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Carbohydrate Chemistry

VOLUME 22

Monosaccharides, Disaccharides, and Specific Oligosaccharides

A Review of the Literature Published in 1988

ROYAL SOCIETY OF CHEMISTRY

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A Review of the Recent Literature Published during 1988

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Preface

This twenty second annual Report of the series on the chemistry of the simpler carbohydrates covers, with few exceptions, the 1988 literature; the format previously used has been retained. It is our objective to note all relevant papers published on the subject, and during the collection of material the reporters have scanned the main primary journals and have accessed references to other material through Chemical Abstracts. When the project was started in 1967 the literature was much easier to search for data, and the publications were much more straightforward to abstract than is the case today, the increased complexity and integration of the subject with other organic chemistry having made the task of producing the material for recent Reports considerably more difficult. In consequence, more relevant chemistry inevitably must slip through the screen - especially when carbohydrates are used in work with non-carbohydrate objectives, and when this fact is not revealed in titles of papers. The last Chapter, on the synthesis of enantiomerically pure non-carbohydrates from sugar derivatives, presents special problems in this regard, and it also is particularly troublesome when it comes to deciding what is relevant carbohydrates chemistry and what is not. Notwithstanding these imperfections, it is hoped this latest volume will continue to assist many chemists with their ever increasing problems of data management, and that a very high proportion of 1988 papers are included.

As incoming Senior Reporter I have had the greatest cooperation from colleagues who now include Dr Regine Blattner, and I thank her for the help she provided while taking over from Dr Bruce Davison whose eleven year contribution to the team I acknowledge with pleasure and thanks. Particular thanks are due to Dr Neil Williams for carrying the responsibilities of Senior Reporter for eleven volumes, for his reporting and editing contributions and especially for doing, by hand, all the art work for eight volumes. Happily he will continue as a team member.

This year we have been able to reduce somewhat the time taken to produce the manuscript, but we accept that we should improve further and believe we can.

The cooperation of Dr P.G. Gardam and Mr A.G. Cubitt of the Royal Society of Chemistry is gratefully acknowledged as is the work of all the typists, but special mention must be made of the contribution of Mrs Teruni Shivaz who, this year, produced with great skill and patience all of the nineteen chapters written in New Zealand.

R J Ferrier
April 1990

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R E P R I N T S

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

Abbreviations

The following abbreviations have been used:

Ac	acetyl
Ad	adenin-9-yl
AIBN	2,2'-azobisisobutyronitrile
All	allyl
BBN	9-borabicyclo[3,3,1]nonane
Bn	benzyl
Boc	t-butoxycarbonyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
c.d.	circular dichroism
CI	chemical ionization
DAST	diethylaminosulphur trifluoride
DBU	1,5-diazabicyclo[5,4,0]undec-5-ene
DCC	dicyclohexylcarbodi-imide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL	di-isobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
EE	1-ethoxyethyl
e.s.r.	electron spin resonance
FAB	fast-atom bombardment
GC	gas chromatography
HMPT	hexamethylphosphorous triamide
i.r.	infrared
LAH	lithium aluminium hydride
LDA	lithium di-isopropylamide
LTBH	lithium triethylborohydride
MCPBA	m-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MOM	methoxymethyl
m.s.	mass spectrometry
Ms	methanesulphonyl
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
n.m.r.	nuclear magnetic resonance
o.r.d.	optical rotatory dispersion
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PTC	phase transfer catalysis
Py	pyridine
SIMS	secondary-ion mass spectrometry
TASF	tris(dimethylamino)sulphonium difluorotrimethyl silicate

TBDMS	t-butyldimethylsilyl
Tf	trifluoromethanesulphonyl
Tfa	trifluoroacetyl
TFA	trifluoracetic acid
THF	tetrahydrofuran
Thp	tetrahydropyranyl
TMS	trimethylsilyl
TPP	triphenylphosphine
TPS	tri-isopropylbenzenesulphonyl
Tr	triphenylmethyl
Ts	toluene p-sulphonyl
U	uracil-1-yl

1
Introduction and General Aspects

The field continues to develop on all fronts, and improvements in synthetic methodology are giving access to substantially more complex products. Nowhere is this move apparent than in oligosaccharide and C-glycoside synthesis and in the use of synthetic procedures which are dependent on carbohydrate-derived carbanions and particularly free radicals. The increasing interest shown by "non-carbohydrate chemists" in carbohydrate chemistry is welcomed; their contributions have enlivened the field appreciably as is best illustrated by their descriptions of novel approaches to glycoside synthesis and, of course, many syntheses of enantiomerically pure non-carbohydrates from sugars.

El Khadem has published a book "Carbohydrate Chemistry: Monosaccharides and their Oligomers",[1] and reviews of general interest have appeared on the chemistry and biochemistry of the sweetness of sugars[2] and on the use of immobilised enzymes in preparative carbohydrate chemistry.[3]

Volume 45 of Advances in Carbohydrate Chemistry and Biochemistry (1987) contains articles on circular dichroism,[4] n.m.r. (proton relaxation rate data in structural analysis)[5] and mass spectrometry (FAB methodology).[6] The volume also contains tributes to the lives and work of Professors B. Helferich and F. C. Gonzalez.

The succeeding volume of the series contains reviews on H.p.l.c. of carbohydrates,[7] n.m.r. of fluorinated monosaccharides,[8] the use of photosensitive protecting groups in carbohydrate synthesis[9] and high-temperature transformations of monosaccharides in aqueous solution.[10]

Appreciations of the lives and work of Professor K. Onedera and V. Deulofeu are also included in this volume.

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2
Free Sugars

1 Theoretical Aspects

Recent progress in the physical chemistry of small carbohydrate compounds has been reviewed. There is accumulating evidence that solvation plays an important part in determining the solution equilibria and conformational properties of sugars.[1] The standard geometries of both anomers of the eight hexopyranoses in the $^4C_1$ conformation have been calculated and are given in the form of orthogonal co-ordinates. The geometries found for pyranose rings corresponded to the averaged ring structures determined from X-ray diffraction analyses of 161 compounds (see B.Sheldrick and D.Akrigg, Acta Crystallogr., 1980, 836, 1615).[2] A revised CHARMM molecular mechanics potential-energy function has been developed for use in the dynamical simulation of simple carbohydrates in aqueous solution. Application to the molecular dynamics simulation of the motions of α-D-glucopyranose in vacuo in both the $^4C_1$ and $^1C_4$ conformation produced a D-glucose molecule less flexible then had previously been determined.[3] CNDO Force constants for both anomers of D-glucopyranose have been evaluated,[4] and an ab initio investigation of the electronic structure of the α-D-glucose molecule by use of the Hartree-Fock-Roothan method has been carried out. The effective charges agreed with those derived from semi-empirical calculations.[5]

The hydrophobic indices, i.e., the ratios of hydrophobic to hydrophilic surface areas, of seven monosaccharides have been determined. They were found to correlate well with the partition coefficients of the polystyrene-water system for monosaccharides. The concept of hydrophobic indices is important in the consideration of the hydrophobic interactions of flat molecules in aqueous solution.[6] In an effort to establish quantitative structure-activity relationships for carbohydrates, an experimental data-matrix containing the R_f values of sixteen monosaccharides in thirteen solvent systems was subjected to principal component analysis (PCA). Four PC's (t_1-t_4) were found

to explain 97.8% of the variance, and the first of these (t_1), which described 90% of the variance, was tentatively interpreted as a hydrophobicity scale.[7] Ab initio Calculations have shown that D-ribose is energetically stabilised relative to its L-enantiomer by parity-violating weak interaction (see Vol. 20, p. 2, ref. 4). The possible significance of these findings with regard to evolution has been pointed out.[8]

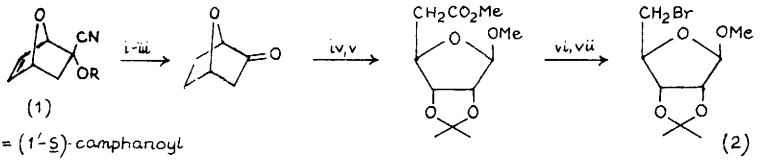
2 Synthesis

A review on the synthesis of complex carbohydrates by a combination of chemical and enzymic methods has been published.[9] A new strategy for the predictable creation of new chiral centres and its application to the synthesis of sugars and macrocycles is presented in a review on the use of double asymmetric induction in the aldol condensation, the Diels Alder cycloaddition, epoxidation and hydrogenation.[10] Two approaches to the construction of appropriately functionalised six-carbon chains are outlined in a review on the de novo synthesis of carbohydrates from achiral precursors: (i), hetero-Diels Alder reaction with inverse electron demand of functionalised 1-oxa-1,3-dienes with dienophiles such as enol ethers followed by diastereoselective addition to the new double bond and (ii), Sharpless oxidation of racemic or meso-divinyl glycols,[11] with concomitant kinetic resolution.

Sugars with four, six, and eight carbon atoms were formed from glycolaldehyde in an aqueous suspension of sodium montmorillonite at 40°C, hexoses being the main products (see Vol. 20, p. 3, ref. 8). The conversion efficiency was 90% and an aldol-type mechanism has been suggested for the reaction.[12] Aldoses are smoothly decarbonylated by chlorotris(triphenyl)rhodium in N-methylpyrrolidin-2-one at 130°C to give the next lower alditols. D-Glucose for example gives D-arabinose and 2-deoxy-D-erythro-pentose gives 1-deoxyerythritol in 90% yield. Ketoses undergo more complex dehydration-decarbonylation reactions; thus furfuraldehyde was formed in 79% yield from fructose. Experiments with [1-^{13}C]-labelled substrate showed that C-1 was lost during the reaction.[13]

2.1 Pentoses.- On reaction with aqueous $Pb(OH)_2$ 3,4-O-isopropylidene-L-arabinose rearranged to 2-deoxy-L-ribono-1,4-lactone which was reduced to 2-deoxy-L-erythro-pentofuranose by

sodium borohydride.[14] 2,4-O-Benzylidene-L-xylose has been prepared in high yield by periodate oxidation of 2,4-O-benzylidene-D-glucitol.[15] Iron(III)trifluoroacetate proved to be an efficient catalyst in the preparation of D-[U-^{14}C]arabinose and D-[U-^{14}C]lyxose by Ruff degradation of universally labelled D-glucose and D-galactose, respectively.[16] A new total synthesis of D- or L-ribose derivatives starts from the optically pure, functionalised oxabicycloheptene (1) (esterified with (-) camphanoic acid) or its enantiomer, respectively. The seven step



(1)

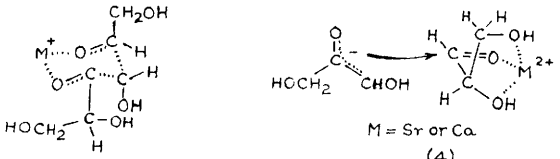
R = (1′S)-camphanoyl (2)

Reagents: i, H_2O_2-OsO_4 (cat.); ii, $Me_2C(OMe)_2$-p-TsOH-Me_2CO; iii, KOH-CH_3O; iv, MCPBA; v, MeOH-H^+-$Me_2C(OMe)_2$; vi, KOH; vii, Br_2-HgO

Scheme 1

reaction sequence leading to the D-product (2) is shown in Scheme 1.[17]

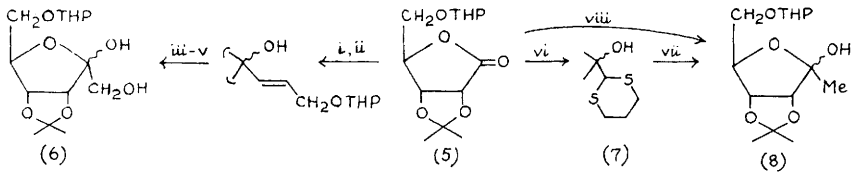
2.2 Hexoses.- Strontium and calcium chloride have a marked effect on the selectivity of the triose aldose condensation. Under ordinary conditions, i.e., in the absence of alkaline-earth metal ions, 3,4-threo configurated products, particularly arabino-2-hexulose (fructose) and xylo-2-hexulose(sorbose), prevail. Typically, the product composition is arabino : xylo : ribo : lyxo = 51 : 38 : 7 : 4. This diastereoselectivity is in accordance with a pericyclic reaction mechanism and the intermediacy of the transition state (3). In the presence of high concentrations of Sr^{2+} or Ca^{2+}, increased proportions of hexuloses with the 3,4-erythro-configuration, especially the lyxo isomer, are formed at the expense of fructose (e.g., arabino : xylo : ribo : lyxo = 22 : 34 : 12 : 32) indicating α-chelation and attack of the complex (4) by the dihydroxyacetone enolate from the least hindered side.[18]



(3) M = Li or Na (4)

Derivatives (6) and (8) of D-psicofuranose and 1-deoxy-D-psicofuranose, respectively, have been synthesised by new routes

from the protected D-ribonolactone derivative (5) as outlined in Scheme 2. Attempts to hydrolyse the dithiane (7) to an aldehyde were unsuccessful.[19]

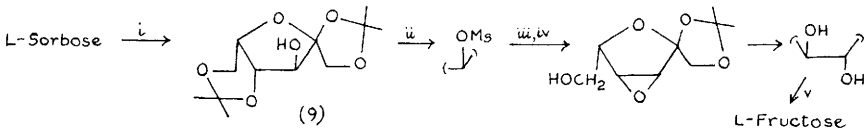


Reagents: i, LiC≡C·CH_2OTHP; ii, H_2-Pd/$BaSO_4$; iii, OsO_4-Me_2NO; iv, $NaIO_4$; v, $NaBH_4$; vi,  ; vii, Raney Ni; viii, MeLi

Scheme 2

A simpler and more efficient version of the traditional Kiliani method has been used to prepare [6-^{13}C]-labelled hexoses. K^{13}CN was added to 1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose. Hydrogenation of the adducts and in situ borohydride reduction followed by deprotection gave D-[6-^{13}C]glucose and L-[6-^{13}C]idose, which were separable on a DOWEX 50 x 8 (Ca^{2+}) column. Molybdate epimerisation of these products afforded D-[6-^{13}C]mannose and L-[6-^{13}C]gulose.[20] Procedures suitable for the large scale (50 g) production of ^{13}C-enriched hexoses have been developed. D-[1-^{13}C]glucose and D-[1-^{13}C]mannose were prepared from D-arabinose by Serianni's modified Kiliani-Fischer reaction in 20 and 39% yield, respectively. Exposure to NaOH and phenylboronic acid converted the D-[1-^{13}C]mannose into a chromatographically separable 1:1:8 mixture of D-mannose, D-glucose, and D-fructose with retention of the label at C-1. D-[x-^{13}C]Fructose (x = 1 or 2) was obtained in 80% yield from D-[x-^{13}C]glucose by use of immobilised glucose isomerase in the presence of sodium germanite to complex the fructose. In addition, [2-^{13}C]dihydroxyacetone was synthesised from [2-^{13}C]fructose by consequential methanolysis, periodate oxidation, borohydride reduction, and acid hydrolysis.[21]

L-Sorbose has been converted to L-fructose via the key-intermediate (9) (Scheme 3), available in >80% yield by



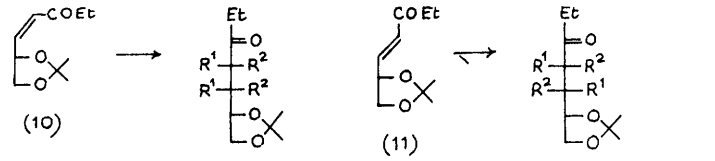
Reagents: i, $Me_2C(OMe)_2$-$(CH_2OMe)_2$-$SnCl_2$; ii, MsCl-py; iii, HOAc(aq); iv, KOH(aq); v, H_2SO_4

Scheme 3

acetonation of L-sorbose with dimethoxymethane and $SnCl_2$ in

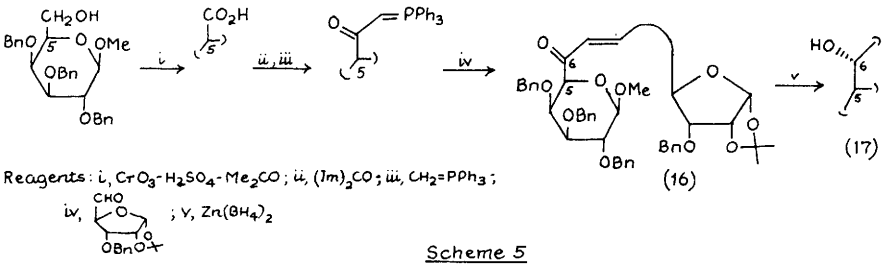
dimethoxyethane.[22] The synthesis of 3,4;5,6-di-O-isopropylidene-D-glucitol and 2,3;4,5-di-O-isopropylidene-aldehydo-D-arabinose from D-glucono-1,5-lactone is referred to in Chapter 18. An improved process for the isolation of D-fructose from the acid hydrolysate of sucrose involves formation of a double salt with $Ca(OH)_2$, followed by decalcification and purification.[23]

2.3 Higher Sugars.- Reaction of isopropylidene-D-glyceraldehyde with triphenyl(propionylmethylene)phosphorane afforded the isomeric enuloses (10) and (11) which were separated by chromatography. Hydroxylation then gave access to the four diastereomeric 1,2-dideoxy-3-heptulose derivatives (12)-(15) (Scheme 4).[24] A recently developed route to higher sugar allylic



Scheme 4

alcohols (see Vol. 20, p. 8) has been exploited in connection with the attempted synthesis of desazatunicamine. It involves coupling of two monosaccharide units derived from D-galactose and D-ribose, respectively, via an additional carbon atom, as shown in Scheme 5.[25] The stereoselectivity of the zinc borohydride reduction of

