonstrated in the analysis of cardiac glycosides and of common food saccharides.[35] In a comparative study of post-column reaction detectors currently used for h.p.l.c., the preparation of fluorescent derivatives of reducing sugars by reaction with 2-cyanoacetamide in slightly alkaline solution has been detailed,[36] while other workers have shown that a 5-10 fold increase in the sensitivity of this method can be achieved by increasing the reaction temperature from 105° to 135°, and that the method is compatible with both primary amine-bonded silica (where acetonitrile is used in the eluant) and ion-exchange columns; they then applied the method to the analysis of beer saccharides.[37]

The loss of aldoses by reaction with the primary amine functions on various amine-bonded silica or dynamically coated silica columns has again been demonstrated, while an attempt to use dimethylamino-functionalized silica, which did not react with sugars, failed to provide sufficient chromatographic separation. Both a diol-modified silica column with an eluant containing diisopropylethylamine to enhance mutarotation, as well as a cation exchange resin in the Ca^{2+}-form with water as eluant (improving signal-to-noise by 10-fold when using refractive index detection), have been successfully used in the separation of sugars generally, and in the accurate assay of lactose in milk.[38] The separation of 63 sugars and polyols has been examined, comparing a dynamically coated amine-modified silica column (using tetraethylenepentamine) with a cation exchange column [Ca^{2+}-form, aqueous $Ca(OAc)_2$ as eluant]. While the former method had advantages of longer column life, and better separation and capacity, the possible reaction of aldoses with the amine was a concern. The ion-exchange method had greater sensitivity and separated ethanol from carbohydrates, but had to be run at higher temperatures and regenerated periodically. Neither column was compatible with salts in the sample.[39] The interference caused by chloride, nitrate, and sulphate ions in the analysis of sucrose and glucose on a silica gel column dynamically coated by pentaethylenehexamine has been described, and overcome by precipitation of chloride (by Ag_2SO_4) then sulphate [by $Ba(OH)_2$]

prior to analysis for these sugars in illicit heroin samples.[40] A baseline separation of L-rhamnose, L-arabinose, D-xylose, D-mannose, D-galactose, and D-glucose has been achieved by initial separation on an amine-bonded silica column to provide fractions containing L-rhamnose, pentoses, and remaining hexoses, the latter two being re-concentrated and separately analyzed on a cation exchange resin column in a "heavy metal" form. The method has been applied to two plant polysaccharide hydrolyzates.[41] The analysis of sugars in various foodstuffs by h.p.l.c. on Separon-NH_2 has been compared favourably with polarimetric analysis.[42] Thermodynamic parameters for the h.p.l.c. separation of fructose, glucose and sucrose on amine and cobalt(III) complex bonded phases have been reported.[43] The following oligosaccharides have been analysed on primary amine bonded silica columns: linear and cyclic (1→4)-α-D-gluco-oligosaccharides in connection with cyclodextrin glycosyltransferase,[44] neutral N-acetyl-D-glucosamine containing oligosaccharides (D.P.2-6) that form part of the complex-type carbohydrate chains of glycoproteins,[45] even- and odd-numbered oligosaccharides (D.P. up to 8) from degradation of hyaluronic acid,[46] and a series of oligosaccharides [$(Man)_2GlcNAc$ to $(Man)_9GlcNAc$] from mannosidosis urine.[47] Product mixtures from the alkaline borate induced isomerization of maltose and cellobiose into maltulose and cellobiulose have been analyzed on a primary amine bonded silica column with an amine modifier in the eluant, and the pure keto-disaccharides have been isolated semi-preparatively by h.p.l.c. on cation exchange resin in the Ca^{2+}-form.[48] The separation of mono-, di- and tri-saccharides and polyols achieved on a reversed-phase column modified by n-dodecylamine or n-tetradecylamine in the mobile phase has been found to be very similar to that obtained with a propylamine bonded silica column, except that a smaller proportion of water in the aqueous acetonitrile eluant had to be used.[49]

Methods of analysing sugars in cane and beet molasses by h.p.l.c. (reversed-phase, amine-bonded silica, and Na^+- and Ca^{2+}-exchange resins) have been compared with the classical Lane-Eynon method; the method employing the Na^+-form resin was found to be the simplest, requiring only prefiltration of the sample.[50] A number of useful separations which appear to be based on normal phase chromatography have been demonstrated in a study of 10 mono-, 5 di- and one tri-saccharide, together with 2 alditols, using a polystyrene-based cation exchange resin in the Na^+-form.[51] The best separations of glucose, maltose, and malto-oligosaccharides that could be achieved on a cation-exchange resin in the Ca^{2+}-form were attained at about 90° using a neutral 50 ppm CaEDTA mobile phase. Heat alone was a good mutarotation catalyst and did not cause the isomerization associated with the use of alkaline catalysts at higher temperatures.[52] The analysis of sucrose, glucose and fructose in plant tissue extracts on a cation exchange resin (Ca^{2+}-form) has been reported.[53]

Reversed-phase separations of cello- and malto-oligosaccharides (D.P. up to 6 and 9 respectively) have been achieved in 5-10 minutes using glass rather than stainless steel cartridges and increased temperatures, to enhance column efficiency.[54] Human milk oligosaccharides have been separated by reversed-phase chromatography (Dextropak), and the system has been used for the preparative isolation of lacto-N-neotetraose.[55]

Reversed-phase h.p.l.c. has been used to separate the products of methanolysis (MeOH-HCl). An effective separation of the methyl glycosides of fucose, galactose, glucose, mannose, and xylose has been achieved, and applied to the analysis of lactose and a polysaccharide sample.[56] A Dextropak column has been used in the h.p.l.c. monitoring of the methanolysis of monosaccharides (including D-galacturonic and D-glucuronic acids) and polysaccharides,[57] and in connection with the analysis of alginate samples for the separation of mixtures of D-mannuronic and L-guluronic acid methyl ester-methylglycoside and lactone-methyl glycoside derivatives.[58]

Analytical and preparative h.p.l.c. of a wide range of water-soluble glycosides has been accomplished on silica with a water-containing eluant, impressive separations of cardiac, monoterpenoid, and flavonoid glycosides, and of saponins, in natural extracts being reported.[59] A post-column immobilized β-glucuronidase enzyme reactor has been described which permits the hydrolysis of phenolic glycosides and glucuronides in a reversed-phase h.p.l.c. eluant, followed by selective electrochemical detection of the released phenolics. The system was also suitable for the analysis of cyanogenic glycosides.[60] The retention of cardiac glycosides on a diphenylsilyl reversed-phase column has been confirmed to be due primarily to the hydrophobic properties of these compounds.[61] Separations of bilirubin isomers and their mono- and di-glucuronide, -glucoside, and xyloside metabolites (reversed-phase),[62] and of phenyl, benzyl, and o-nitrophenyl glycosides of 2-acetamido-2-deoxy-D-galactopyranoside and various mucin-type di- to tetrasaccharides (amine and nitrile functionalized silica phase)[63] have been reported. Automation of an analytical scale h.p.l.c. separation of benzyl α- and β-D-gluco-furanosides and pyranosides on silica has permitted the preparative fractionation of 2.5-3 g mixtures in 24 h.[64]

More sensitive detection of sugars can be achieved by derivatization prior to analysis. The chromatography of per(dimethylphenylsilyl)ated alditols, and mono- and di-saccharides on silica has been examined, but while these derivatives had reasonable stability towards hydrolysis and good u.v.-detectability, each sugar gave rise to several peaks, and sugar isomers were not particularly well resolved.[65,66]

100 pg-1 ng Amounts of sugars (including amino- and acetamido-sugars) have been characterized by conversion to per-p-bromobenzoylated or pernaphthoylated methyl glycosides, separation by h.p.l.c. on silica, and unequivocal identification by m.s. or c.d. measurements; procedures for predicting the latter values were discussed.[67] Selected mixtures of seventeen monosaccharides, oligosaccharides, and uronic acids have been separated as their O-methyloxime derivatives, which absorb in the u.v. at 215 nm ($\varepsilon > 6,000$), and to a lesser extent as their O-benzyl- and O-p-nitrobenzyl-oximes, on amine-bonded silica.[68] The preparation and reversed-phase analysis of dansyl (i.e.,5-dimethylaminonaphthalene-1-sulphonyl) hydrazone derivatives of reducing sugars has been carefully optimized, and a detection limit of 2-5 pmol established using fluorescence detection; the method was applied to the analysis of physiological fluids, beverages, and wood hydrolyzates.[69] Analysis of some 23 neutral and amino-sugars as their alditol benzoates (on silica), and the effect of varying the ternary eluant on resolution, have been studied.[70]

Analyses of gallotannins forming an homologous series of tetra- to undeca-galloylglucoses based on a 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose core (reversed-phase),[71] and of α-D-glucose 1-phosphate (strong base anion exchange resin) suitable for monitoring α-glucan phosphorylase activity,[72] have been reported.

Galactosamine and glucosamine have been detected down to 200 pmol by h.p.l.c. (strong cation exchange resin) with a post-column reactor based on the Hantzsch reaction (2,4-pentanedione and formaldehyde) and fluorimetric detection.[73] Muramic acid [2-amino-3-O-(D-1'-carboxyethyl)-2-deoxy-D-glucose] could be separated (reversed-phase) from amino acid constituents after derivatization with o-phthalaldehyde.[74] The rate constants for the mutarotation of muramyldipeptides have been calculated from their observed reversed-phase h.p.l.c. behaviour, interconverting material appearing as a plateau between the peaks for each anomer.[75] The asparagine-bound oligosaccharide moieties of glycoproteins have been examined by regiospecific degradation using hydrazinolysis (to cleave the glycosylamide linkage and N-deacetylate), nitrosation (to cleave 2-amino-2-deoxy-glycosyl linkages), and reduction ($NaBH_3CN$), followed by h.p.l.c. analysis of the products on an amino- and cyano-bonded silica phase.[76]

D-Mannuronic and L-guluronic acids in alginate hydrolyzates have been assayed using a silica-based anion-exchange column, with detection down to 10 μg.[77] D-Glucaric acid and its 1,4- and 3,6-mono- and 1,4:3,6-di-lactones have been separated on a primary amine bonded silica column used as a weakly basic anion exchanger,[78] while D-[U-^{14}C]-glucaric acid and other metabolites of D-glucuronic acid in urine have been examined on a polystyrene-based quaternary ammonium ion-exchange resin using both u.v. and radioactivity detection.[79] Other papers report the analysis of ascorbic acid and dehydroascorbic acid in fruit and vegetables, using an amine-bonded silica column and dual wavelength u.v. detection,[80] and the estimation of these two compounds in sum, together with diketogluconic acid, in beer, employing iodine oxidation, 2,4-dinitrophenylhydrazone formation, and reversed-phase chromatography.[81]

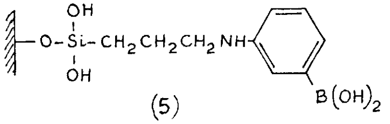
Partially methylated glucitol, galactitol, mannitol and myo-inositol derivatives have been separated by reversed-phase chromatographic procedures that are applicable to large scale recovery and for quantifying radiolabelled derivatives.[82] Cyclitols, cyclitol-derived oligosaccharides, and sucrose α-D-galactosides present in legume seeds have been analysed on a primary amine bonded silica column.[20]

The following antibiotics have been analysed by h.p.l.c. methods: lincomycins A and B in fermentation beers (reversed-phase ion-pairing),[83] gentamicin C complex (reversed-phase, using pre- or post-column derivatization with o-phthalaldehyde-thioglycollic acid reagent),[84] tunicaminyluracil-based antibiotics[85] and the aminoglycoside amikacin as its tetra-N-(2,4-dinitrophenyl) derivative[86] (reversed-phase), and the aminoglycoside sisomicin,[87] macrolides related to tylosin,[88] and glycosylated anthracycline derivatives[89] (reversed-phase ion-pairing).