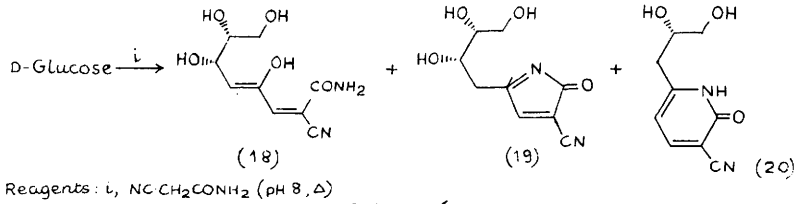


Scheme 5

compound (16) and similar higher sugar enones implies complexation of the ring and the carbonyl oxygen atoms with zinc ion in accordance with the Cram cyclic model for 1,2-asymmetric induction,[26] and the steric course of the osmylation of higher sugar enones and allylic alcohols such as compounds (16) and (17) is rationalised in terms of Kishi's rule.[27]

3 Analytical Methods

A colorimetric assay for glucose in the presence of fructose, based on the selective reduction of ketoses by sodium borohydride and $CeCl_3$ has been developed.[28] An analytical method for the determination of fructose and other ketoses in the presence of aldoses, sucrose, and insulin is mentioned in Chapter 22. In h.p.l.c. separations, reducing sugars may be detected fluorometrically after post-column reaction with 2-cyanoacetamide. The fluorescent species derived from glucose have been identified as the pyrrolidine derivative (19) and the pyridine derivative (20) formed, presumably, as indicated in Scheme 6, from the dehydrated Knoevenagel adduct (18) and its 4-deoxy-5-hydroxy-isomer by cyclisation, further dehydration and, in the case of product (20), reduction. The dienamide (18) itself is strongly u.v. absorbing and susceptible to electrochemical oxidation, which might permit additional methods of detection.[29]



Scheme 6

A D-glucose-sensitive electrode has been constructed by coating of a platinum electrode with a cross-linked poly(vinylalcohol) layer containing immobilised D-glucose oxidase and ferrocene.[30]

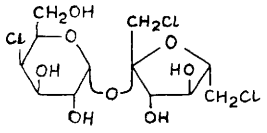
4 Physical Measurements

The solubilities of D-xylose and D-mannose in aqueous ethanol (0-100%) at 25°C have been measured by use of refractometry and h.p.l.c.,[31] and some physical properties (m.p., solubilities) of crystalline anhydrous α-lactose, α,β-lactose, and β-lactose have been reported.[32] The excess Gibbs free energies of aqueous solutions of carbohydrates and other polyols at 25°C have been determined and correlated with the sugar configurations.[33] The standard enthalpy of formation (1263.4 ± 1.2 $kJmol^{-1}$) of α-D-mannose at 298.15 K has been calculated from the corresponding standard energy of combustion (-15.6123 ± 0.0065 kJg^{-1}) which was

measured by use of precision static oxygen bomb calorimetry.[34]

The catalytic activity of hydrated metal sulphates in the mutarotation of D-glucose has been examined, and the relations between logKa, ΔH, and ΔS of the reaction and the parameters of the metal ions, were discussed.[35]

The apparent molal volumes and molal compressibilities of several monosaccharides, disaccharides and methyl pyranosides in dilute aqueous solution have been studied at 5, 15, and 25°C. The results were discussed in the light of solute-solvent interactions and a model for the hydration of galactose and lactose was proposed.[36] The molal volumes of small carbohydrate molecules have been measured in an attempt at elucidating the relationship between molecular properties and sweetness. Molal volumes reflect fine differences in structure (e.g., axial or equatorial disposition of particular hydroxy groups) which are in turn related to differences in taste.[37] In order to interpret differences in sweetness the viscosimetric constants and the heats of dilution of three monosaccharides, three disaccharides and the very sweet chlorinated sugar (21) have been determined, and their i.r. and Raman spectra have been recorded.[38] The osmotic



(21)

pressures of aqueous glucose, sucrose, and raffinose solutions have been calculated from their freezing point depressions. To obtain the apparent volumes of the hydrated species (0.1865, 0.3525, and 0.5105 nm^3, respectively) their partial molal volumes were determined together with the partial molal volumes of the water of their solutions.[39]

The u.v. and i.r. spectra of oligomeric acid products from the alkaline degradation of fructose and glucose have been evaluated.[40] E.s.r. measurements on γ-irradiated crystals of α- and β-D-glucose hydrate confirmed that the structures of the primary paramagnetic centres derived from the hydrated species differ from those from the anhydrous analogues. The existence of several novel free radicals is reported.[41] ^{13}C-n.m.r. spectroscopy has been used to determine the anomeric configuration and the ring-size of D-fructose obtained from sucrose by the action of yeast and Candida utilis invertases. The hydrolysis was

complete within 5 min yielding initially β-fructofuranose almost exclusively. After 60 min a mixture containing 74% β-fructopyranose, 22% β-furanose and 3.8% α-furanose had formed.[42]

5 Isomerisation

The epimerisation of aldoses by metal complexes of alkylenediamines with long N-alkyl substituents has been reported. In a study involving various ligands, N,N′-dialkylethylenediamines showed the highest activity for epimerisation of glucose at C-2, equilibrium being reached within a few minutes under mild conditions. The equilibrium was shifted towards glucose by the more hydrophobic ligands with longer N-alkyl chains.[43] Molybdate ions in aqueous solution at 90-125°C catalysed the isomerisation of D-glucose to a 3:1 mixture of D-glucose and D-mannose.[44] At 120-150°C a mixture of D-glucose, D-mannose, D-allose, and D-altrose was obtained from which the first two sugars were removed by yeast fermentation leaving D-allose and D-altrose (3:2) in 14-17% yield.[45] Several epimerisation reactions are mentioned in Section 2 of this Chapter.

The $Ca(OH)_2$ promoted anomerisation of D-glucose has been studied by ^{13}C-n.m.r. spectroscopy. The degree of anomerisation was found to vary with the $Ca(OH)_2$ concentration and it is thought that Ca^{2+} ions bind to O-1 and O-3 of the α-pyranose anomer, whereas in the β-anomer O-1 and O-2 are involved in complexation.[46]

6 Oxidation

In a new approach to the study of the electrochemical oxidation of glucose in aqueous solution at pH 7.4 (phosphate buffer) the CO_2 produced by decarboxylation of gluconate during a potential scan was measured directly by on-line mass spectroscopy. Application of a flow-cell technique in combination with mass spectroscopy to solutions of ^{13}C-labelled glucose allowed the examination of intermediates absorbed on the electrode.[47] Anomalous temperature behaviour was observed during the electrooxidation of glucose at platinum electrodes in alkaline media, which was monitored by electrochemical, chromatographic, and polarimetric methods. It was concluded that true oxidation of glucose, *i.e.*, release of hydrogen from the hemiacetal group, is observed at low temperature (-5°C), whereas on warming to 25°C, slow isomerisation to fructose also takes place. No evidence for different reactivity of the

anomers was found.[48] Pt(100), (110), and (111) single crystal electrodes have been shown to be more active than polycrystalline Pt in the electrocatalytic oxidation of glucose in acidic solution. The effects of added foreign metals (Bi, Pb, Ti) are discussed.[49] The electrochemical oxidation of glucose to gluconate has been investigated in an undivided bipolar flow reactor with narrow inter-electrode gaps operating under optimised conditions (c.d., electrolyte concentration, temperature, flow rate). A detailed material balance was established and a comparative evaluation, based on energy consumption, of the flow reactor with a rotating electrode cell was made.[50]

In the electrolytic oxidation of lactose, electrogenerated Br^-/OBr^- has been employed as redox mediator. The process which uses rotating graphite anodes, stationary graphite cathodes, and NaBr solution as electrolyte has been optimised for yield of calcium lactobionate.[51] Fructose, sucrose, sorbitol and glucose have been absorbed from acidic aqueous solutions onto a platinum surface pretreated with either oxygen or hydrogen and the extent of oxidation and reduction, respectively, has been studied.[52]

The effects of pressure on the rates of oxidation of D-glucose, D-galactose, D-mannose, D-fructose, L-sorbose, L-arabinose, D-ribose, and D-xylose by vanadium(V) in perchloric acid have been investigated. All eight substrates had activation volumes of $\overset{\ddagger}{V}$ 7.5 ± 1.3 $mlmol^{-1}$ with negligible dependence on pressure up to 200 MPa which indicates the formation of activated monosaccharide-vanadium(V) complexes by a common mechanism. It is thought that in the rate-determining decomposition of these complexes hydrogen transfer takes place to give a carbohydrate radical which undergoes rapid C-C or C-H bond fission.[53] $V(OH)_3^{2+}$ and $V(OH)_2^{3+}$ are assumed to be the active species in the oxidation of D-xylose by vanadium(V) in perchloric acid, electron transfer from the sugar to these ions preceding cleavage of the C-1 - C-2 bond.[54] D-Lyxose was oxidised by Cu^{2+} in sulphuric acid at 130°C to give glycolic, glyceric, butyric, trihydroxybutyric, carbonic, pyromucic and maleic acids in 26, 18, 12, 10, 10, 4 and 3% yield, respectively.[55] The oxidation of melibiose by cuprammonium sulphate in ammoniacal and in buffered media was zero order in Cu^{2+}, first order in carbohydrate, and 0.5 order in NH_3; it was retarded by added NH_4Cl due to the common ion effect. The reaction is believed to proceed via an enediol anion intermediate, enolisation being the rate-determining step.[56]

Formic acid, CO_2, and Ce(III) were formed in the oxidation

of D-mannose by Ce(IV) in perchloric acid. The activation parameters (ΔH^{+}, ΔS^{+}) of the reaction have been determined.[57] The kinetics of the oxidation of sucrose and of lactose by chromic acid have been studied spectrophotometrically under a variety of experimental conditions. Activation parameters have been calculated and a reaction mechanism is proposed.[58] On the basis of kinetic measurements a common mechanism is thought to apply to the oxidation of D-ribose and D-erythrose (but not glyceraldehyde) by tetrachloroaurate(III).[59] A study of the kinetics of reduction of dodecatungstocobaltate(III) by D-fructose, D-glucose, and D-mannose has shown that ketoses and aldoses react by different mechanisms. The reduction by D-fructose was pseudo-zero-order and acid-dependent indicating that attack on the metal complex is preceded by rate determining, acid-dependent enolisation. With D-glucose and D-mannose pseudo-second-order rates and catalysis by metal ions (K>Na>>Li) was observed, and reaction via a free-radical bound activated metal species in the transition state is proposed. The reaction products were arabinonic acid from fructose and arabinose from the two aldoses.[60]

The oxidation of aldoses by N-bromosuccinimide in aqueous media containing $Hg(OAc)_2$, H_2SO_4, or HOAc has been investigated. The reaction is first order in oxidising agent and in substrate and its rate decreases on addition of protons. The order of reactivity amongst the five aldoses studied was D-arabinose > D-xylose > D-galactose > D-mannose > D-glucose. A reaction mechanism is suggested on the basis of kinetic measurements.[61] The ozonisation of a 0.03M aqueous D-glucose solution has been monitored by g.l.c. The initial products were D-glucuronic acid and D-gluconic acid in a ratio dependent on temperature and pH.[62]

7 Other Aspects

L-Altrose has been identified as a component of an exocellular bacterial polysaccharide from B. fibrisolvens. This is the first report of L-altrose occurring in nature.[63]

The action of ultrasound on deoxygenated aqueous solutions of D-glucose produces results very similar to those obtained with ionising radiation under anaerobic conditions. Hydroxyl radicals generated by cavitation abstract carbon-bound hydrogen from all six positions, and the resulting glycosyl radicals either disproportionate to yield D-gluconic acid, D-gluco-hexodialdose, and hexosuloses (2 C-OH → C=O+HC-OH) or rearrange and abstract

hydrogen to give deoxyhexonic acids. There is little evidence of C-C bond fission in contrast to the effect of sonication on aerated D-glucose solutions.[64]

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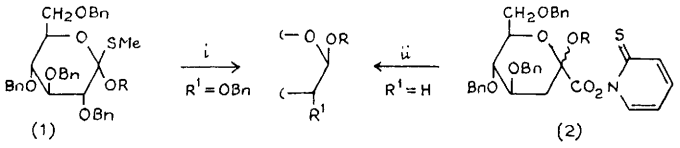
3
Glycosides and Disaccharides

A Review[1] covering the formation, structures and chemical reactivities of free radicals at the anomeric centres of carbohydrate derivatives is of relevance to aspects of the chemistry covered in this Chapter.

1 O-Glycosides

1.1 Synthesis of Monosaccharide Glycosides.- Further reviews have dealt with the synthesis of 1,2-cis-glycosides,[2] the stereoselectivity of glycoside formation using 1,2-O-cyanoalkylidene derivatives[3] and general features of glycosidation reactions and the hydrolysis of glycosides under reducing conditions.[4]

Two complementary approaches have utilised the fact that anomeric free radicals also bearing alkoxy groups at the anomeric centre can be expected to abstract hydrogen from the axial direction and thus give access to β-D-glucopyranosides, for example. In the first,[5] hemithio-orthoesters were reduced with tributyltin hydride under radical conditions, compound (1, R=Me) giving methyl tetra-O-benzyl-α- and β-D-glucopyranoside in the ratio 1:12. The corresponding ratios were 1:18 and 1:6 in the D-manno- and 2-deoxy-D-arabino-series. The starting materials were made from the thionolactones by treatment with methyl iodide and alcohols in the presence of 2,6-di-tert-butyl-4-methylpyridine, and the procedure can be extended to the synthesis of disaccharides (see later).[5] Alternatively, radical production by the Barton O-acylthiohydroxamate decarboxylation method starting



Reagents: i, Bu_3SnH, AIBN; ii, hν, $Me(CH_2)_8CMe_2SH$

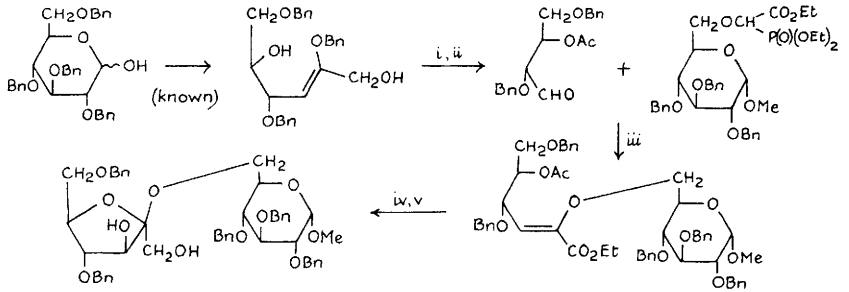
Scheme 1

from ulosonic acid glycosides (2) can be used with similar selectivity.[6] These procedures are outlined in Scheme 1.

Reaction of 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride with alcohols in the presence of tetramethylurea and molecular sieve gives the corresponding pyranosides with free hydroxy groups at C-2, but with poor anomeric selectivity.[7] On the other hand, 2,3,4,6-tetra-O-benzyl-D-glucose, following tosylation by use of a phase-transfer catalyst, and reaction with alcohols, gives yields in the region of 70% of glycosides with an α/β ratio of 3-20.[8]

Not surprisingly, trifluoromethanesulphonic acid can be used effectively as catalyst for the Fischer glycosidation of free sugars,[9] and phosphorus oxychloride catalyses the reaction between sugar peracetates and alcohols. For aryl, alkyl and aralkyl D-glucoside esters β-anomers (the kinetic products) are favoured if the reactions are carried out in benzene solution, whereas the more stable α-products predominate if no solvent is used.[10]

Good β-selectivity (α:β as high as 1:16) was found on reaction of 4-O-acetyl-6-deoxy-2,3-di-O-methyl-β-D-allopyranosyl fluoride (D-mycinosyl fluoride) with alcohols in the presence of silver perchlorate and bis(cyclopentadienyl)zirconium dichloride in benzene,[11] and in related fashion a desosamine fluoride has been used to produce β-glycosides under mild conditions involving a hafnium complex[12] and the methods have been combined in a total synthesis of the macrocyclic glycoside mycinamycin IV.[13]



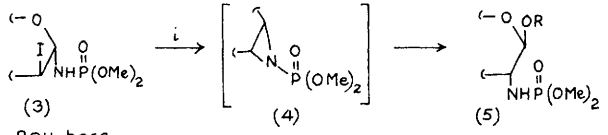
Reagents: i, Ac_2O-Py ; ii, O_3 ; iii, KH ; iv, DIBAH ; v, MCPBA

Scheme 2

A route to ketofuranosides by way of enol ether derivatives and their epoxidation is illustrated in Scheme 2, but the procedure affords Z and E alkenes and stereoisomers following the opening of their products of epoxidation. The authors, nevertheless, claim moderate to good yields, good stereoselectivities and separable products and rationalise the

stereochemical aspects of their findings.[14]

An interesting new approach to 1,2-trans-related 2-amino-2-deoxyaldosides involves treatment of 1,2-trans-related 2-deoxy-2-iodoglycopyranosyl phosphoramidates (3) with base in the presence of alcohols. The 2-deoxy-2-phosphoramidoglycopyranosides (5) are produced by way of the aziridines (4), inversion occurring at C-1 and C-2 so that β-D-gluco-compounds are produced from those with α-D-manno-stereochemistry and vice versa. Likewise, α-D-lyxo-iodides give β-D-xylosides and vice versa (Scheme 3).[15]

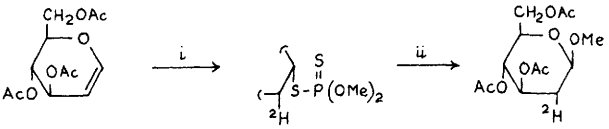


(3) (4) (5)

Reagents: i, ROH, base

Scheme 3

Di-O-alkylphosphorodithioc acids add cis- to peracetylated glycals to give high yields of predominantly 2-deoxy-α-D-glycosyl adducts. In this way specifically labelled glycosides e.g. (6) can be obtained (Scheme 4).[16] Further in the area of glycosides



Reagents: i, $(MeO)_2P(S)SH$; ii, NaOMe, MeOH; iii, Ac_2O-Py (6)

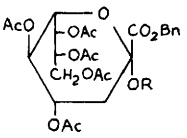
Scheme 4

of deoxysugars, methyl 2,6-dideoxy-α-D-arabino-hexopyranoside can be made readily from 2,6-dibromo-2,6-dideoxy-α-D-mannopyranosyl bromide by methanolysis followed by reductive debromination (Chapter 12).