A number of studies have reported reversed-phase analyses of nucleosides. From a study of 86 purine bases, nucleosides and nucleotides, the contribution of substituents on the purine moiety to retention behaviour has been determined, and the data used for predicting structure-retention relationships.[90] The effects of stationary phase variables, (e.g., length of bonded alkyl chain, and accessibility of free silanol groups) on the chromatographic behaviour of nucleosides, nucleotides and bases has been examined,[91] while the use of a trimethylsilica phase has permitted the isocratic separation of 18 deoxyribo- and ribo-nculeosides.[92] A simple procedure for extending the life of 3 μm packings, involving the use of a compressed guard column, has been demonstrated using the separation of adenosine, 2'-deoxyadenosine, and S-adenosyl-L-homocysteine.[93] Separations of ribo- and deoxyribonucleosides and related bases, nucleotides and cyclonucleotides have been developed for examining nucleoside phosphorylation (KH_2PO_4-formamide) products.[94] Quantitative analyses of the structurally similar nucleosides adenosine, adenine arabinoside and 2'-deoxyadenosine have been achieved using reversed-phase methods, even when one component is present only as an impurity in another, and it has been suggested that these results are of general relevance when the purity of chemically modified biologically active materials must be determined.[95] Other reversed-phase separations reported were: adenine, adenosine, and related nucleotides as their fluorescent 1,N^6-etheno-derivatives,[96] and 1-β-D-arabinofuranosyl-cytosine and -uracil in the presence of ribonucleosides,[97] methylthioadenosine,[98] and the anticancer C-nucleoside riboxamide (2-β-D-ribofuranosylthiazole-4-carboxamide)[99] all in biological samples.

Alternative dual-column analyses of the cytosine and uracil arabinosides (using reversed-phase then cation-exchange media),[100] and of riboxamide (on silica then reversed-phase media both coated with hexadecyltrimethylammonium bromide),[101] have been developed to enable the desired separation of these components from other constituents in biological samples.

The biochemically important S-adenosyl-L-methionine and its metabolites, S-adenosyl-L-homocysteine, 5'-deoxy-5'-methythioadenosine, S-adenosyl-(5')-3-methylthiopropylamine, and adenine have been separated on a silica-based strong cation exchanger.[102] A hydrophobic anion exchange packing material obtained by derivatization of silica with a mixture of chlorosilanes to give both octyl and quaternary amine functionalities, was shown to be superior for the separation of deoxynucleosides and their mononucleotides than that obtained from physically mixing commercial C_8 and anion exchange packings.[103] In a study of the operating parameters for preparative scale displacement chromatography using analytical size h.p.l.c. columns, the benzyl tributylammonium chloride induced displacement separation of adenosine, inosine, and their 2'-deoxy-analogues on a reversed-phase column was demonstrated.[104] Arylboronic acid substituted silica (5) has been used to pre-


(5)

fractionate polyols, the cis-diol containing components (e.g. fourteen ribonucleoside examples) being selectively retained at alkaline pH, then eluted at acidic pH onto a reversed phase column for analysis.[105,106]

Column Chromatography.- Gel-filtration has been used for determining the levels of glucose, sucrose, raffinose, stachyose, and verbascose in developing lupin seeds.[107] Nucleobases, nucleosides, and nucleotides have been separated by ion chromatography (on a low-capacity anion-exchange resin) with dual conductimetric and u.v. detection, the nucleobases and nucleotides acquiring a negative charge in the carbonate eluants used.[108] The medium-pressure anion-exchange chromatography of organic acids including glucuronic and galacturonic acids, and oligogalacturonic acids (D.P. up to 8) from pectin hydrolysates, on a partially quarternized DEAE-Spheron (hydroxyethyl methacrylate copolymer) medium has been described.[109]

2 Electrophoresis

Analytical isotachophoresis has been used for the determination of 5'-deoxy-5-fluorouridine and its metabolite 5-fluorouracil in plasma,[110] while data for gluconic and glucuronic acids have appeared in a compilation of isotachophoretic indices.[111]

3 Other Analytical Methods

Glucose reacted readily under acid catalysis with solid-phase Girard reagents consisting of a polystyrene-based matrix functionalized either with acid hydrazide ($RCH_2SCH_2CONHNH_2$) or alkylhydroxylamine groups (RCH_2ONH_2); the sugar could be recovered by exchange with acetone under mildly acidic conditions.[112] A new method for the assay of serum D-glucose employs the glucose oxidase catalysed oxidation of D-glucose to generate hydrogen peroxide, which in the presence of catalase, converts methanol to formaldehyde, the released formaldehyde being determined by g.l.c. analysis as its O-pentafluorobenzyloxime derivative.[113] Sucrose has been determined using either an oxygen Clark electrode or a platinum disc electrode, coated by a film of invertase, mutarotase, and glucose oxidase cross-linked by glutardialdehyde together with serum albumin. The decrease in oxygen content or the formation of hydrogen peroxide in the enzyme reaction layer is measured, and a steady state response proportional to the concentration of sucrose in the 0.03-1.5 $mmol.l^{-1}$ range can be attained in 1-2 min.[114]

Small amounts of fructose on the surface of anhydrous glucose crystals prepared from sucrose have been measured by selective dissolution, reaction with a modified diphenylamine reagent that is 147 times more sensitive to fructose than glucose, and spectrophotometric analysis at 640 nm.[115] An automated Elson-Morgan colourimetric assay for 2-amino-2-deoxyhexoses has been described which overcomes many of the problems associated with this assay.[116] Streptomycin has been selectively determined by its colour reaction with a manganese(II)-o-hydroxyhydroquinonephthalein complex in weakly basic solution, which appears to involve the guanidino moiety.[117]

An ion-exchange h.p.l.c. method for assaying the formic acid released on periodate cleavage of carbohydrates has been described, and the approach can be used to quantify monosaccharides.[118] A simple, rapid, and sensitive (0.5-5 nmol) spectrophotometric method for determining formaldehyde and acetaldehyde using alkaline solutions of 4-amino-5-hydrazino-3-mercapto-1,2,4-triazole has been shown to be suitable in the periodate analysis of glycols, sugars, and polyols.[119]