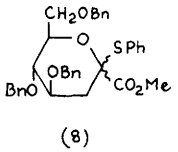
In the area of ulosonic acids, condensation of D-mannose with oxalacetic acid gave 3-deoxy-D-glycero-D-galacto-2-nonulopyranosonic acid from which a protected glycosyl bromide and hence glycosides e.g. (7) were prepared,[17] and the phenylthioglycosides (8), made from tri-O-benzyl-D-glucal, can be converted into O-glycosides.[18]

Considerable effort has gone into the synthesis of aminoacid glycosides mainly because of their significance in glycopeptide chemistry. Reaction of the dimer of tri-O-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride with methyl N-substituted-L-serinate (and L-threoninate and L-tyrosinate) gave mixed anomers of the oximes (9),[19] and their deacylated products on deoximation, reduction and reacetylation afforded the corresponding α-D-

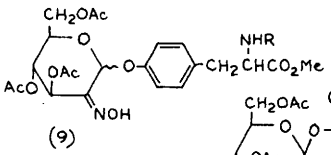
glucopyranosides and β-D-mannopyranosides from the α- and β-anomers, respectively.[20] The hydroxyproline glycoside (10) has



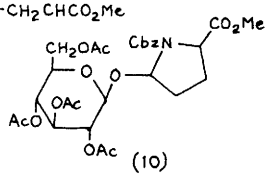
(7) R = Me, 5-Cholesten-3-β-yl



(8)

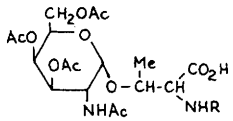


(9)



(10)

been used for the synthesis of a glycosylated peptide of interest in neurochemistry,[21] and the glycosylated threonine compound (11)



(11) R = 9-Fluorenylmethoxycarbonyl

Ala-Gly-Ala-Gly-Thr-Ala
3
↑
1
(12) α-D-GalNAc

Ala-Thr-Val-Thr-Ala-Gly
3 3
↑ ↑
1 1
α-D-GalNAc α-D-GalNAc (13)

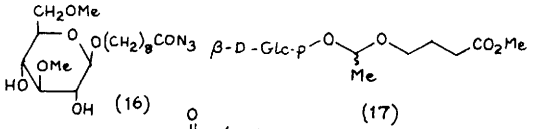
Ala-Ser-Gly-Thr
↑
β-D-Seyl (14)

Thr-Ala-Thr-Thr
↑
(15) α-D-Gal

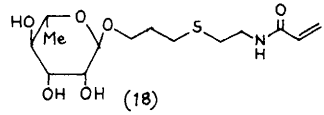
has been applied in a solid phase peptide synthesis of compounds (12) and (13).[22] Other glycopeptides to have been synthesised are (14) which is the N-terminal portion of the protein core of proteodermatan sulphate[23] and (15) (in a fully protected form) which was required in connection with studies of the contribution of the carbohydrate moieties to the biological activity of snake venom.[24]

Glycosides having long chain aglycones have attracted much attention for a variety of biological reasons. Compound (16) was prepared and coupled to bovine serum albumin for use in the serodiagnosis of leprosy,[25] and the double acetal (17), made by acid catalysed condensation between trimethylsilyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside and the appropriate acetaldehyde acetal, was bonded by way of the spacer arm to amino acids and peptides in work aimed at making antibodies which carry such acetals to tumour surfaces on which hydrolysis would occur to provide means of delivering cytotoxic aldehydes.[26] The acrylamide

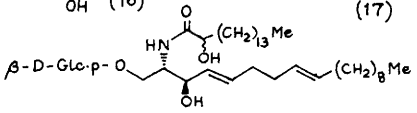
derivative (18) was copolymerized with acrylamide to give a water soluble "pseudopolysaccharide" containing α-L-rhamnoside groups which has antigenic properties binding to lectins and antisera.[27] A similar copolymer was made from the corresponding α-glycoside of N-acetylneuraminic acid.[28]



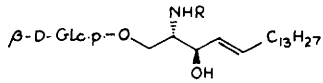
(16) (17)



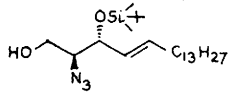
(18)



(19)



(20) R = H (21) R = $C_{18}H_{37}$



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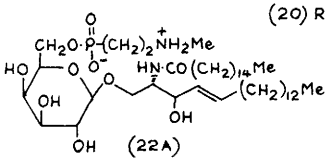


(22A)

Schmidt has reviewed his work on the synthesis of glycosphingolipids[29] and has reported preparations of both epimers of compound (19) which are naturally occurring cerebrosides with anti-ulcerogenic activities.[30] His group has likewise made psychosines of D-glucose (20), D-galactose and lactose which were N-acylated to the corresponding glycosphingolipids (e.g. 21).[31] Nicolaou and his group have also been active in this field and have prepared the azide (22) for synthesis of sphingosines, ceramides and glycosphingolipids. Using the glycosyl fluoride method they made galactosylceramide.[32] The phosphonosphingoglycolipid (22a), found in a marine snail, has been synthesised.[32a]

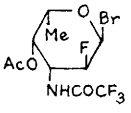
Treated with $C_6F_{13}CH_2CH_2OH$ and silver carbonate tetra-O-acetyl-α-D-glucopyranosyl bromide gave a 1,2-orthoester which, with mercury (II) bromide, was converted into the α,β-glycosides (4:6). The corresponding maltosyl bromide with $C_6F_{13}CH{=}CHCH_2CH_2OH$ gave the β-glycoside as expected, and these results are difficult to reconcile.[33] Alcoholysis studies of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose with long chain alcohols indicated that crystalline α-pyranosides were obtainable in the long term. The reaction intermediates were, as was to be expected, complex.[34]

Micelles formed from dodecyl glycosides allowed asymmetric sodium borohydride reduction of alkyl phenyl ketones. The α-D-glucopyranoside gave 98% enantiomeric excess with phenyl ethyl

ketone, but the sodium β-glucopyranuronate was inactive.[35]

In the related field of glycosylated glycerols, 1,2-di-O-palmitoyl 3-O-(β-D-galactopyranosyl)-DL-glycerol was prepared by glycosylation of the diester, and the analogue having a sulphur atom linking the sugar and glycerol was made using a 1-thio-D-galactose ester and 3-deoxy-3-iodoglycerol diester.[36] Similarly, a set of 1,2-di-O-acyl-3-O-(β-D-glucopyranosyl)-sn-glycerols has been reported having 12-20 carbon acyl chains.[37] The authors have also reported a calorimetric study of these compounds, polymorphic phase behaviour of aqueous dispersions having been examined by differential scanning calorimetry.[38]

Many glycosides have been made in the course of studies of medicinal compounds. In the anthracycline field the 2-fluorodaunosamine glycosylating agent (23) has been coupled to daunomycinone to give 2(S)-2'-fluorodaunorubicin.[39] Other work has involved fluorine substitution in the aglycone, e.g. 2-fluoro- and



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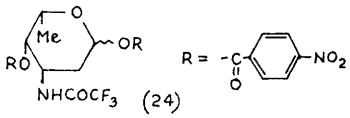
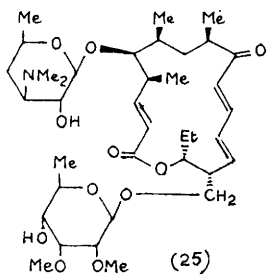


(24)

3-fluoro-4-demethoxydaunomycinone which were glycosylated using the p-nitrobenzoate (24) which afforded the desired α-linked products. Previously high yields reported for this reaction were not, however, achieved.[40] The same reagent has been used in glycosylations of (+)-14-fluorodaunomycinone and its 4-demethoxy analogue[41] and of (±)-11-deoxyanthracyclinone derivatives.[42]

Three papers have reported on glycosylations of macrocyclic compounds. Mycinamycin IV (25), containing mycinose and desosamine, was made by the glycosylation methods noted in references 11 and 12,[13] and oleandomycin (26) has been synthesised



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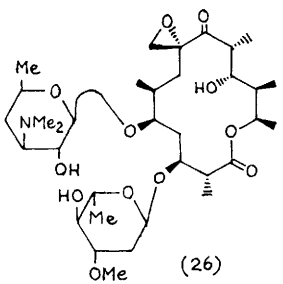

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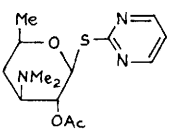

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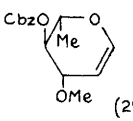
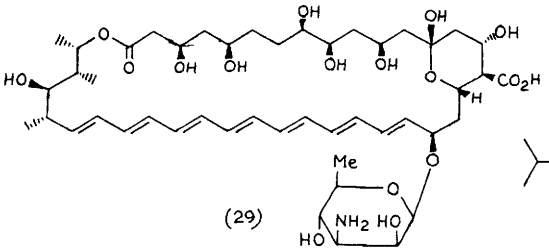


(28)

by glycosylation of the aglycone using compounds (27) and (28) for introduction of the desosamine and oleandrose, respectively.[43]

Attempts to effect the glycosylation of amphoteronolide B to obtain the polyether antibiotic amphotericin B (29) were unsuccessful using a glycosyl fluoride or an S-phenyl 1-thioglycoside, and other reagents gave predominantly the α-glycosides. To obtain the required β-anomer 1-O-acetyl-3-azido-3,6-dideoxy-4-O-tert-butyldimethylsilyl-α-D-glucopyranosyl trichloroacetamidate was used followed by deprotection, oxidation and reduction at C-2.[44]

Other compounds of interest in medicinal chemistry to have been prepared are the β-D-ribofuranoside the β-D-glucopyranoside and the β-D-galactopyranoside of the ellipticine derivative (30) which have improved water-solubility for action as anticancer agents.[45]



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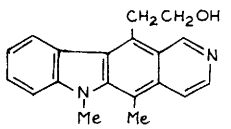

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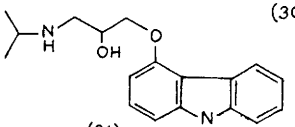
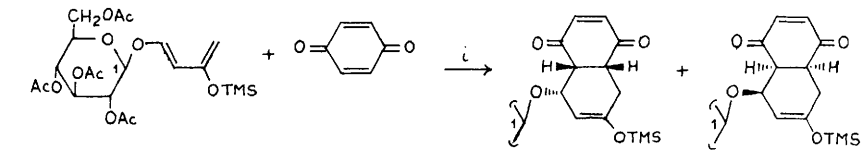


(31)

The glucuronides of the (R) and (S) forms of carazolol (31) - a beta-blocking agent - which are proposed metabolites of the drug have been synthesised.[46]

Reference is made to the four isomeric pseudo-trehaloses, i.e., the disaccharides having a methylene group in place of the ring oxygen atom in one of the glucose moieties, in Chapter 18. Compounds which are somewhat related have been produced by Diels-Alder reaction of the butadien-1-yl glycoside (32) with benzoquinone (and other dienophiles) (Scheme 5). The isomers (33) and (34) were produced in the ratio 1:1.[47]



Reagent: i, Δ

(33) (34)

Scheme 5

In the steroid series reports have appeared on mono- and di-glucosides derived from a 3,12,18-trihydroxysteroid[48] and on 2-glucuronides of 2-hydroxyestriol, 2-hydroxyestradiol and 2-

hydroxyestrone.[49] D-Glucosylation products of dammarane triterpenes[50] and L-rhamnosylation products of glyrrhetic and ursolic acids have been reported.[51]

2,3,5-Tri-O-benzoyl-α-L-arabinosyl bromide treated with phenols with pK_a <8 in acetone in the presence of potassium carbonate affords means of synthesising aryl α-L-arabinofuranosides,[52] and aryl β-D-mannopyranosides were made using 4,6-di-O-acetyl-α-D-mannopyranosyl bromide 2,3-carbonate and the potassium phenates in acetonitrile in the presence of 18-crown-6.[53] A set of hydroxybenzoic acid β-D-glucosides [of salicylic acid, 4-hydroxybenzoic acid, protocatechuic acid, vanillic acid, syringic acid and gallic acid] were made as reference compounds for the examination of plant extracts[54] and the uronoside (35) was synthesised together with several related compounds and their melanoma-inhibiting properties were examined. While compound (35) inhibited the growth of B_{16} melanoma in mice its methyl ester was relatively unreactive.[55]

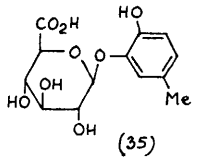
Methyl 2,3,4-tri-O-acetyl-β-D-glucuronat-1-yl fluoride has been used to obtain the uronosides of p-nitrophenol, 4-methylumbelliferone and 4-trifluoromethylumbelliferone,[56] and the β-D-galactopyranoside of this last compound, which is a fluorigenic substrate for β-galactosidase studies, has also been reported.[57] α-L-Arabinofuranosides of α- and β-pellatins and a β-cellobioside of the latter have been made[58] as have the α- and β-naphthyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside which can be converted into the respective C-glycosides (see Section 3 of this Chapter).[59]

Specific, relatively simple glycosides to have been synthesised include t-butyl-β-D-galactopyranoside tetra-acetate, the corresponding lactoside[60] and 2-phenylpropan-1-yl β-D-glucopyranuronoside. The stereochemistry within the aglycone is not noted in the abstract.[61]

Interesting German work on glycosides of acetals has continued. Condensation of 2,3,4,6-tetra-O-acetyl-D-galactose with bromoacetaldehyde dimethyl acetal followed by separation and deacetylation of the diastereoisomeric products afforded the isomers (36) and (37); compound (38) was also available and the iodides corresponding to the two bromides were made by halogen exchange. The ethyl compound was a substrate for green coffee α-D-galactosidase while all the halogenated glycosides were irreversible inhibitors - it was presumed because of haloacetaldehyde release and alkylation of the protein. Similar

work was carried out in the D-glucose series.[62]

Related methyl β-D-glucopyranosiduronates were made from the acetylated β-trimethylsilyl glycoside and aldehyde dialkylacetals in the presence of trimethylsilyl triflate. Following deacetylation the products were tested as enzyme substrates, compound (38) giving the free carboxylic acid with pig liver esterase and hydrolysing to release butanol with β-D-glucuronidase, the latter illustrating the potential of such substances as releases of cytotoxic aldehydes.[63]



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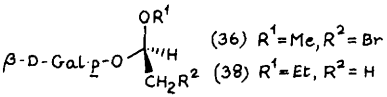
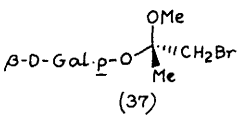


(36) R^1=Me, R^2=Br
(38) R^1=Et, R^2=H



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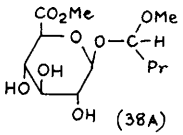

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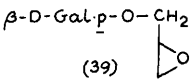

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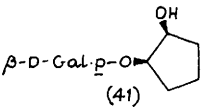

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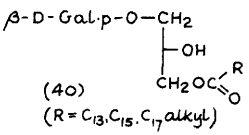
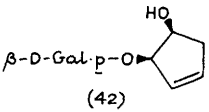


(40)
(R = C_{13}, C_{15}, C_{17} alkyl)



(42)

Several reports of the synthesis of specific glycosides by enzymic methods have appeared. β-Galactosidase, acting as a transferase, catalyses the formation of allyl, benzyl and trimethylsilylethyl β-D-galactopyranoside on a 1-20g scale from lactose and the corresponding alcohols. In parallel fashion raffinose and allyl alcohol afforded allyl α-D-galactopyranoside under the action of α-D-galactosidase.[64] β-Galactosidase also catalysed transglycosidation from lactose or o-nitrophenyl galactopyranoside to 2,3-epoxypropanol to give compound (39) from which 3-esters (40) were produced by epoxide ring opening in the presence of tetraethylammonium bromide.[65] Likewise an immobilised *E. coli* β-D-galactosidase was used to obtain compounds (41) and (42) in 89 and 50% diastereomeric excess, respectively, from the meso-diols.[66]

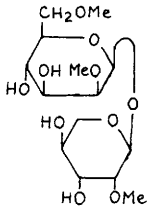
Specific other applications of the technique have given alkyl β-D-xylopyranosides by use of a bacterial xylosidase and water soluble or water insoluble alcohols,[67] and alkyl β-D-fructofuranosides (5-40% yield) by invertase-catalysed alcoholysis of sucrose in aqueous primary alcohols containing up to 70% alcohol. A detailed mechanistic discussion of the reaction was

provided.[68]

1.2 Synthesis of Disaccharides and Their Derivatives.- Several reports relevant to n.m.r. studies of disaccharides are covered in Chapter 21, and a new analytical approach of potential value for the structural determination of disaccharides and more complex carbohydrates is based on the analysis of the carbonyl carbon resonances of peracetylated derivatives. Assignments were made by correlating shifts with those of previously assigned ring protons and of acetyl methyl protons, and specific patterns were recognised for all those signals which allow the recognition of different types of residues.[69]

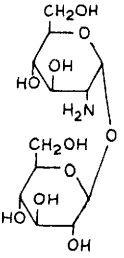
A review of block synthesis of oligosaccharides describes glycosylation approaches and protecting group strategies and contains material of relevance in disaccharide synthesis.[70]

In the area of non-reducing disaccharides evernose (43) and



(43)

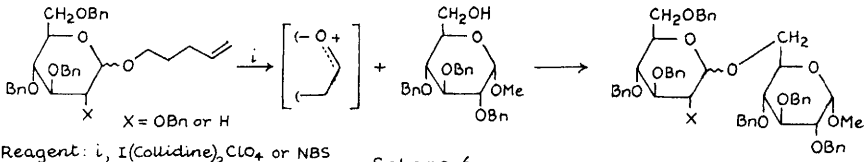
(44) (α-D-Man-p-linked isomer)



(45)

isoevernose (44) have been produced synthetically[71] as has pseudo-trehalosamine (45) the pseudo-sugar analogue of the antibiotic trehalosamine.[72] Compound (56) is also a non-reducing disaccharide.

Reducing disaccharides are now treated according to their non-reducing moieties. An interesting and potentially useful new glycosylating method involving the use of pent-4-enyl glycosides as glycosyl donors has been applied to disaccharide syntheses as illustrated in Scheme 6. It has also been applied likewise with



X = OBn or H

Reagent: i, $I(Collidine)_2ClO_4$ or NBS

Scheme 6

D-mannopyranosyl donors and with a range of primary and secondary

monosaccharide hydroxy compounds. The anomeric ratios of the products varied with solvent and reactant combinations, the best α-selectivity occurring with ether-dichloromethane.[73] Another novel synthetic method, this time of β-D-glucosides with high selectivity, involves the use of thio-orthoesters and their radical-mediated desulphurisation. Applied in the disaccharide series it gave a β-1,6-linked glucobiose derivative in 75% yield with a β:α ratio of 10:1.[5]

Several reactions have been applied to the synthesis of a range of glucobiose derivatives. These include the Helferich procedure used with methyl tri-O-acetyl-D-glucopyranosides and tetra-O-acetyl-α-D-glucopyranosyl bromide or 3,4,6-tri-O-acetyl-2-O-methyl-α-D-glucopyranosyl bromide,[74] conventional glucosylation (and mannosylation and rhamnosylation) of methyl β-D-galactopyranoside with substituents at O-3 and O-4,[75] and enzymic procedures using an α-glucosidase, a β-glucosidase and glucoamylase either in batch processes or immobilised on a column.[76]

S-Methyl tetra-O-benzyl-1-thio-β-D-glucopyranoside coupled with methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside by use of benzeneselenonyl triflate as catalyst gave the 1,6-linked D-glucobiose products in 91% yield with an α,β ratio of 1:7 illustrating again the value of thioglycosides as glycosylating agents.[77]

Tri-O-acetyl-1,2-cyanomethylidene-α-D-glucopyranose condensed with methyl 3,4,6-tri-O-acetyl-2-O-trityl-α-D-glucopyranoside in the presence of trityl perchlorate gave 78% of 1,2-linked products with an α,β-ratio of almost 1:30,[78] and Helferich glucosylation of benzyl 2-acetylamido-4,6-O-benzylidene-2-deoxy-α-D-gluco- or galacto-pyranoside has been used to obtain the β-1→3 linked disaccharides.[79]

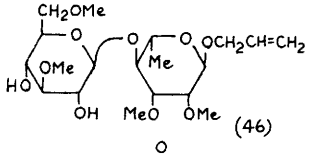
Several derivatives of maltose have been synthesised: the stereospecifically (R) and (S) C-6 deuterated methyl β-D-maltosides were required for inter-unit conformational analytical studies, and were made following photobromination of the 1,6-anhydroperacetate.[80] The same glycoside substituted at C-6 with fluoro, iodo, azido, amino, acetamido groups were made for studies of amyloglucosidase specificity[81] as were the 3-, 4′-, 6′-methyl ethers and the 3-, 4′- and 2′-epimers.[82] A novel and efficient means of making 6′-sulphonylated maltoses involves enzymolysis of 6-O-arylsulphonyated γ-cyclodextrins with Taka-amylase A. The tosyl and p-nitrobenzenesulphonyl compounds were obtained in 94 and 88% yield, respectively, under carefully controlled

conditions.[83]

In the series of monofluoroglucobioses methyl 6′-deoxy-6′-fluoro-α-D-sophoroside and -laminaribioside were made by use of 2,3,4-tri-O-benzoyl-6-deoxy-6-fluoro-α-D-glucopyranosyl chloride and methyl α-D-glucopyranoside derivatives with free hydroxyl groups at C-2 and C-3, respectively.[84] On the other hand, methyl 6′-deoxy-6′-fluoro-α-kojibioside and α-nigeroside were made by way of the corresponding 6′-hydroxy compounds which were subjected to fluorination with dimethylaminosulphur trifluoride (DAST)[84] and also by standard glycosylation methods.[85]

The allyl glucosylrhamnoside derivative (46), which is an antigenic determinant specific for *Mycobacterium leprae*, was synthesised and copolymerized with polyacrylamide for use as a diagnostic for leprosy,[86] and the repeating units of *Haemophilus influenzae*, 2-O-β-D-glucopyranosyl-L-ribitol 4′- and 1-phosphate, have also been prepared synthetically.[87]

In the field of disaccharides having D-galactose as non-reducing moieties, halide ion catalysed glycosylation of benzyl 4,6-O-benzylidene-β-D-galactopyranoside with 1.5 mol. equivalents of tetra-O-benzyl-α-D-galactopyranosyl bromide gave the α-(1→2) and α-(1→3) linked products in 22 and 40% yield, respectively. ^{13}C n.m.r. studies indicated that the derived 2-O-α-D-galactopyranosyl-D-galactose exists in solution as a mixture of pyranose (2 parts) and furanose (1 part) forms.[88] The allyl, benzyl and trimethylsilylethyl β-D-galactopyranosides, noted earlier as having been made enzymically, have been used as acceptors for further galactosylation and the following disaccharides have been made: allyl, benzyl and trimethylsilylethyl 3-O-β-D-galactopyranosyl-β-D-galactopyranoside; allyl and benzyl 6-O-β-D-galactopyranosyl-β-D-galactopyranoside; allyl 3-O-α-D-galactopyranosyl-α-D-galactopyranoside.[64] The glycopeptide (47) has been synthesised



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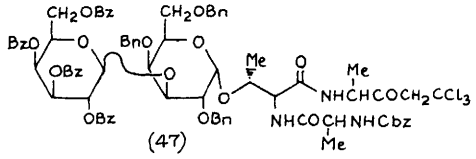

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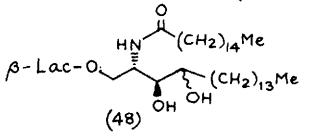

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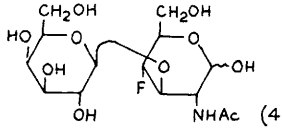


(49)

by coupling of the disaccharide and the tripeptide units and

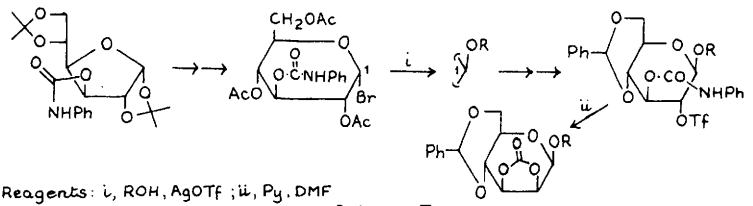
converted into deprotected derivatives,[89] and the methyl (1→6)α- and β-linked galactobiosides were made by standard glycosylation methods.[90]

The epimeric glycosylsphingolipids (48) have been prepared by separate glycosylation reactions,[91] β-1→2, 1→3, 1→4 and 1→6 linked galactosylglucosides have been produced by application of immobilised β-D-galactosidases[92] and 6-O-α-D-galactopyranosyl-D-glucose has been found to undergo oxidation with galactose oxidase.[93]

Several papers have reported the preparation of disaccharides comprising D-galactopyranose bonded to 2-amino-2-deoxyhexose derivatives: D-galactopyranosyl-2-acetamido-2-deoxy-D-galactoses have been made from lactose (or in low yield from D-galactose) and 2-acetamido-2-deoxy-D-galactose by use of immobilised β-galactosidase,[94] and methyl 2-acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-α-D-galactopyranoside has been synthesised by standard procedures using an azido-sugar[95] and also with the C-6 methylene group of the amino-sugar moiety stereospecifically deuterated for conformational studies.[96] The unlabelled (methyl nonano-9-yl) 2-acetamido-2-deoxy-3-O-(α-D-galactopyranosyl)-α-D-galactopyranoside was made and coupled to bovine serum albumin and Sepharose for immunological work.[97] Separate reports have dealt with lactosamine [2-amino-2-deoxy-(4-O-β-D-galactopyranosyl)-D-glucose] chemistry, the compound itself having been made by immobilised enzymic synthesis,[92] and the methyl glycoside derivative was made for polycondensation to give the polysaccharide of Streptococcus pneumoniae.[98,99] The 4-fluorinated compound (49) has been produced in independent work.[100]

Less usual galactosyl disaccharides to have been reported are 1→1, 1→3, 1→4 and 1→6 linked β-D-galactosyl-D-fructoses[92] and 3-O-α-D-galactopyranosyl-L-arabinose (n.m.r. analysis).[101]

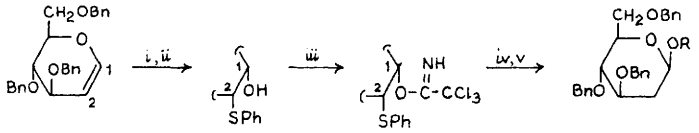
An interesting way of making β-D-mannopyranosides from β-D-glucopyranosides is illustrated in Scheme 7 and has been used in



Scheme 7

the syntheses of various products including derivatives of methyl 6-O-(β-D-mannopyranosyl)-α-D-glucopyranoside and 2-amino-2-deoxy-4-O-(β-D-mannopyranosyl)-D-glucose.[102] The latter has been N-O-diacylated within the reducing moiety to give analogues of lipid A.[103] Methods involving inversion at C-2 of a galactosyl unit have been used to synthesise methyl 3-O-(D-mannopyranosyl)-β-D-talopyranoside.[104]

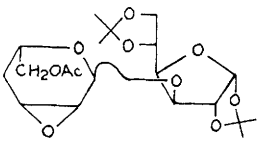
A convenient synthesis of 2-deoxy-β-D-arabino-hexopyranosides is illustrated in Scheme 8. It gives good β-selectivity.[105]



Reagents: i, PhSCl; ii, Na_2CO_3, H_2O; iii, CCl_3CN, NaH; iv, ROH, BF_3; v, Raney Ni

Scheme 8

Specifically the 4-deoxyhexosyl disaccharide (50) has been repeated and structurally characterised by X-ray diffraction,[106] and the following 6-deoxyhexosyl compounds have been prepared: 2-O-α-L-fucopyranosyl-D-galactose,[107] 2-acetamido-2-deoxy-(3- and 4-O-α-L-fucopyranosyl)-D-glucose as their trifluoroacetamidopropyl β-glycosides,[108] methyl 3[3-(2-O-α-L-rhamnopyranosyl-α-L-rhamnopyranosyloxy)decanoyloxy] decanoate (51, the rhamnolipid of *Pseudomonas aeruginosa*),[109] and methyl 3-O-(L-rhamnopyranosyl)-β-D-talopyranoside.[104]



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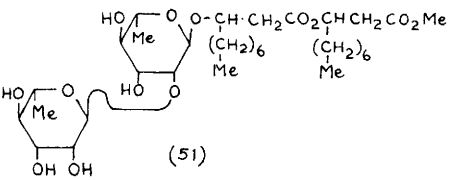

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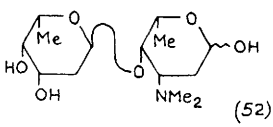

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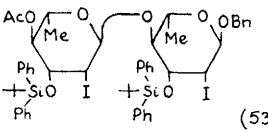
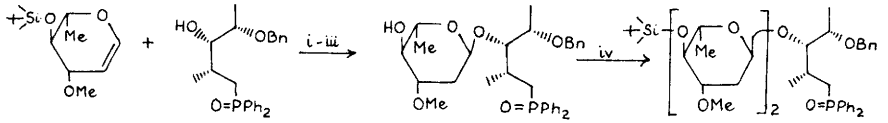


(53)

In the 2,6-dideoxyhexose series full details have appeared (c.f. Vol 17, p 48; Vol 20, p 27) of the synthesis of the disaccharide moiety (52) of the anthracycline antibiotics musettamycin, marcellomycin and aclacinomycin A,[110] and the disaccharide-containing fragment for avermectin synthesis has been produced as outlined in Scheme 9.[111] Selective silylation of L-

rhamnal gave 3-ethers and N-iodosuccinimide glycosylations allowed



Reagents: i, $PhSeCl$; ii, Ph_3SnH; iii, Bu_4NF; iv, Repeat.

Scheme 9

access to such 2,6-dideoxyhexosyl disaccharide derivatives as (53).[112]

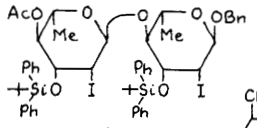
Considerable interest has been shown in disaccharides having N-acetylneuraminic acid as the non-reducing group. One report described the use of dimethyl(methylthio)sulphonium triflate - catalysed condensations of a methyl thioglycoside. β-Linked disaccharides were obtained with good selectivity from the β-thioglycoside, whereas the α-anomer gave poor selectivity.[113] Only modest yields of disaccharides were obtained by use of the analogous phenylthio glycosides activated by phenylmercury triflate.[114] Alternatively, glycosyl chlorides with the phenylthio-group at C-3, made following additions to 2-enes, have proved useful in the preparation of α-linked disaccharides, the sulphur-containing substituents being removed by radical reductions.[115,116] Specifically, N-acetylneuraminic acid has been α-linked to O-6 of D-glucosamine-4-phosphate,[117] and of L-serinyl 2-acetamido-2-deoxy-α-D-galactoside,[118] and also to O-8 of the 2,3-unsaturated derivative of N-acetylneuraminic acid.[119] Halides of acetylated N-acetylneuraminic acid allyl ester can be used successfully to give disaccharides, the β-glycosyl fluoride and chloride affording mainly β- and α-linked products, respectively.[120] The standard β-glycosyl chloride acetate was used in the synthesis of the nucleosides (54).[121]

3-Deoxy-D-manno-2-octulosonic acid (KDO) has been linked with the following sugars: allyl KDO glycoside (4-linkage, α- and β-anomers),[122] D-glucosamine 4-phosphate(6-α-linkage),[123,123a] and methyl α-D-glucopyranoside (6-α-linkage).[124]

In the area of aldobiouronic acids, compounds containing L-iduronic acid linked α-1,4- to 2-amino-2-deoxy-D-glucose derivatives have been reported[125,126] as have compounds with D-glucuronic acid linked 1→4 to 1,6-anhydro-2-azido-2-deoxy-D-glucose.[126a] Attempts to produce a 1,4-linked D-galacturonic acid dimer by use of a glycosyl fluoride as glycosylating agent did not succeed.[127]

In the field of 2-amino-2-deoxy-D-glucose disaccharides the sugar in various derivatised forms has been linked to D-galactose (β-1,3-link)[128,129] (and β-1,6-link),[130] D-glucose (β-1,3-link),[130] 2-amino-2-deoxy-D-glucose (β-1,4-link),[77] D-galacturonic acid (β-1,2-link)[131] and L-iduronic acid (α-1,4-link).[126] The 2-amino-2,4-dideoxy-4-fluoro compound (55) has been prepared by the oxazoline method[132] and 2-amino-2-deoxy-β-D-mannopyranosyl disaccharides have been produced from oximo-products obtained by use of a 2-deoxy-2-oximo-D-arabino-hexosyl bromide.[133] A 4-amino-4-deoxy-D-rhamnosyl disaccharide (α-1,2-linked) has been made by way of 4-azido-compounds.[134]

In the area of pentosyl disaccharides D-ribofuranose derivatives have featured most prominently. Compounds linked α-1,5 to D-ribose and α-1,3- to D-glucose[135] and β-1,2 and β-1,3 and β-1,5 to D-ribose have been reported.[136] Four papers have appeared on derivatives of D-ribofuranose linked β-1,1 to D-ribitol[136a] and complex oligomers of this compound bonded by phosphate diester bridges between O-5 of the alditol and O-3 of D-ribofuranose of a second disaccharide.[137-139]



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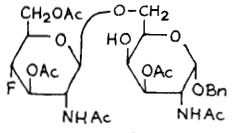

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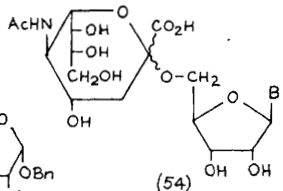

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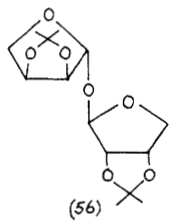


(56)

The synthesis of benzyl 6-O-β-D-apiosyl-β-D-glucopyranoside has been described[140] as has the non-reducing tetrose dimer derivative (56).[141]

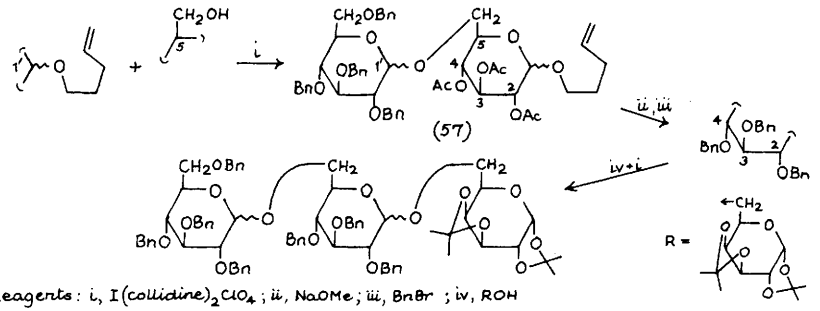
1.3 O-Glycosides Isolated from Natural Products.- As always, only compounds having notable features in the carbohydrate portions are noted.