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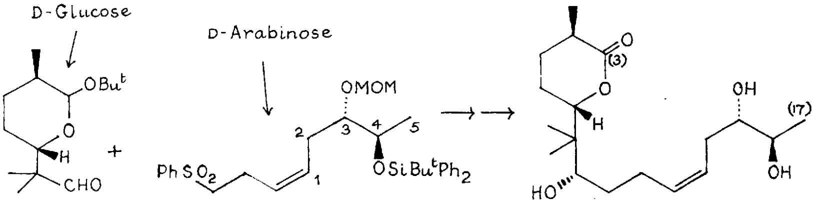
24

Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

A monograph has been published on the use of naturally-occurring chiral compounds as synthons for the preparation of chiral compounds, with special reference to carbohydrates.[1] Reviews published during the year have included the use of carbohydrates for the synthesis of prostaglandins[2] and leucotrienes,[3] the use of D-mannitol for the synthesis of chiral natural products via (S)-glycerol derivatives,[4] and the general use of carbohydrates for the asymmetric synthesis of natural products.[5]

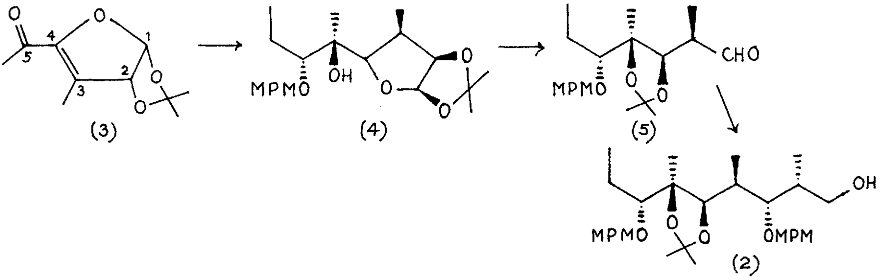
1 Antibiotics and their Components

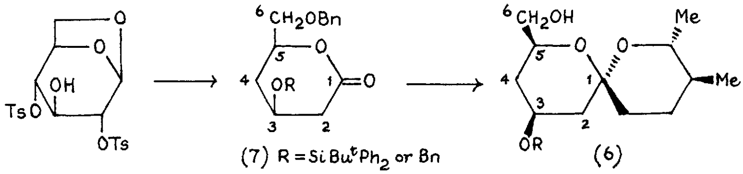
The C-3 ⟶ C-17 segment (1) of the boron-containing antibiotic boromycin has been synthesized by condensing two intermediates prepared from D-glucose and D-arabinose respectively, as outlined in Scheme 1.[6] (sugar numbering in the intermediate) Other syntheses of segments of macrolide rings have included the left-hand segment (2) of 9-dihydroerythronolide A, containing six consecutive chiral centres, from D-glucose via the intermediates (3)-(5), using Wittig reactions and stereoselective oxidations to set up the stereochemistry at the ends of the sequence,[7] and the synthesis of the spiroacetal moiety (6) present in avermectins and milbemycins, prepared from laevoglucosan via the lactone (7).[8] A series of papers from Kochetkov's laboratory describe the use of laevoglucosan in preparing segments of macrolide rings from the intermediates (8),[9] (9)(R=OBn),[10] (9)(R=H) and (10),[11] (11),[12] and (12).[13]
The C-9 ⟶ C-13 segment (13) of the macrolide methynolide has been

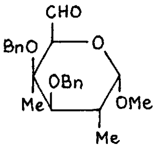


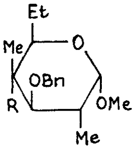
Scheme 1

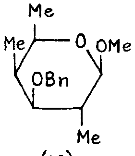
(1)






(8)


(9) R=H or OBn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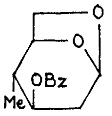
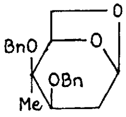
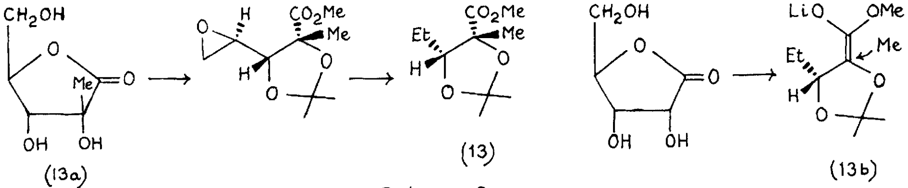

(11)


(12)

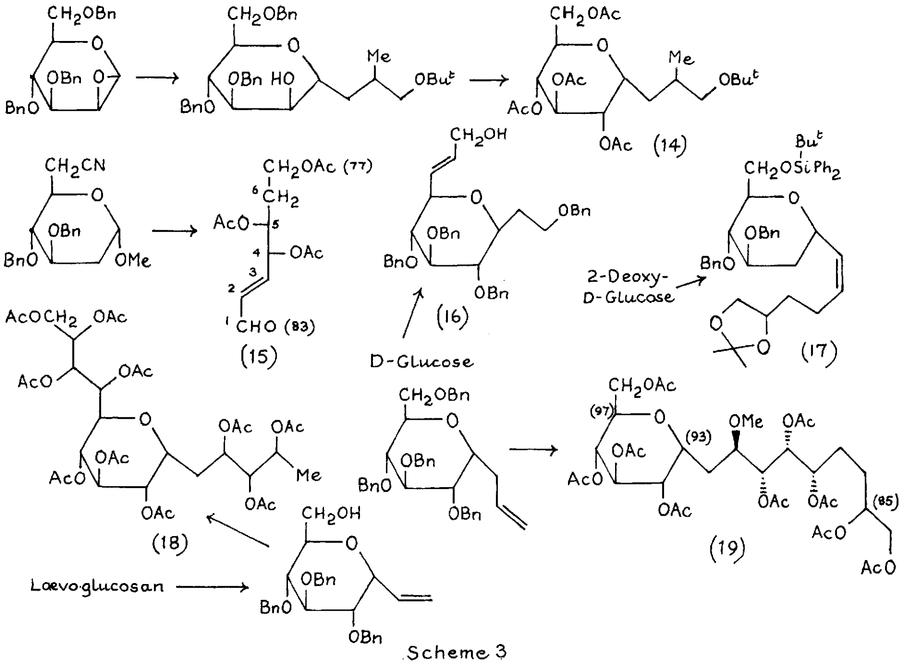
prepared from D-glucosaccharinolactone (13a) via the intermediates shown in Scheme 2. An analogous sequence from D-ribonolactone unexpectedly gave the <u>cis</u> isomer predominantly on C-2 methylation of the lithium enolate (13b), methyl addition being anticipated <u>trans</u> to the ethyl group.[14] Another series of papers by Kishi and



Scheme 2

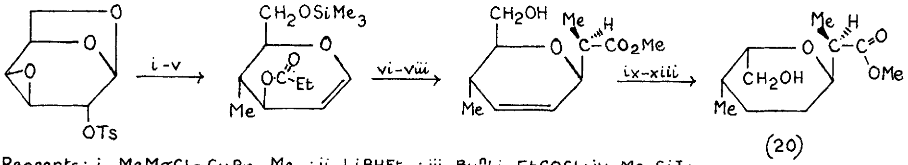
his coworkers has described the synthesis of the palytoxin degradation fragments (14),[15] (15)-(17),[16] (18),[17] and (19),[18] from D-glucose, 2-deoxy-D-glucose, or laevoglucosan, as illustrated in Scheme 3.

In a total synthesis of the ionophore antibiotic X-14547A, the



Scheme 3

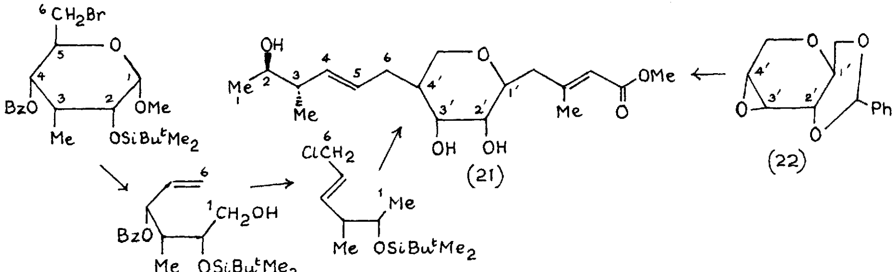
tetrahydropyran fragment (20) was synthesized from laevoglucosan as outlined in Scheme 4, utilizing a Claisen ester enolate rearrangement to form the C-glycoside diastereoisomers, and a 5,6-ene intermediate to epimerize the C-5 hydroxymethyl group.[19]



Reagents: i, MeMgCl-CuBr. Me$_2$; ii, LiBHEt$_3$; iii, Bu^{n}Li-EtCOCl; iv, Me$_3$SiI; v, DBU; vi, LDA-Me$_3$SiCl-NEt$_3$; vii, Bu$_4$F; viii, CH$_2$N$_2$; ix, H$_2$-PtO$_2$; x, I$_2$-Ph$_3$P; xi, AgF-Py; xii, BH$_3$.THF; xiii, H$_2$O-NaOH

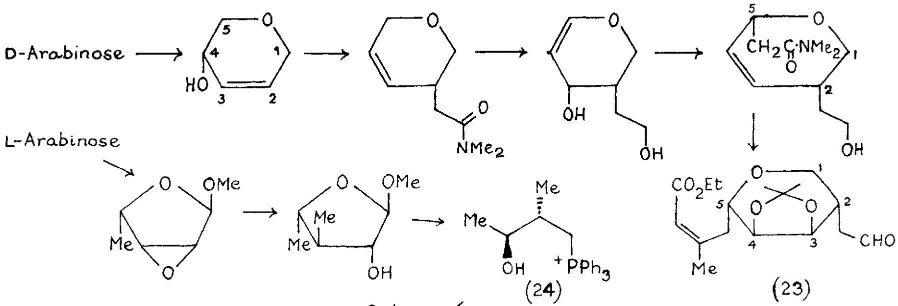
Scheme 4

In a synthesis of (+)-methyl pseudomonate (21), D-xylose provided the tetrahydropyran fragment (22) via a C-cyano glycoside derivative, and the chiral sidechain was elaborated from D-glucose as indicated in Scheme 5.[20] In another enantiospecific synthesis of pseudomonic acids, D- and L-arabinose were used to prepare the two fragments (23) and (24) respectively, which were then condensed in

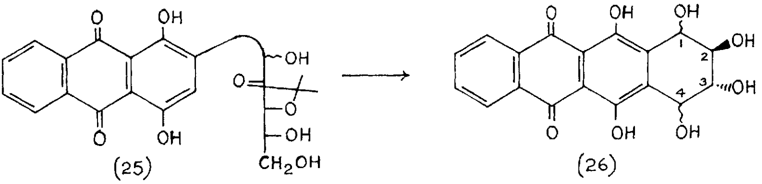


Scheme 5

a Wittig reaction (Scheme 6).[21,22] D-Arabinose has also been used to prepare the polyhydroxy-alkylated anthraquinone (25), which could then be oxidized with periodate and cyclized to give the chiral anthracyclinone analogue (26).[23]

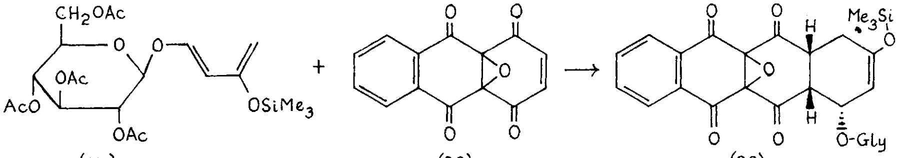


Scheme 6



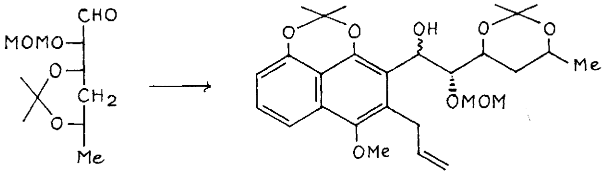
(25) (26)

A synthesis of (+)-4-demethoxy-daunomycinone has utilized the dienyl glucoside (27) to achieve a Diels-Alder reaction on the