The first report of an L-lyxose-containing compound, 2-(3,4-dihydroxyphenyl)ethyl O-α-L-lyxopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→3)-4-O-caffeoyl-β-D-glucopyranoside, has been appeared, the compound having been isolated from Teucrium chamaedrys.[142] A further similar plant glycoside was based on 2-O-α-L-rhamnopyranosyl-D-allose.[143]

1.4 Hydrolysis and Other Reactions and Features.- A review has been written on the hydrolysis of glycosides under reducing conditions.[41] Examination of the hydrolysis of sucrose in $H_2{}^{18}O$ and followed by ^{13}C n.m.r. spectroscopy using ^{18}O- induced shifts led to the conclusion that the fructosyl-oxygen bond underwent selective cleavage.[144]

2-(Trimethylsilyl)ethyl glycosides, unprotected, acetylated or benzylated or mono- or di-saccharide derivatives can be selectively cleaved almost quantitatively to the reducing analogues by use of trifluoroacetic acid in dichloromethane.[145] The same reagent or titanium tetrabromide similarly permit the hydrolysis of tert-butyl glycosides without reaction at the inter-unit bonds of disaccharide derivatives.[60]

Fraser-Reid's group have provided further interesting data on the hydrolysis of their pentenyl glycosides. Reaction in moist acetonitrile with NBS requires that <1% water is used otherwise bromohydrin formation competes with the cleavage. The efficiency of the hydrolysis is dependent on the protecting groups on the hydroxy groups of the glycoside.[146] Ether groups permit glycoside hydrolysis much faster than do ester groups and this led to the ingenious application, illustrated in Scheme 10, whereby



Reagents: i, I(collidine)$_2$ClO$_4$; ii, NaOMe ; iii, BnBr ; iv, ROH

Scheme 10

disaccharide (57) was synthesised and then reactivated by replacement of the acetates by benzyl groups to give a product which was converted into a trisaccharide.[147]

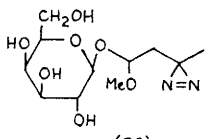
The use of an immobilised enzyme for the hydrolysis of flavonoid, anthraquinone and steroidal α-L-rhamnopyranosides has been described,[148] and a related paper has reported studies of the treatment of 2-deoxy-2-fluoro-β-D-glucopyranosyl fluoride with a β-glucosidase (see Chapter 8).

Efficient cleavage of bleomycin to deglycobleomycin was effected by use of hydrogen fluoride at 0°C.[149] The relative rates

of the acetolysis of the inter-unit bonds of O-α-D-mannopyranosyl-(1→6)-D-mannose, O-β-D-mannopyranosyl-(1→2)-D-mannose and O-α-D-mannopyranosyl-(1→2)-D-mannose were α-1,6 > β-1,2 >> α-1,2.[150] Base-catalysed anomerisation of some acetylated 2,4-dinitrophenyl β-D-glucopyranosides was determined to occur by nucleophilic attack at the ipso-position,[151] and acid-catalysed methanolysis of the methyl D-glucofuranosides led to anomerisation and also, unlike in the case of the pyranosides, to the formation of the dimethylacetal.[152]

1,6-Linked disaccharides, on treatment with a Ni(II) diamine complex, undergo epimerisation at C-2. For example, isomaltose can be converted into a mixture containing 6-O-α-D-glucopyranosyl-D-mannose as the major epimer. The reaction, which has been reported before for monosaccharides (Vol 20, p 11-12), did not proceed with 1,4-linked dimers e.g. cellobiose.[153] Similarly, 1,6-linked disaccharides are more reactive towards Fenton's reagent (Fe(II), H_2O_2) than are 1,4-bonded isomers.[154]

The azirine derivative (58), when photolysed in the presence of an immunoglobulin, labelled the galactan-binding area.[155] Also in the area of carbohydrate-protein binding, novel descriptors have been used in the analysis of the quantitative structure-activity relationship of the binding of p-substituted phenyl glycosides to concanavalin A.[156]



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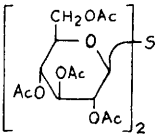

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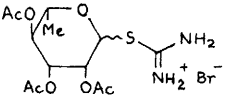


(60)

A theoretical study has been reported on the stereochemistry of methyl α- and β-D-glucopyranosides in 10 different solvents.[157]

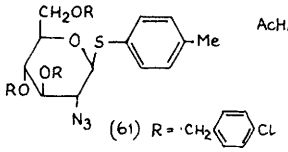
2 S-Glycosides

Two reviews have appeared on the use of thioglycosides in oligosaccharide synthesis,[158,159] and several applications are described in papers referred to in this and in the following Chapter. The activations of thioglycosides for O-glycoside synthesis by methylsulphenyl bromide and by o-nitrobenzylsulphenyl chloride have been described.[160]

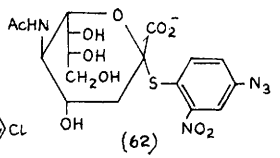
Treatment of tetra-O-acetyl-α-D-glucopyranosyl bromide with sodium sulphide gave the disulphide (59), and related

unsymmetrical compounds were obtained by condensation of glycosyl halides and 1-thiosugars.[161] Methylation of the isothiouronium salt (60) with methyl iodide and ethyldi-isopropylamine gave a separable mixture of methyl 1-thio-α- and β-L-rhamnopyranoside which were converted into various benzyl ethers.[162]

Compound (61) was made from the corresponding glycal by azido-nitration followed by chloride treatment to give the α-glycosyl chloride and thence the thioglycoside which is a useful galactosamine synthon.[163] Alternatively, the azidoacyl



(61) R = ·CH$_2$-C$_6$H$_4$-Cl



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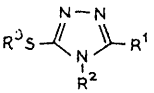


(63)

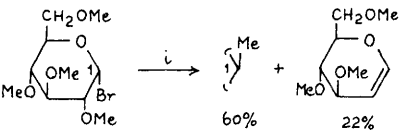
R^1 = H, Me, Ph, 4-pyridyl
R^2 = H, Ph
R^3 = D-Glc, D-Gal, D-Xyl, L-Ara

thioglycoside (62) has been prepared as a potential photoaffinity probe for analysis of sialidases and sialic acid binding proteins.[164] Compounds (63) showed significant antiinflammatory, analgesic, neurotropic and antihypoxic activities.[165]

3 C-Glycosides

3.1 Pyranoid Compounds.- A review has appeared on anomeric free radicals which encompasses the synthesis of C-glycosidic compounds.[166]

Reaction of tetra-O-methyl-α-D-glucopyranosyl bromide with lithium dimethylcuprate gave mainly the β-C-glycoside as did other dialkylcuprates (Scheme 11). Grignard reagents, on the other

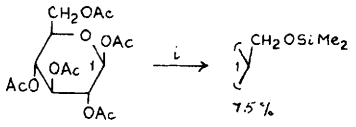


Reagent: i, Li Me$_2$Cu

Scheme 11

hand, afforded large proportions of α-linked C-glycosides, and alkyllithium reagents led mainly to elimination and therefore 2-hydroxyglycal production.[167]

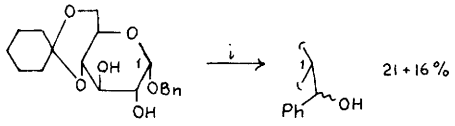
A range of reactions have led to means of obtaining substituted C-methyl glycosides. Thus aldopyranose and aldofuranose peracetates can be efficiently converted into silyloxymethyl compounds (Scheme 12).[168] Benzyl glycosides can be converted in very modest yields into hydroxybenzyl C-glycosides



Reagents: i, $HSiMe_3$, CO, $Co(CO)_8$(cat)

Scheme 12

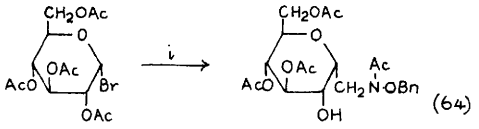
with retained stereochemistry by application of the Wittig rearrangement (Scheme 13).[169]



Reagents: i, BuLi, TMEDA, THF

Scheme 13

Glycosyl radicals produced from tetra-O-acetyl-α-D-glucopyranosyl bromide by use of trimethyltin radicals generated by thermolysis of bis-O-(trimethylstannyl)benzpinacol were trapped by O-benzylformaldoxime to give the C-(N-methyl)glycoside (64) (Scheme 14) which had undergone migration of the acetyl group at O-2.[170]



Reagents: i, $Ph_2C(OSnMe_3)C(OSnMe_3)Ph_2$, $CH_2{=}NOBn$

Scheme 14

Otherwise aminomethyl C-glycoside derivatives may be obtained by reduction of glycosyl cyanides (Chapters 21, 22).[171]

Condensation of enamines of β-ketoesters and ketones with tetra-O-benzyl-α-D-glucopyranosyl chloride activated with silver triflate gave α-C-glucosides as epimeric mixtures in 80-85% yield (Scheme 15).[172]

Reagents: i, 

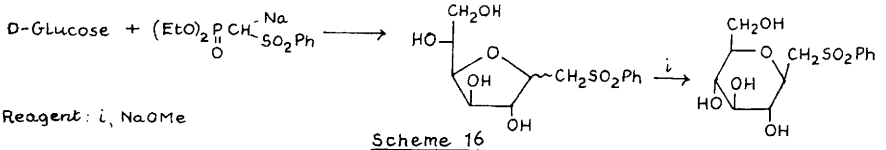
or 

, AgOTf

Scheme 15

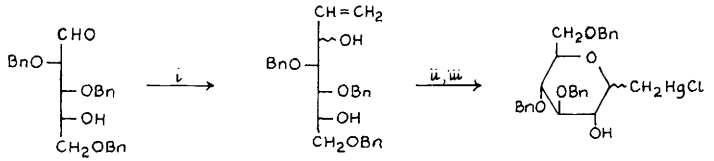
Free sugars on treatment with phosphonate sulphones give

furanosyl C-glycosides which rearrange to pyranosides (Scheme 16).[173] Alternatively α-mercurimethyl C-glycosides may be made



Scheme 16

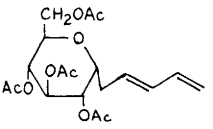
from vinyl Grignard products as shown in Scheme 17. In this way routes to C-glycosides with the following configurations were



Scheme 17

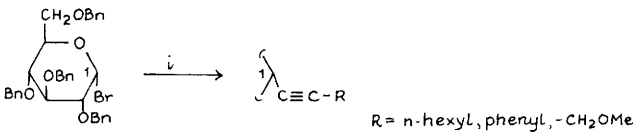
developed: α-allo, β-altro, α-gluco, α-manno, α- and β-gulo, β-ido, α-galacto and β-talo.[174]

In the area of C-glycosides with unsaturated aglycones allyl compounds can be made by use of sugar peracetates and allyltrimethylsilane and a Lewis acid, and corresponding pent-2,4-dienyl analogues such as compound (65) are obtainable similarly by



(65)

use of 1-trimethylsilylpent-2,4-diene.[175] In related fashion tetra-O-benzyl-α-D-glucopyranosyl bromide with tributyltinalkynes afford glycosylalkynes (Scheme 18).[176] Alternatively,

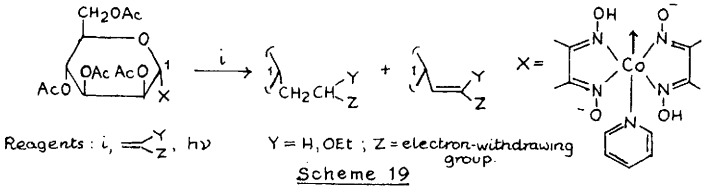


Scheme 18

2-substituted vinyl C-glycosides are obtainable together with 2-substituted ethyl analogues by the reaction indicated in Scheme 19.[177]

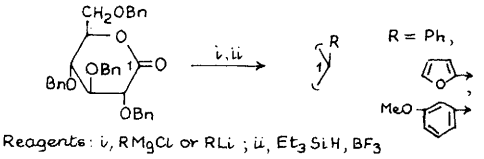
An interesting novel route to aromatic β-C-glucopyranosides

involves reaction of a lactone with organometallic reagents



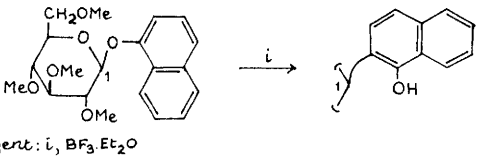
Scheme 19

followed by reduction of the initial products (Scheme 20).[178] An alternative method of making such anomeric 2-furanosyl compounds involves treatment of benzylated glycosyl fluorides with 2-(diethylaluminium)furan. Pyrrole analogues can be made by use of N-methyl-2-(diethylaluminium)furan.[179]



Scheme 20

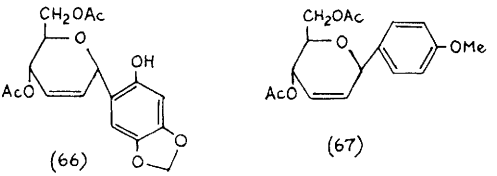
The O- and C-glycosidic products formed by reaction of tetra-O-acetyl-α-D-glucopyranosyl chloride with various methoxy-substituted phenylmagnesium bromides have been examined.[180] That aryl O-glycosides can rearrange to aryl C-glycosides is illustrated in Scheme 21, and likewise the β-naphthylglycoside



Scheme 21

gives the 1-C-glycosyl-β-naphthol in good yield.[59]

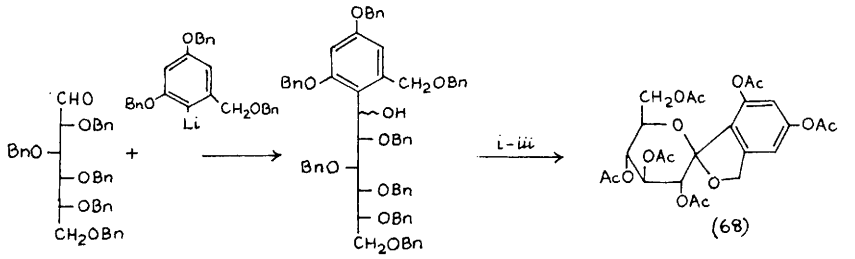
Reactions of tri-O-acetyl-D-glucal with various bromomagnesium phenates are reported to give α-linked 2,3-unsaturated glycosides e.g. (66),[181] but great care must be taken



with the assignment of configuration to products of reactions of

this type because it has now been shown by X-ray diffraction analysis that the compound isolated following treatment of tri-O-acetyl-D-glucal with anisole in the presence of tin (IV) chloride is the β-linked compound (67) and not the α-anomer as previously indicated.[182]

The tricyclic spiroketal structure (68) is found in the antibiotic substances papulacandins and has been synthesised as indicated in Scheme 22 or from the corresponding methyl gluconate



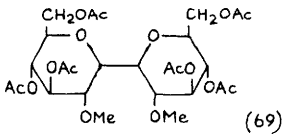
Reagents: i, DMSO-Ac_2O; ii, H_2-Pd/C; iii, Ac_2O-Py

Scheme 22

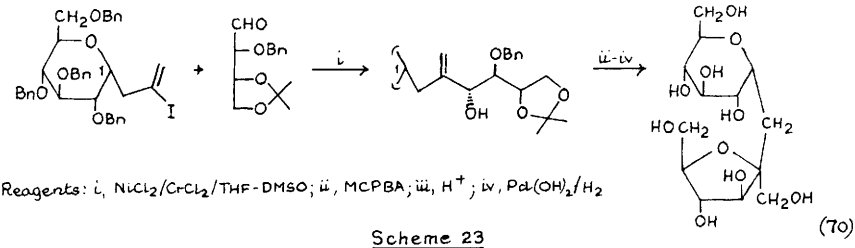
tetrabenzyl derivative thus obviating the oxidation step.[183]

A review has appeared on flavonoid C-glycosides,[184] and in this series the new compound severtisin 2″-arabinoside has been isolated from dried leaves of Achillea fragrantissima.[185]

Considerable attention has been paid to C-C-linked disaccharides. Most members of this group have a one-carbon atom linking the sugar units, but the C-1—C-1 linked compound (69) has



been made by the dimerisation of glycosyl radicals produced from 3,4,6-tri-O-acetyl-2-O-methyl-α-D-glucopyranosyl bromide or the



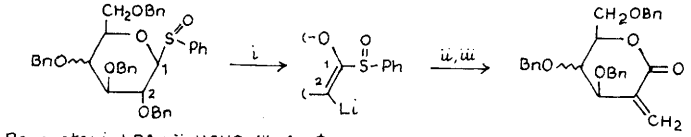
Reagents: i, $NiCl_2/CrCl_2$/THF-DMSO; ii, MCPBA; iii, H^+; iv, $Pd(OH)_2/H_2$

Scheme 23

corresponding phenylselenide derivative. The reaction was also

conducted without a substituent at O-2, but was unsuccessful with an acetate at this position since this group migrated to the anomeric centre.[186]

A notable synthesis of C-linked sucrose (70) is illustrated in Scheme 23.[187] In Scheme 24 a route to methylene lactones from