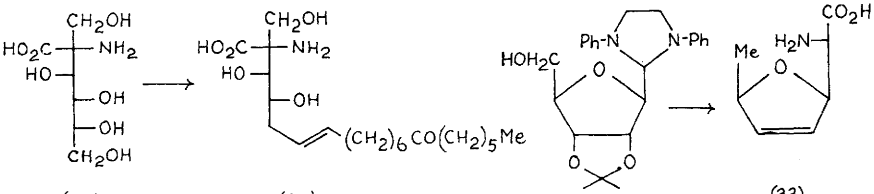
(27) (28) (29)

quinone epoxide (28) with high diastereo-control, giving the tetracycle (29).[24] Alkylation of the 4,6-dideoxy-L-ribo-hexose derivative (30) with a naphthyl-lithium reagent provides the intermediate (31) required for the synthesis of (+)-griseusin A.[25]

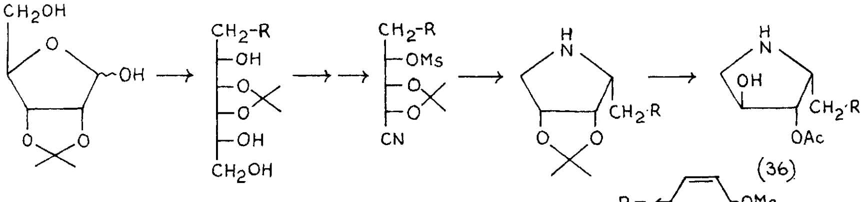


(30) (31)

Chiral syntheses of the amino-acid antibiotics thermozymocidin (32) and (+)-furanomycin (33) have been reported, starting from the D-fructose derivative (34)[26] and the D-ribose derivative (35)[27] respectively, the latter thereby establishing the stereochemistry of the antibiotic. D-Ribose has also been used as the chiral starting material for a synthesis of the alkaloid antibiotic anisomycin (36), outlined in the sequence shown in Scheme 7, the initial Grignard addition being stereospecific,[28] and for a synthesis of the cyclopentene moiety (37) of neplanocin A via the acyclic phosphonate (38)(Scheme 8).[29] D-Glucose has been used to prepare the chiral amino-acid component (39) of the anti-tumour bis-alkylator carzinophilin A (Scheme 9).[30]

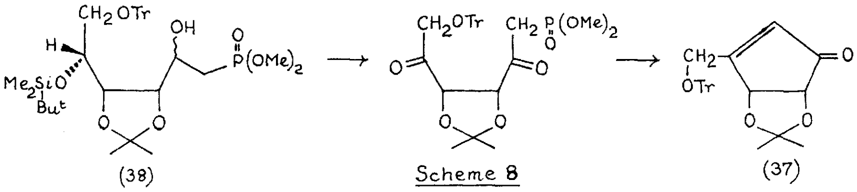


(34) (32) (35) (33)

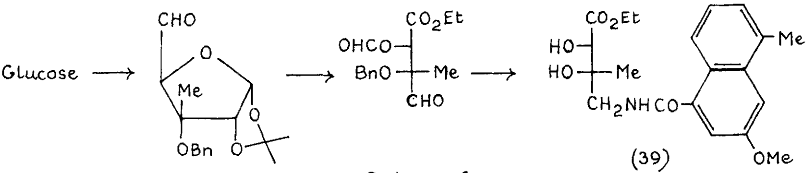


Scheme 7

Finally, although not strictly using a carbohydrate as a chiral source, a synthesis of the β-lactam (40) uses the Sharpless epoxid-

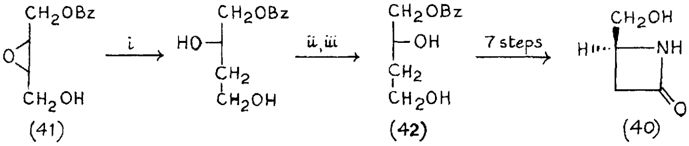


Scheme 8



Scheme 9

ation procedure to convert an alkene to the chiral 2,3-anhydroerythritol (41) which was then converted to the (R)-triol (42), and hence to (40)(Scheme 10).[31]

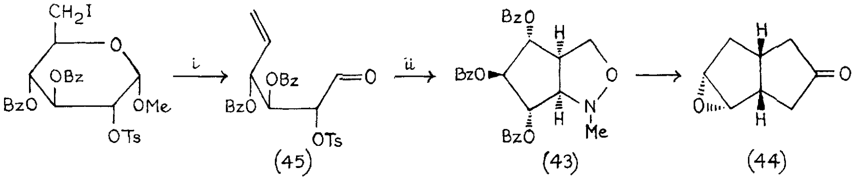


Reagents: i, $(MeOCH_2CH_2O)_2AlH$; ii, MsCl-Py; iii, KOAc-Ac_2O

Scheme 10

2 Prostanoids

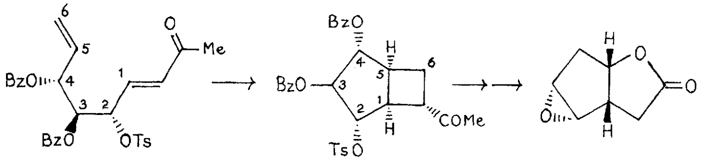
Ferrier's group have reported theconversion of a series of D-glucose derivatives to corresponding cyclopentane-oxazoline bicycles,[32] the derivative (43) then being used to make the prostaglandin intermediate (44)(Scheme 11).[33] Alternatively the intermediate (45)



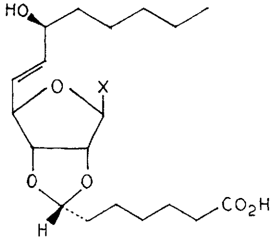
Reagents: i, Zn-EtOH; ii, MeNHOH

Scheme 11

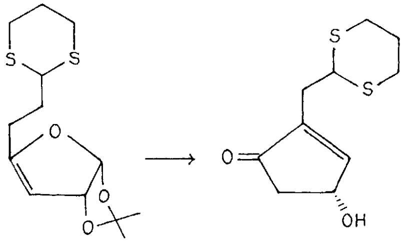
could be converted by a Wittig reaction to the dienone (46), which on irradiation yielded a bicyclo[3,2,0]heptane, leading in turn to the oxa-analogue (47) of (44).[34] Ribose was also used to prepare the prostacyclin analogues (48).[35] The synthesis of leucotrienes using chiral intermediates derived from L-ascorbic acid and D-glucose has also been described.[36] Another paper describes the conversion of D-glucose to the dithiane derivative (49), and hence to the cyclopentenone analogue (50).[37] Horton's group has made further studies on the use of Diels-Alder adducts with unsaturated sugar acids as prostaglandin precursors (see Vol. 15, p.259); in the presence of Lewis acids, the arabinose derivative (51) gave the stereoisomer (52) instead of the previously reported isomer, (52) then being converted to the 9,11-bishomoprostanoid synthon (53) (Scheme 12).[38,39]



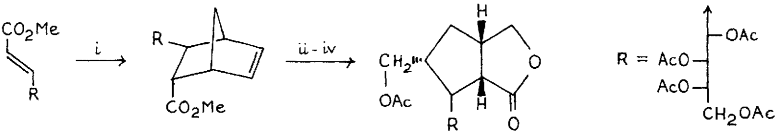
(46) (47)



(48) X=OMe or H



(49) (50)



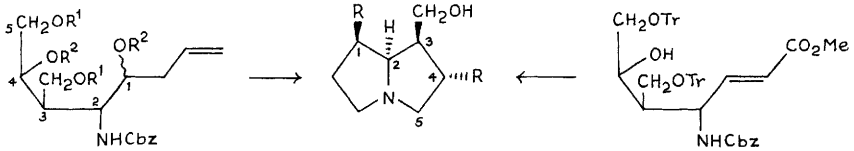
(51) (52) (53)

Reagents: i, $-AlCl_3$; ii, OsO_4-NaIO_4 ; iii, $NaBH_4$; iv, Acetylation

Scheme 12

3 Alkaloids

D-glucosamine has been used as the chiral source in a synthesis of (-)-rosmarinecine (54), with the branched-chain sugar (55) as an intermediate; likewise the Wittig product (56) was used to prepare the related alkaloid (-)-isoretronecanol (57).[40] D-Mannose provides



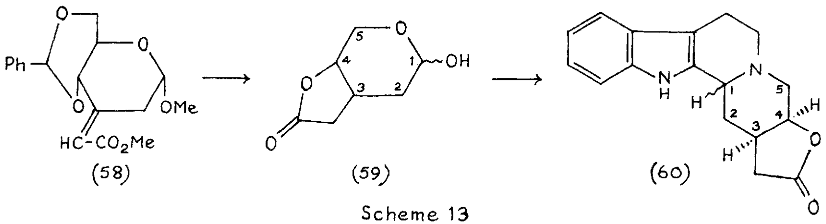
(55) $R^1 = SiBu^tMe_2$, $R^2 = CH_2OMe$

(54) R=OH

(57) R=H

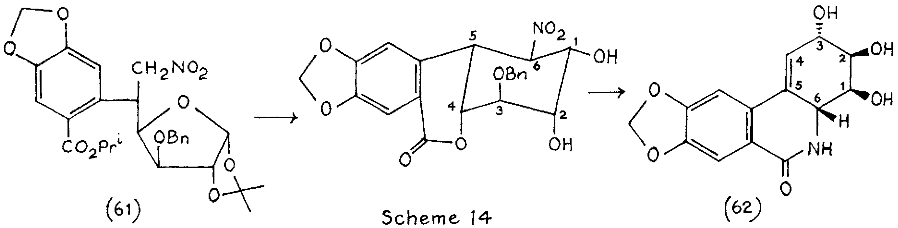
(56)

the unsaturated branched-chain sugar (58) used as a source of the lactone (59) which was then elaborated to (-)-ajmalicine (60) (Scheme 13).[41] D-Glucose furnished an unsaturated nitro-sugar which underwent Michael addition with an aryllithium reagent to yield the intermediate (61), leading on to (+)-lycoricidine (62)(Scheme 14).[42]



(58) (59) (60)

Scheme 13

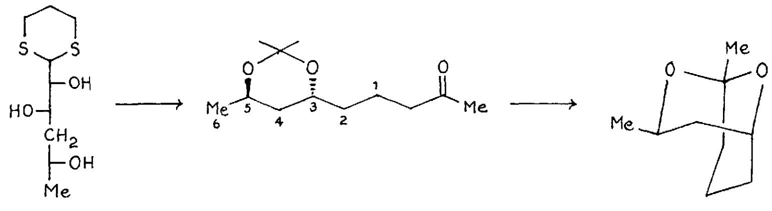


(61) (62)

Scheme 14

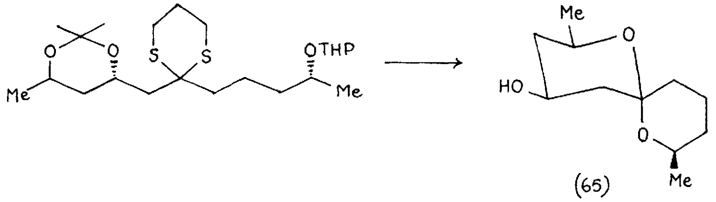
4 Miscellaneous Compounds

The dienone intermediate (46) mentioned above has been used in a new synthesis of the insect pheromone (+)-exo-brevicomin.[43] Four isomeric 1,3-dimethyl-2,9-dioxabicyclo [3,3,1] nonanes (63), one of which is claimed to be a beetle behavioural factor, have been synthesized from D-glucose via the key intermediate (64); the isomers were produced after appropriate inversions on acyclic precursors.[44] The intermediate (64)(or its enantiomer) was also