Reagents: i, LDA ; ii, HCHO ; iii, Δ, H+

Scheme 24

which C-disaccharides can be made by radical addition processes is outlined; in this way the C-linked analogues of α-D-Glcp-(1→2)-D-Glcp, α-D-Manp-(1→2)-D-Glcp and α-D-Fucp-(1→2)-D-Galp were made.[188]

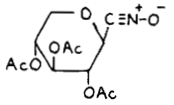
Treatment of nitrile oxide (71), obtainable from the xylopyranosylnitromethane, with the alkene (72) gave isoxazolines which were ring opened to the carbonyl-linked disaccharide analogues (73) and (74), the latter being produced following an epimerisation at C-2.[189]

In C-linked disaccharides having a methylene group in place of the oxygen atom, the C-1'--C-2' bond is antiperiplanar to the bond joining the methylene group to the reducing sugar ring.[190]

3.2 Furanoid Compounds.- D-Ribose, treated with nitromethane in basic conditions, gave compound (75) in high yield and this, with acetic anhydride and pyridine followed by phosphorus trichloride in the same solvent, gave the glycosylcyanide (76). Related compounds with the β-D-xylo-, α- and β-D-galacto-configurations were made.[191]

Compounds (77) were synthesised by alkaline reduction of the furan Diels-Alder adduct (78) which ring opened by a retro-aldol procedure,[192] and the related diester (79) was made by addition of a glycosyl radical derived from a glycosyl xanthate to dimethyl maleate. It was then converted to (80) which has previously been converted to shodomycin, and a new synthesis of this antibiotic was therefore claimed. In the course of the work radical addition reactions were used to produce C-glycosides derived from butenone and methyl acrylate.[193] Compound (81), made by application of the Wittig reaction to the corresponding D-ribofuranose derivative, was used to make the t-butyldimethylsilyl analogue of the dihydroshodomycin (80) and, in the same work, the diene (82) was

cyclised by use of phenylselenyl chloride to the pyranoid compound (83).[194]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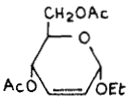
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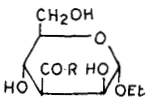
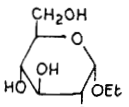
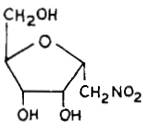

(73)


(74)

R = tri-O-Ac-β-D-Xyl-p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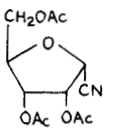
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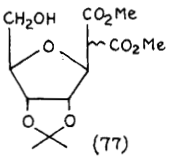
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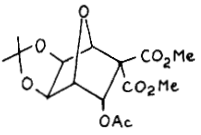
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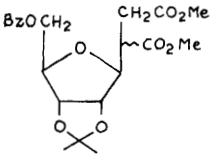
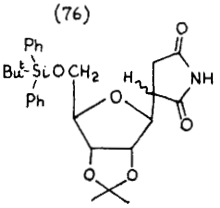
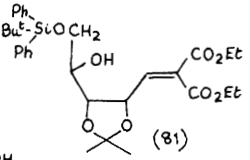
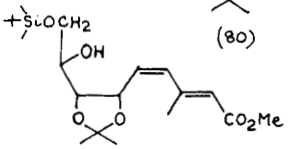

(79)


(80)


(81)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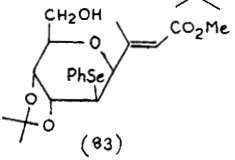
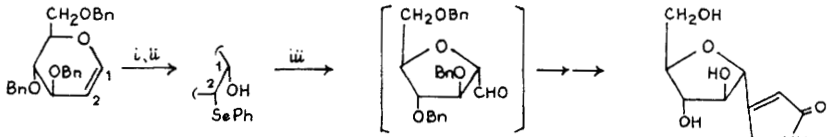

(83)

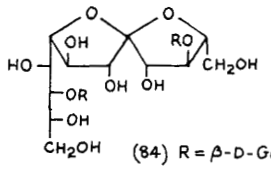
A new approach to an analogue of shodomycin is illustrated in Scheme 25, and the α-D-lyxo-isomer was likewise made from tri-O-benzyl-D-galactal.[195]

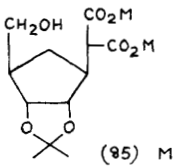


Reagents: i, PhSeCl; ii, $Et_3N.H_2O$; iii, MCPBA

Scheme 25

Compounds (84) (tentative identification) and (85), which can also be classified as a ketose and a racemic cyclitol

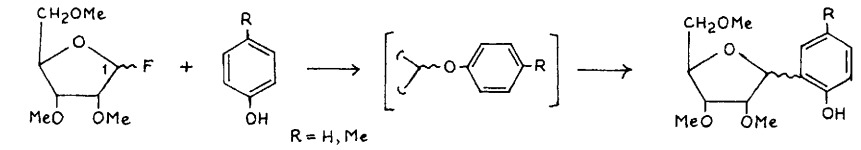

(84) R = β-D-Gal-p


(85) M = (-)-Menthyl

derivative, have been isolated from commercial preparations of lactulose[196] and synthesised by a Diels-Alder approach,

respectively.[197]

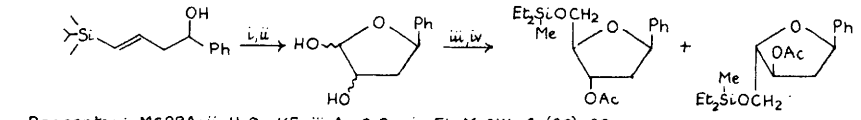
In the area of aryl C-furanosides it has been shown that O-furanosides with a dimethyl(p-tolyl)silyl ether group at O-2, on treatment with tin (IV) chloride, give 1,2-cis-related p-tolyl C-glycofuranosides. In similar fashion C-vinyl glycosides can be made.[198] A related rearrangement occurs as indicated in Scheme 26.[199]



Reagents: i, $Cp_2HFCl_2/AgClO_4$, -78°

Scheme 26

A de novo synthesis of C-phenyl pentofuranosides is illustrated briefly in Scheme 27.[200] A further phenyl



Reagents: i, MCPBA; ii, H_2O_2, KF; iii, Ac_2O, Py; iv, Et_2MeSiH, $Co(CO)_8CO$

Scheme 27

C-furanoside is referred to in Chapter 24.

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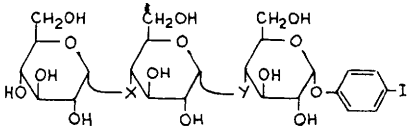
4
Oligosaccharides

1 General

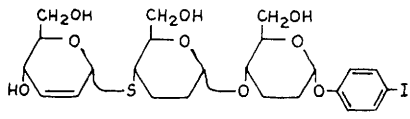
As before, this Chapter deals with specific tri- and higher oligosaccharides; most references relate to their syntheses by specific chemical methods. It does not deal with compounds made by the oligomerization of monosaccharide derivatives, nor does it cover the cyclodextrins. The synthesis of, e.g.,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

A list of reviews on the synthesis of oligosaccharides published since 1980 has appeared,[1] as has a new review on the subject[2] and one on the synthesis of the oligosaccharides of glycoconjugates.[3] Further reviews have appeared on (i) the synthesis of oligosaccharides using penta-O-acetyl-N-acetylneuraminic acid methyl ester β-glycosyl chloride, 2β,3α-dibromoneuraminic acid peracetate and sialyl transferase,[4] (ii) the synthesis of biologically active pseudo-oligosaccharides derived from maltose and maltotriose by application of Ferrier's carbocyclization reaction,[5] and (iii) structural and conformational characterization of carbohydrate differentiation antigens.[6]

Full details have appeared on the di- and tri-saccharide moieties of the anthracycline antibiotics musettamycin, marcellomycin and aclacinomycin A (c.f. Vol. 17, p. 48; Vol. 20, p. 27, 46).[7]



(1) X = S, Y = O
(2) X = O, Y = S



(3)

Oligosaccharides containing N-acetylamino groups can be quantitatively de-N-acetylated by use of calcium in liquid ammonia. Polysaccharides were not fully N-deacetylated.[8]

2 Trisaccharides

2.1 Linear Homotrisaccharides.- Two linear D-glucotriose derivatives with deoxyfluoro-groups at C-6 of the non-reducing terminal unit and α-(1→6),α-(1→6) and β-(1→6),α-(1→6) linkages have been synthesized,[9] as have compounds (1)-(3) which are a new class of potential enzyme inhibitors.[10] The α-(1→2)-linked trimer of 4-deoxy-4-formylamino-D-rhamnose as the methyl α-glycoside was prepared and found to be a potent inhibitor of the binding of Brucella O-polysaccharide by Brucella-specific monoclonal antibodies.[11] Likewise the α-(2→8)-linked trimer of KDOp was made as the α-allyl glycoside and copolymerized with acrylamide to give a specific antigen. The trimer is structurally related to the genus lipopolysaccharide epitope of Chlamydia.[12]

2.2 Linear Heterotrisaccharides.- Compounds of this class are now dealt with according to their reducing termini and then according to the adjacent moieties. The preparation has been reported of O-β-D-ManNAcp-(1→4)-O-α-D-Glcp-(1→4)-D-Glc and the β,β-linked compound which are components of capsular polysaccharide repeating units of various Streptococcus pneumoniae types.[13] Glycosyl ceramides of O-α-D-Galp-(1→4)-O-β-D-Galp-(1→4)-β-D-Glcp[14] and O-α- and β-D-NeuGc-(2→3)-O-β-D-Galp-(1→4)-β-D-Glc[15] have been prepared, and a further paper has described a new synthesis of the first of these latter anomers.[16] Two reports of related ceramide glycosides of O-β-D-GlcNAcp-(1→3)-(and 1→4)-O-β-D-Galp-(1→4)-β-D-Glcp have appeared.[17,18] O-β-D-GlcNAcp-(1→2)-O-α-D-Manp-(1→6)-β-D-Glc and five analogues having various modifications at the reducing moiety have been prepared as octyl glycosides and examined as substrates for N-acetylglucosaminyltransferase-V.[19] O-α-D-Glcp-(1→4)-O-α-L-Rhap-(1→3)-D-Glc was prepared, and it and several derivatives were conformationally examined by ^{1}H and ^{13}C n.m.r. methods.[19a] O-β-D-Glcp-(1→3)-O-β-D-Glcp-(1→6)-D-Gal has been made by use of a disaccharide glycosyl bromide prepared by photobromination of a 1,2-O-benzylidene compound,[20] and the following similar compounds having a 2-amino-2-deoxyhexose as central unit have been reported: O-α-L-Fucp-(1→3)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-$OC_6H_4NO_2$p,[21] the methyl analogue of this compound

and its (1→4),(1→3) and (1→6),(1→3) linked isomers[22] and O-β-D-Galp-(1→4) and (1→6)-O-β-D-GalNAcp-(1→3)-β-D-Galp-OMe.[23]

O-β-D-Galp-(1→4)-O-β-D-GlcNAcp-(1→2)-α-D-Manp-$O(CH_2)_6NHCOCH_2Br$ has been made in order to attempt to determine the Phaseolus vulgaris leukoagglutinin sugar binding site by affinity labelling.[24]

In the area of trisaccharides which have a 2-aminohexose at the reducing end the following have been synthesized as derivatives bearing long chain fatty acid moieties on the nitrogen atoms and on certain of the hydroxyl groups: O-β-D-Manp-(1→4)-O-β-D-$GlcNH_2$p-(1→6)-β-D-$GlcNH_2$p-OMe[25] and O-α-D-KDOp-(2→6)-O-β-D-$GlcNH_2$p-(1→6)-D-$GlcNH_2$.[26] In connection with studies of heparin various N- and O-sulphated forms of O-α-D-$GlcNH_2$p-(1→4)-O-α-L-Idop-(1→4)-α-D-$GlcNH_2$p were prepared,[27] and O-α-L-Fucp-(1→3)-O-β-D-Galp-(1→4)-D-GlcNHAc, which is part of a human milk oligosaccharide, was synthesized.[28]

O-α-D-NeuNAcp-(2→3)-O-β-D-Galp-(1→3)-D-GalNAcp has also been synthesized.[29]

In the family of compounds terminating in 6-deoxyhexose reducing units O-β-D-ManNAcp-(1→4)-O-α-D-Glcp-(1→3)-L-Rha,[13,30] O-β-D-ManNAcp-(1→4)-O-α-D-Glcp-(1→2)-L-Rha,[13,30a] O-α-D-Galp-(1→3)-O-β-D-GlcNAcp-(1→4)-α-L-Rhap-OMe,[31] O-β-D-GlcNAcp-(1→3)-O-α-L-Rhap-(1→3)-L-Rha[32] and O-α-L-Araf-(1→6)-O-β-D-GlcNAcp-(1→3)-L-Tal have been reported.[33] The trisaccharide of the Mycobacterium leprae - specific phenolic glycolipid I O-(3,6-di-O-methyl-β-D-glucopyranosyl)-(1→4)-O-(2,3-di-O-methyl-α-L-rhamnopyranosyl)-(1→2)-3-O-methyl-L-rhamnose has been synthesized and the immunoreactivity of derived glycoproteins has been studied.[33a,33b]

2.3 Branched Homotrisaccharides.- The four stereoisomers of methyl 4,6-di-O-D-glucopyranosyl-β-D-glucopyranoside with the α,α; α,β; β,α and β,β anomeric configurations were prepared with the pro-S C-6 proton replaced by a deuteron and used in the conformational analysis of the compounds.[34] In contrast, prop-2-yl 3,6-di-O-[α-D-mannopyranosyl]-β-D-glucopyranoside was synthesized with each of the carbohydrate carbon-bonded protons replaced by deuterons.[35]

2.4 Branched Heterotrisaccharides.- As with compounds in Section 2.2, the branched substances reported are listed according to their reducing moieties and are: 3,6-di-O-(α-D-galactopyranosyl)-α-

D-glucose (as various glycosides);[36] O-α-L-Rhap-(1→4)-O-[β-D-Glcp-(1→2) and (1→6)]-D-Glc;[37] O-α-L-Fucp-(1→2)-O-[α-D-Galp]-β-D-Galp-$OCH_2CH_2C_6H_4NHCOCF_3$;[38] O-β-D-GlcNAcp-(1→6)-O-[α-D-Galp]-α-D-GalNAcp-$OCH_2CH_2C_6H_4NHCOCF_3$;[39] O-β-D-GalNAcp-(1→4)-O-[α-NeuAcp-(2→3)]-D-Gal;[40] O-β-D-GlcNAcp-(1→4)-O-[α-L-Fucp-(1→6)]-D-GlcNAc;[41] O-β-D-GlcNAcp-(1→6)-O-[β-D-Galp-(1→3)]-D-GalNAcp.[42,43]

3 Tetrasaccharides

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

3.1 Linear Tetrasaccharides.- 6-Mono-O-arenesulphonyl-γ-cyclodextrins on hydrolysis catalysed by Taka-amylase A have provided several oligosaccharide esters including maltotetraose sulphonylated at C-6 of glucose residue no. 3 in good yield.[44] Chemical glycosylation of methyl β-D-maltotrioside gave the tetrasaccharide having α-L-arabinofuranose bonded to O-6 of the terminal unit.[44a] The non-reducing compound O-β-D-Glcp-(1→3)-O-β-D-Glcp-(1→4)-O-α-D-Glcp-(1→1)-α-D-Glcp, the core oligosaccharide of the lipopolysaccharide antigens from M. kansaii, has been synthesized from α,α-trehalose.[45] Synthesis has been repórted of the capsular polysaccharide repeating unit of S. pneumoniae type 14: O-β-D-Galp-(1→4)-O-β-D-$GlcNH_2$p-(1→3)-O-β-D-Galp-(1→4)-D-Glc.[46] The related compound of the type 3 organism has also been prepared: O-β-D-GlcUp-(1→4)-O-β-D-Glcp-(1→3)-O-β-D-GlcUp-(1→4)-D-Glc.[47] O-α-L-Rhap-(1→2)-O-α-L-Rhap-(1→2)-O-α-L-Rhap-(1→1)-Glc-itol, the oligosaccharide of the antigen of Group B streptococci, has also been prepared.[48] The following mucin tetrasaccharides have been produced synthetically: O-α-L-Fucp-(1→3)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→3)-β-D-GlcNAcp-$OC_6H_4NO_2$,[49] O-α-L-Fucp-(1→3)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→3)-β-D-GalNAcp-$OC_6H_4NO_2$,[49] O-β-D-Galp-(1→3)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→3)-O-β-D-GalNAcp-OBn.[50] Likewise, the following synthetically produced bacterial polysaccharides have been reported: O-α-D-KDOp-(2→4)-O-α-D-KDOp-(2→6)-O-β-D-$GlcNH_2$p-(1→6)-D-$GlcNH_2$,[51,52] O-α-L-Rhap-(1→3)-O-α-D-Galp-(1→3)-O-β-D-GlcNAcp-(1→4)-α-L-Rhap-OMe.[31] O-α-L-Rhap-(1→3)-O-α-L-Rhap-(1→3)-O-α-L-Rhap-(1→4)-α-L-Rhap-$OC_{12}H_{25}$ has been isolated from the stem bark of Cleistopholis glauca.[53]

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

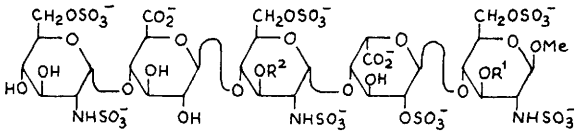
1. D-Mannose reducing terminus: O-β-D-GlcNAcp-(1→2)-O-[β-D-GlcNAcp-(1→6)]-O-α-D-Manp-(1→6)-β-D-Manp-O-$(CH_2)_8CO_2Me$.[54]