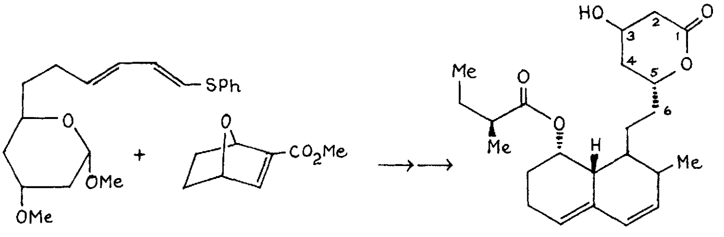
(64) (63)

condensed with a 5-iodopentan-2-ol derivative leading to the enantiomeric forms of 2,8-dimethyl-1,7-dioxaspiro [5,5] undecan-4-ol (65), one of which is an insect pheromone.[45] Triacetyl-D-glucal



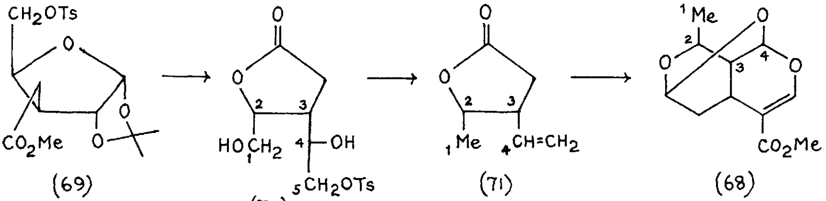
(65)

provides a source for the chiral intermediate (66) which was used in a Diels-Alder condensation leading to the hypocholesterolemic agent (+)-compactin (67).[46] D-Glucose has also been used for a



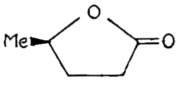
(66) (67)

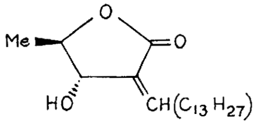
synthesis of the tricyclic monoterpene (-)-sarracenin (68), via intermediates (69)-(71).[47]

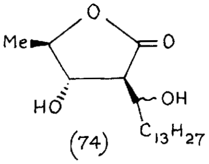


(69) (70) (71) (68)

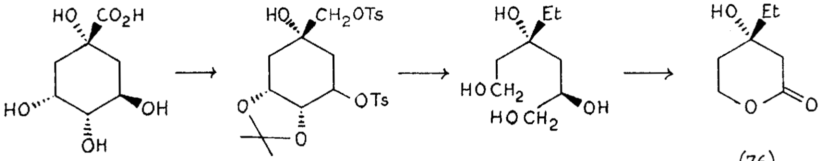
D-Ribonolactone has been a starting material for a chiral synthesis of (-)(R)-β-angelica lactone (72) by established deoxygenation reactions,[48] and also for total synthesis of the plant lactones (-)-litsenolides C_1 and C_2 (73), together with their C-3 epimers, in which the lithium enolate of its 2,5-dideoxy derivative adds to tetradecanal to give the intermediate diols (74).[49]


(72)


(73), E + Z isomers

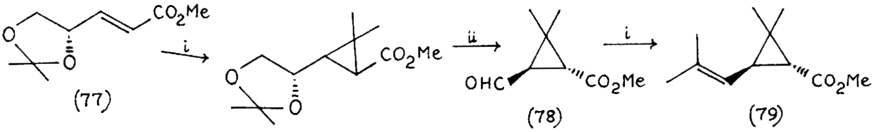

(74)

The inositol analogue quinic acid (75) has been used as a chiral source for a synthesis of (3S)-homomevalonolactone (76), establishing that the natural compound has the enantiomeric (3R) configuration.[50]


(75)

(76)

2,3-O-Isopropylidene-D-glyceraldehyde (readily obtained from D-mannose) has been used to prepare the αβ-unsaturated ester (77) by a Wittig reaction, and hence the cyclopropyl derivatives (1R,3R)-caronaldehyde methyl ester (78) and (1R,3R)-chrysanthemic acid methyl ester (79) following isopropylidene addition to the double bond (Scheme 15).[51] The same intermediate (77) has been utilized

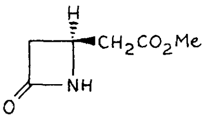


Reagents: i, Me_2C PPh_3 ; ii, $NaIO_4$-2N H_2SO_4

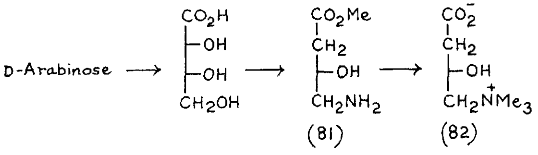
Scheme 15

for a synthesis of a β-amino-acid leading to the β-lactam (80).[52] The steric course of addition of organometallic reagents to 2,3-O-isopropylidene-D-glyceraldehyde has been studied.[53]

Sedoheptulosan is a convenient chiral reagent for a simple, one-step synthesis of 5-(D-glycero-1,2-dihydroxyethyl)-2-furaldehyde,[54] and D-arabinose has been used to prepare S-(+)-4-amino-3-hydroxybutyric acid (81) and S-(+)-carnitine (82); likewise L-arabinose or L-ascorbic acid served as precursors for their R-enantiomers.[55] 1,3;4,6-Di-O-benzylidene-D-mannitol serves as a suitable precursor for the synthesis of 2-O-alkyl-D-glyceric acid derivatives and related optically-active glycerol compounds.[56]

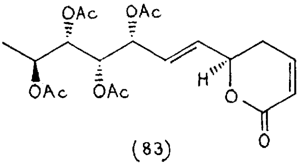


(80)



(81) (82)

D-Gulonolactone has been used to prepare 1-deoxy-D-gulitol and hence 2,3,4,5-tetra-O-acetyl-6-bromo-1,6-dideoxy-D-gulitol required for the synthesis of the sidechain in the bioactive δ-lactone (+)-anamarin (83).[57]



(83)

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In this index the number given in parentheses is the chapter number, which is followed by the reference numbers

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'Heterocyclic Chemistry' is an annual publication which combines material previously reviewed in three separate SPR titles: 'Saturated Heterocyclic Chemistry', 'Aromatic and Heteroaromatic Chemistry', and the heterocyclic sections of 'Organic Compounds of Sulphur, Selenium, and Tellurium'. 'Heterocyclic Chemistry' has now reached its fourth volume, which reviews the literature published on the subject during the period July 1981 to July 1982.

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