2. 2-Amino-2-deoxy-D-glucose reducing terminus: O-α-L-Fucp-(1→2)-O-β-D-Galp-(1→3)-O-[α-L-Fucp-(1→4)]-β-D-GlcNAc,[55] O-α-L-Fucp-(1→2)-O-β-D-Galp-(1→4)-O-[α-L-Fucp-(1→3)]-D-GlcNAc,[55] O-β-D-Galp-(1→4)-O-β-D-Glcp-(1→6)-O-[β-D-Galp-(1→4)]-β-D-$GlcNH_2$-OMe.[56]

3. 2-Amino-2-deoxy-D-galactose reducing terminus: O-α-D-NeuNAcp-(2→3)-O-β-D-Galp-O-[α-D-NeuNAcp-(2→6)]-α-D-GalNAcp-O-Ph,[57] O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-O-[β-D-Galp-(1→6)]-β-D-GalNAcp-OBn.[58]

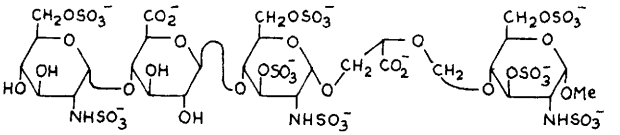
4 Pentasaccharides

O-β-D-Galp-(1→3)-O-β-D-GalNAcp-(1→3)-O-α-D-Galp-(1→4)-O-β-D-Galp-(1→4)-β-D-Glc is a stage specific embryonic antigen (SSEA-3) and has been synthesized as its ceramide glycoside.[59] The following mucin pentasaccharides have been prepared: O-β-D-Galp-(1→3)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→3)-O-β-D-GlcNAcp-(1→3)-β-D-Galp-OMe,[50] O-β-D-Galp-(1→3)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→3)-O-[β-D-GlcNAcp-(1→6)]-β-D-GalNAcp-OBn.[50] Chitopentaose has been converted into the β-p-nitrophenyl glycoside which was found to be an excellent substrate for lysozyme.[50]

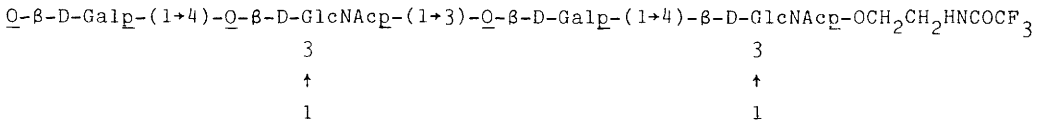


(4) $R^1 = H$, $R^2 = SO_3^-$
(5) $R^1 = SO_3^-$, $R^2 = SO_3^-$
(6) $R^1 = H$, $R^2 = H$

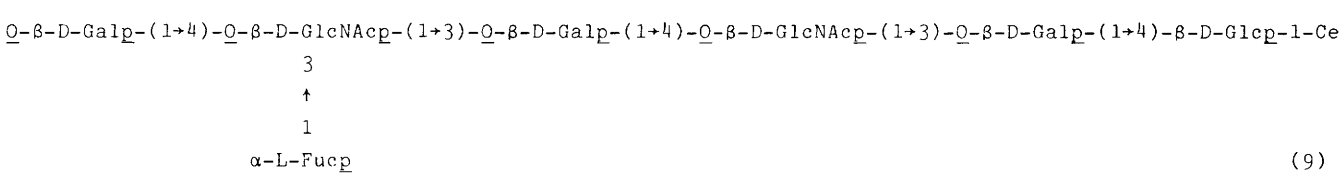
Appreciable further work on the heparin pentasaccharide has been reported. Compound (4) was synthesized and found to bind to antithrombin (III) with an association constant similar to that of high-affinity heparin.[61] The 3-sulphate (5) is a very potent analogue,[62] but the desulphated compound (6) has none of the biological properties of (4).[63] Other inactive analogues of compound (4) are the compound with α-L-idopyranose 2,6-disulphate in place of the iduronosyl 2-sulphate[64] and the pentasaccharide



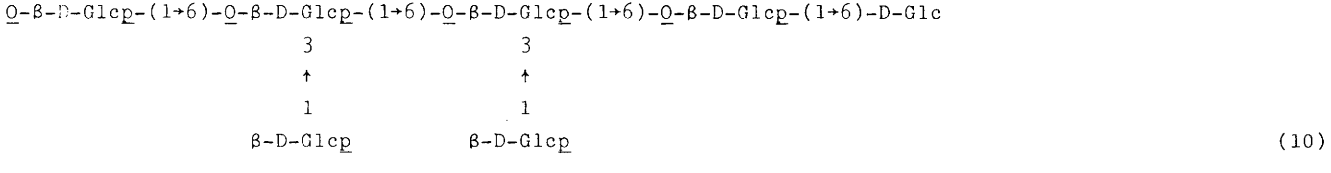
(7)


O-β-D-Galp-(1→4)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→4)-β-D-GlcNAcp-OCH2CH2HNCOCF3
3
↑
1
α-L-Fucp
3
↑
1
α-L-Fucp

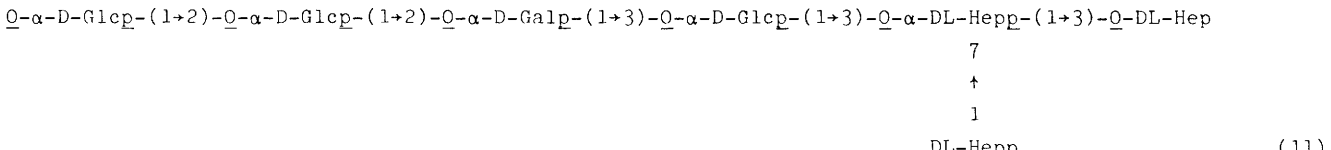
(8)


O-β-D-Galp-(1→4)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→4)-O-β-D-GlcNAcp-(1→3)-O-β-D-Galp-(1→4)-β-D-Glcp-1-Cer
3
↑
1
α-L-Fucp

(9)


O-β-D-Glcp-(1→6)-O-β-D-Glcp-(1→6)-O-β-D-Glcp-(1→6)-O-β-D-Glcp-(1→6)-D-Glc
3
↑
1
β-D-Glcp
3
↑
1
β-D-Glcp

(10)


O-α-D-Glcp-(1→2)-O-α-D-Glcp-(1→2)-O-α-D-Galp-(1→3)-O-α-D-Glcp-(1→3)-O-α-DL-Hepp-(1→3)-O-DL-Hep
7
↑
1
DL-Hepp

(11)

with a hydrogen atom in place of the carboxylic acid group of the iduronic acid moiety - i.e., a D-xylose - containing derivative.[65] Alternatively, the interesting modified compound (7) still activates antithrombin III.[66]

5 Hexasaccharides

Chitohexaose and hexa-N-acetylchitohexaose have been reported to have in vivo antitumour activity.[67] Two reports have appeared on the synthesis of the dimeric Lewis X hexasaccharide corresponding to part of a tumour-associated glycolipid (8).[68,69]

6 Heptasaccharides

Selective glucosylation of hexakis(2,3-di-O-acetyl)α-cyclodextrin led to 6-O-α-D-glucopyranosyl-α-cyclodextrin,[70] and polymerization of 1,6-anhydro-2-O-benzoyl-3,4-di-O-benzyl-β-D-galactopyranose with phosphorus pentafluoride as catalyst followed by deprotection gave the β-(1→6)-linked galactoheptaose.[71] Compounds (9), a stage specific embryonic antigen,[72] and (10), a putative phytoelicitor of Phytophthora megasperma,[73] have been synthesized.

7 Octasaccharides

An octasaccharide analogous to the α-cyclodextrin-based heptasaccharide above (ref. 70) has been made by selectively α-D-glucosylating a partially protected cyclomaltoheptaose.[74] A set of oligosaccharides based on α-(1→6)-linked glucopyranose units from the dimer to octamer were made using a partially benzylated isomaltose β-glycosyl chloride as key intermediate.[75]

The antigen (10) derived by α-(1→3)-fucosylation of the second N-acetylglucosamine unit of compound (9) has been synthesized,[76] and the core octasaccharide of a Citrobacter (11) has been structurally and conformationally characterized by 500 MHz ^{1}H n.m.r. methods.[77]

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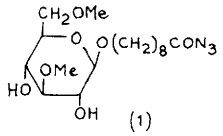
5
Ethers and Anhydro-sugars

1 Ethers

Methyl Ethers.- Pregnane glycosides from Trachelospermum asiaticum plants have been found to contain 2,6-dideoxy-3-O-methyl-L-xylo-hexose and its 4-acetate, present as the α-pyranosides.[1]

The effect of O-alkylation on the anomeric solution equilibrium of D-glucopyranose and of methyl D-glucopyranoside has been studied. A considerable increase in the proportion of α-anomer for 2-O-methyl-D-glucopyranose was observed, but there was no change for methyl D-glucopyranoside on O-alkylation.[2] A method has been reported for the preparation of all of the methyl ethers of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside.[3] Methylation of methyl (methyl α-D-mannopyranosid)uronate,[4] methyl (methyl α-D-glucopyranosid)uronate,[5] and methyl (methyl β-D-galactopyranosid)uronate[6] employing methyl iodide and silver oxide in methanol has given mixtures of all the mono-, di-, and tri-O-methyl ethers which were separated by h.p.l.c. Methylation of 1,2-O-isopropylidene-α-D-xylofuranose with either silver oxide/methyl iodide or diazomethane/stannous chloride afforded a good yield of the 5-O-methyl ether.[7] In an investigation of the substrate specificity of amyloglucosidase the 3′-, 4′- and 6′-O-methyl ethers of methyl β-D-maltoside have been prepared.[8] The synthesis of methyl 2,6-dideoxy-4-O-methyl-α-D-arabino-hexopyranoside is mentioned in Chapter 12, and the synthesis of 3-O-methyl-L-xylose is covered in Chapter 6. The 3,6-di-O-methyl-D-glucose derivative (1) has been coupled by reaction of the acyl



(1)

azide moiety to bovine serum albumin and the product used in the serodiagnosis of leprosy.[9] A study of the relative rate constants

for the reaction of 1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses with methyl iodide and silver oxide in acetonitrile has been reported.[10] The preparation of methyl 6-O-methyl-β-D-galactobioside has been described.[11] The non-reducing sugar of the tetrasaccharide moiety of the major phenol glycolipid of Mycobacterium kansasii has been identified as 2,6-dideoxy-4-O-methyl-D-arabino-hexopyranose by the synthesis of its α-methyl glycoside.[12] A study of the anomerisation of a number of 5-O-methyl-pentoses in aqueous solution by ^{13}C n.m.r. is described in Chapter 21.

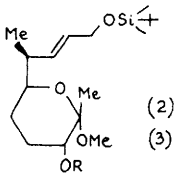
Other Alkyl and Aryl Ethers.- A number of 3-O-alkyl-2-amino-2-deoxy-D-glucopyranose compounds have been prepared from benzyl 2-acetamido- 4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside, and their properties as surfactants have been tested.[13,14] The synthesis of 6-O-(Z-2,7-octadienyl)-α-D-galactopyranose has been described.[15] The relative reactivity of hydroxy groups of methyl α-D-glucopyranoside and methyl mono-O-pentyloxymethyl-α-D-glucopyranosides in reaction with pentyloxymethyl chloride has been shown to be 3-OH > 6-OH ~ 2-OH > 4-OH.[16] Aldol condensations of $EtOCH_2CHO$ has afforded 2,4,6-tri-O-ethyl-β-D,L-galacto- and glucopyranose.[17]

The 3-methoxybenzyl (3-MPM) and 3,5-dimethoxybenzyl (3,5 DMPM) groups have been introduced as useful O-protecting groups. They have greater acid stability than the 4-methoxybenzyl (4-MPM) group, and are removed by DDQ oxidation at room temperature. This oxidation can be used to selectively remove a 4-MPM group in the presence of 3-MPM or 3,5 DMPM ether groups, and the 3-MPM and 3,5-DMPM groups in the presence of a benzyl ether.[18] Treatment of alcohols with bis(p-nitrophenyl)diazomethane in the presence of BF_3 etherate gives p,p'-dinitrobenzhydryl ethers which are relatively acid- and base-stable protecting groups and which can be readily removed by catalytic hydrogenation or chemical reduction followed by mild acid hydrolysis.[19] The partial benzylation of all the 1,6-anhydro-β-D-hexopyranoses has been investigated employing bis(tributyltin)oxide to activate the hydroxyl groups. For regioselective benzylation of a hydroxyl group the presence of a neighbouring cis-axial hydroxyl group was required.[20] The dibutylstannylene derivative of 1,6-anhydro-β-D-glucopyranose has been used to effect alkylation at O-4 with moderate selectivity.[21] Glycosyl fluorides have been per-O-alkylated in good yield employing RX,Ag_2O,DMF or RX,KOH,DMF

conditions. Methyl, allyl, butyl, benzyl and octyl ethers were prepared as was hepta-O-benzyl-α-D-lactosyl fluoride by this procedure.[22] The crown ether catalysed per-O-alkylation of a number of carbohydrate compounds in tetrahydrofuran at room temperature has been reported.[23] In some selective benzylation studies benzyl 2-acetamido-3-O-benzyl-2-deoxy-α-D-glucopyranoside with BnCl, DMF, NaO^{i}Pr gave 5% of the 3,4,6-tri-O-benzyl, 15% 3,4-di- and 50% 3,6-di-O-benzyl ethers along with 30% recovered starting material. Benzyl 2,3,6,2′,3′-penta-O-benzyl-β-D-lactoside with benzyltrichloroacetimidate and trifluoromethanesulphonic acid afforded a 2:1 mixture in which the 4′- and 6′-positions respectively had been benzylated. Benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside on treatment with BnBr, DMF, TlOEt gave the corresponding 6-O-benzyl ether in 80-90% yield.[24] The phase-transfer catalysed benzylation of 1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol gave a 2:1 mixture of the 4-O- and 3-O-monobenzyl ethers, whereas conventional silylation with ^{t}BuMe$_2$SiCl or ^{t}BuPh$_2$SiCl afforded specifically the 3-O-monosilyl ethers.[25] S-Methyl 1-thio-α-L-rhamnopyranoside has been converted into its 2,4-di-O-benzyl and its 2-O- and 3-O-benzyl ethers.[26] A study of the chemical shift of the benzyl methylene carbon atoms in the ^{13}C n.m.r. spectra of per-O-benzylated methyl glycopyranosides is mentioned in Chapter 21.

The reductive ring opening of *p*-methoxybenzylidene acetals employing either NaBH$_3$CN, CF$_3$COOH, DMF or NaBH$_3$CN, Me$_3$SiCl, CH$_3$CN has been reviewed. The two reagents give opposite regioselectivity in the formation of the mono-O-*p*-methoxybenzyl ether.[27] Reductive opening of the per-O-benzoyl-4^5,6^5-O-benzylidene derivative of *p*-nitrophenyl α-maltopentaoside with dimethylaminoborane has afforded the corresponding 6^5-O-benzyl ether.[28]

The benzyl ether (2) has been converted to its parent alcohol (3) by a novel debenzylation procedure employing lithium

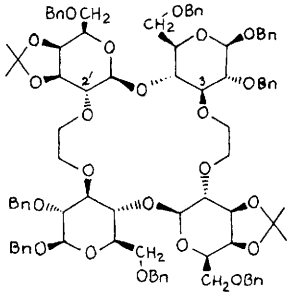


(2) R = Bn
(3) R = H

di-tertbutylbiphenyl radical anion.[29] The hydrogenolysis of benzyl ethers in the presence of a glycosyl fluoride moiety has been accomplished using standard conditions.[30] Methyl 2,3-di-O-

benzyl-4,6-O-benzylidene-α-D-glucopyranoside has been selectively debenzylated at the 2-position using catalytic transfer hydrogenolysis.[31]

The bis-lacto-18-crown-6 derivatives (4) and (5) have been



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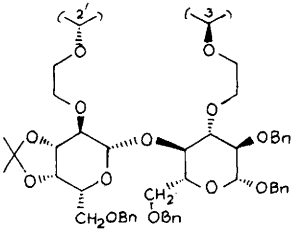
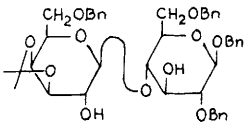


(5)

synthesized from the lactose diol (6), and their complexing abilities and use as catalysts for asymmetric induction were



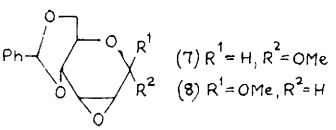
(6)

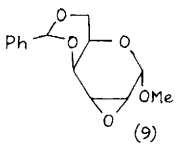
compared with related macrocycles reported earlier by these workers.[32] Other similar chiral macrocycles incorporating lactitol and 4-O-(1-deoxy-D-galactitol-1-yl)-D-glucitol residues have been synthesized.[33] Treatment of 3,5:4,6-di-O-ethylidene- and benzylidene-D-sorbitol with the bis-tosylate of diethylene glycol under basic conditions afforded low yields of chiral macrocycles.[34]

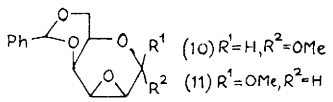
Silyl Ethers.- The reductive cleavage of silyl ethers employing NaH in HMPA or DMPU has been reported. Methyl 6-O-tert-butyldimethylsilyl-α-D-glucopyranoside and the 4,6-di-O-tert-butyldimethylsilyl ether of D-glucal were each deprotected in 90% yield under these conditions.[35] The deprotonation of a silyl ether with base is mentioned in Chapter 13. The trimethylsilyl ethers of a number of D-glucose derivatives have been prepared and characterized by ^{1}H-, ^{13}C- and ^{29}Si-n.m.r. spectroscopy and mass spectroscopy.[36]

2 Intramolecular Ethers (Anhydro-sugars)

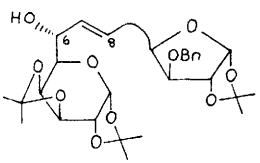
Oxirans.- The synthesis of epoxides from 1,2-diol bis-sulphonates utilising phase-transfer catalysis has been described. Methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulphonyl-α-D-glucopyranoside under these conditions [C_6H_6, 40% aq KOH, Bu_4NHSO_4, $MeOCH_2CH_2OH$ (trace)] afforded 91% of the allo-epoxide (7), whereas for the β-anomer 84% of the corresponding epoxide (8) was obtained. Methyl 4,6-O-benzylidene-2,3-di-O-p-toluenesulphonyl-α-D-galactopyranoside under the same conditions afforded 64% of the gulo- (9) and 27% of the talo-epoxide (10), whereas the β-anomer gave only 79% of the corresponding talo-product (11).[37] Epoxidations of allylic

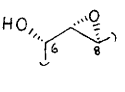


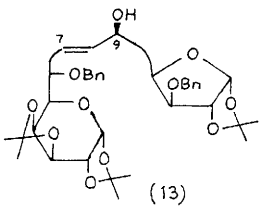


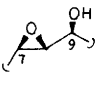


alcohols (12) and (13) have afforded the syn-epoxyalcohols (14) and (15) respectively as the major products.[38] The synthesis of

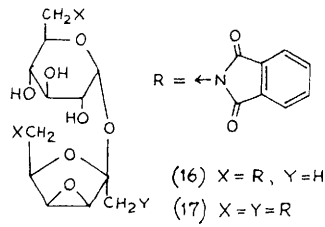


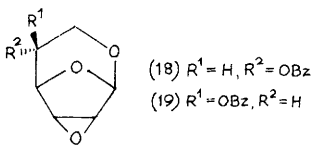


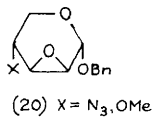




stereoisomers of valienamine epoxide is described in Chapter 18. Sucrose has been converted selectively into the di- or tri-phthalimido-tagato-epoxides (16) and (17) by reaction under Mitsunobu conditions (Ph_3P, phthalimide, diisopropyl azodicarboxylate).[39] 1,6-Anhydro-β-D-manno- and allo-furanose have been converted into the epoxides (18) and (19) respectively.[40]

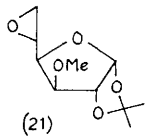






Treatment of benzyl 3,4-anhydro-2-O-p-toluenesulphonyl-β-L-arabinopyranoside with nucleophiles (MeO^-, N_3^-) gave rise to the

2,3-anhydro derivatives (20) with incorporation of the nucleophiles at C-4.[41] Nucleophilic opening of benzyl 3,4-anhydro-α-D-ribopyranoside has yielded 3-substituted D-xylose products exclusively. It was postulated that in such a conformationally labile system the direction of ring opening is controlled by repulsive interactions between the nucleophile and the ring oxygen lone pair.[42] Epoxide (21), when treated with alcohols under phase-transfer conditions, afforded products of attack at C-6.[43] The enantiomerically pure epoxide (22), derived



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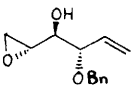
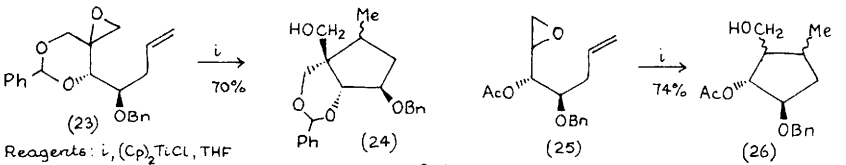


(22)

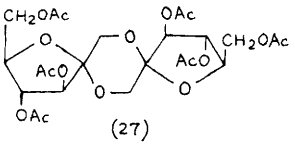
from meso-divinylglycol by way of Sharpless epoxidation, has been cleaved with different nucleophiles at C-1 followed by standard manipulation to give, for example, 2,5-di-O-benzyl-D-ribose and 3,6-di-O-benzyl-2-deoxy-D-ribo-hexose.[44] All of the 2,3,6-trideoxy-3-aminohexoses have been synthesized from hept-1,4-dien-6-ol by way of Sharpless epoxidation and subsequent manipulation of the chiral products.[45] A titanium (III) - induced cyclisation of epoxyolefins has afforded a new synthesis of cyclopentanes (Scheme I). Thus epoxide (23) on treatment with



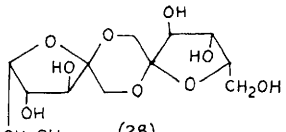
Scheme 1

bis(cyclopentadienyl)titanium (III) chloride in THF afforded cyclopentanes (24) with an endo : exo ratio of 83:17, and epoxide (25) under the same conditions gave a mixture of the four diastereomers (26).[46] A study of the ability of some 1,6:2,3- and 1,6:3,4-dianhydrohexopyranoses to undergo anionic polymerization by epoxy ring cleavage has found that polymers could be formed only from 1,6:2,3-dianhydro-4-O-alkyl-β-D-mannopyranose and 1,6:3,4-dianhydro-2-O-alkyl-β-D-galactopyranose.[47,48] The lanthanide - induced shifts in the ^{1}H-n.m.r. spectra of the methyl 2,3-anhydro-4,6-O-benzylidene-D-hexopyranosides are mentioned in Chapter 21.

Other Anhydrides.- A laboratory scale apparatus has been designed for the pyrolysis of cellulose in large quantities to give 1,6-anhydro-β-D-glucopyranose,[49] and the preparation of this compound uniformly labelled with ^{14}C by pyrolysis of a [U-^{14}C] glucan has been reported.[50] Pyrolysis of plant cell wall materials has afforded 1,5-anhydro-β-L-arabinofuranose in up to 78% yield based on the amount of L-arabinose present in the glycan.[51] The treatment of acetylated inulin with anhydrous HF has allowed the formation of the fructofuranose 1,2′:2,1′-dianhydride (27), whereas 2,3:4,6-di-O-isopropylidene-α-L-sorbopyranose on brief treatment under the same conditions afforded the sorbofuranose 1,2′:2,1′-dianhydride (28) isolated as its crystalline hexaacetate.[52] The

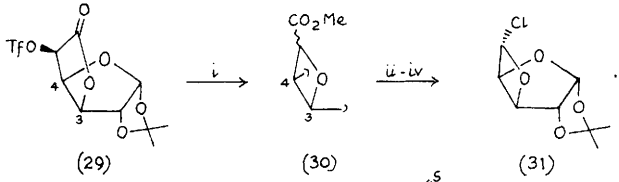


(27)



(28)

^1H- and ^{13}C-n.m.r. data of the dimeric anhydride formed on treating methyl D-ribosides with acetone, $CuSO_4$, H_2SO_4 are mentioned in Chapter 21. 1,5-Anhydro-D-fructose has been prepared from starch, or other 1,4-α-glucans, in 40-50% yield by use of a semi-purified enzyme extract from the microthecin - deficient strain of Morchella vulgaris fungus.[53] A report that treatment of sucrose with Ph_3P-DEAD gave a 1:1 mixture of the 3′,4′-anhydro- and the 1′,4′-anhydro derivatives has been corrected and the second product is now shown to be the 3′,6′-anhydride, but with different physical properties to those previously described.[54] The uronate triflate (29) has been converted into the 3,5-anhydro derivative (30) (Scheme 2) which was transformed into the unusual, and



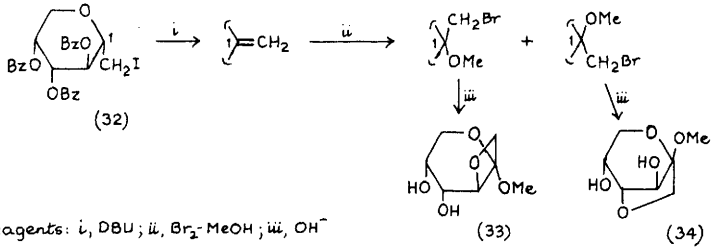
(29) (30) (31)

Reagents: i, K_2CO_3-MeOH; ii, NaOH; iii, $(COCl)_2$; iv, 

Scheme 2

stable, α-chloro-oxetane (31).[55] Reaction of some aldehydo-sugar derivatives with allyltrimethylsilane and BF_3-etherate has given predominantly the oxetane [2+2] adducts rather than the expected allylated products.[56] 1,5-Anhydro-D-mannitol has been converted

into iodide (32) from which two methyl anhydro-D-fructopyranosides (33) and (34) have been prepared (Scheme 3).[57] Some reactions of



Scheme 3

methyl β-D-galactobioside derivatives to form the 3,6-anhydro compounds are noted in Chapter 8. A study has been made of the kinetics and mechanism of the acid - catalysed butanolysis of 1,6-anhydro-β-D-glucopyranose.[58] The ^{1}H- and ^{13}C-n.m.r. spectra of the eight 1,6-anhydro-hexofuranoses is mentioned in Chapter 21.

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6
Acetals

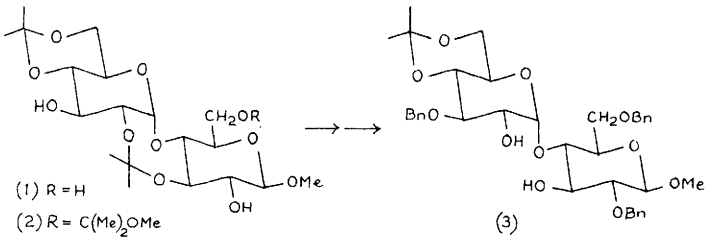
1 Isopropylidene Acetals

On heating 1,6-di-*O*-benzoyl-D-mannitol with excess of 2,2-dimethoxypropane in the presence of toluene-*p*-sulphonic acid an inseparable mixture of the 2,3:4,5- and 2,4:3,5-diacetals was obtained in 72% yield in addition to 17% of the 3,4-monoacetal.[1] Acetonation of D-glucose trimethylenedithioacetal gave a mixture of the 2,3:5,6-, 2,4:5,6-, and 3,4:5,6-di-*O*-isopropylidene derivatives.[2] 1,2:4,6-Di-*O*-isopropylidene-α-L-sorbofuranose, usually a minor product in the acetalation of L-sorbose, was formed in 80% yield when 2,2-methoxypropane in DME was used with tin(II) chloride as the catalyst.[3] The conversion of L-sorbose to L-fructose by way of this diacetonide is described in Chapter 2.

Treatment of several α- and β-D-galactopyranosides with 2,2-dimethoxypropane and camphorsulphonic acid led to the formation of 3,4-*O*-isopropylidene-6-*O*-(2-methoxyprop-2-yl) derivatives in yields of >90%. Neutralization of the crude reaction mixtures with triethylamine followed by heating in aqueous methanol allowed the selective hydrolysis of the acyclic acetal groups.[4] In the kinetic acetonation of the same D-galactopyranosides with 4.5 equivalents of 2-methoxypropene and traces of toluene-*p*-sulphonic acid in DMF at ambient temperature the 2,3:4,6-diacetals were produced in 80-85% yield. The presence of dioxolane rings *trans*-fused to the pyranose rings was verified by n.m.r. spectroscopy and further substantiated by X-ray structural analysis of both anomers of methyl 2,3:4,6-di-*O*-isopropylidene-*D*-galactopyranoside (c.f. Chapter 22). Treatment of benzyl β-D-galactopyranoside with 2 equivalents of 2-methoxypropene gave, apart from 20% of the 2,3:4,6-diacetal, the 4,6- and 3,4-monoacetals in the ratio 30:1.[5]

The reaction of methyl β-maltoside with 2-methoxypropene has been studied. Use of 3.7 equivalents of reagent and toluene-*p*-sulphonic acid as the catalyst at ambient temperature for 1 h gave the 4′,6′-*O*-isopropylidene- and the 4′,6′-*O*-isopropylidene-6-*O*-(2-methoxyprop-2-yl) derivatives in 24 and 11% yield respectively.

With excess of 2-methoxypropene and toluene-p-sulphonic acid at ambient temperature for 20 h the same two products were obtained, and in addition the diacetals (1) and (2) each in 30% yield. Compound (1) was perbenzylated, and selective hydrolysis of the eight membered ring was then effected by exposure to pyridinium toluene-p-sulphonate to give the useful diol synthon (3).



Treatment of methyl β-maltoside with 3.7 equivalents of 2-methoxypropene in the presence of pyridinium toluene-p-sulphonate for 20 min at 0°C led to exclusive formation of acyclic acetals at the primary positions.[6]

2 Benzylidene Acetals

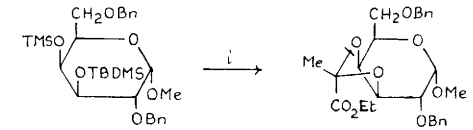
4,6-O-Benzylidene derivatives can be prepared conveniently and in high yields by heating either anomers of methyl gluco- or galacto-pyranoside with benzaldehyde diethylacetal and traces of camphorsulphonic acid in chloroform until homogeneous solutions have formed. The method is unsuitable for use with methyl mannopyranosides or with free sugars.[7] Selective monobenzylidenation of some free sugars and methyl glycosides has been achieved in moderate to good yields with benzaldehyde dimethylacetal and pyridinium toluene-p-sulphonate in DMF at 80°C. Methyl α-D-mannopyranoside, for example, gave the 4,6-monoacetal in 51% crystalline yield. The structure of the novel (S)-2,3-O-benzylidene derivative (4), a minor by-product of this reaction, has been determined by X-ray crystallography (see Chapter 22).[8]

The 4^5,6^5-O-benzylidenated p-nitrophenyl α-maltopentaoside has been prepared using benzaldehyde dimethylacetal and toluene-p-sulphonic

acid.[9] Reduction of the perbenzoylated product to the 6[5]-O-benzyl ether is referred to in Chapter 5.

3 Other Acetals

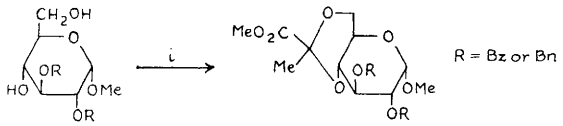
When D-ribose was exposed to acetone and sulphuric acid in the presence of formaldehyde the unusual derivative (5) was formed in >80% yield. Mild acid hydrolysis removed the isopropylidene group preferentially.[10] 1-Carboxyethylidene derivatives (pyruvate acetals) have been synthesized from vicinal bis-silyl ethers of hexopyranosides by reaction with methyl or ethyl pyruvate in the presence of trimethylsilyl triflate. An example is given in Scheme 1.[11] By use of methyl pyruvate diphenyldithioacetal and



Reagents: *i*, $MeCOCO_2Et$–TMSOTf

Scheme 1

one of the catalysts indicated in Scheme 2, methyl 2,3-di-O-benzoyl- and methyl 2,3-di-O-benzyl-4,6-O-(1-carbomethoxyethylidene)-α-D-glucopyranoside were obtained directly

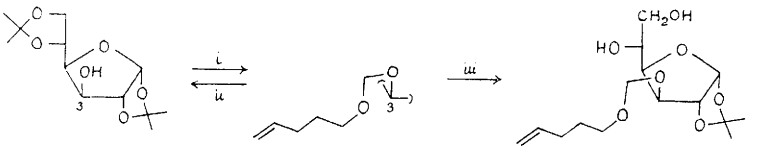


Reagents: *i*, $PhS(Me)C(SPh)CO_2Me$, MeOTf or $MeS\overset{+}{S}Me_2\bar{O}Tf$ or $NO^+BF_4^-$

Scheme 2

from the 4,6-diols. As a rule, the diastereoisomer with an (S) configurated acetal centre preponderated.[12] (1-Carbomethoxy ethylidene) derivatives have been converted to their (1-cyanoethylidene) analogues by consequential amminolysis and dehydration.[12a] The reverse process (*i.e.* methanolysis of the cyano group) has also been effected.[12b] 3,4-O-Diphenylmethylidene acetals, a previously unknown class of compounds, have been prepared from S-methyl-1-thio-α- and β-L-rhamnopyranosides. They were intermediates in the synthesis of partially O-benzylated 1-thio-L-rhamnose derivatives.[13] Further details are given in Chapters 3 and 5. As an extension of Fraser-Reid's work with 4-pentenyl glycosides (*J. Am. Chem. Soc.*, 1988, **110**, 2662, 5583) new protecting groups for alcohols and diols have been developed. 4-

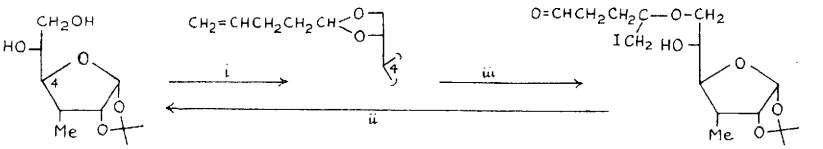
Pentenyloxymethyl ethers (POM ethers) are formed on reaction of an alcohol with 4-pentenyloxymethyl chloride and Hunigs base (Scheme 3). Like MEM and MOM ethers, they are stable under mildly acidic



Reagents: i, ≈∿O∿Cl, Hunig's Base; ii, NBS·H_2O; iii, 75% HOAc

Scheme 3

conditions such as those employed for removing the 5,6-O-isopropylidene group of diacetone glucose. They are liberated by 5% HCl or, more selectively, by oxidative hydrolysis with aqueous N-bromosuccinimide. Diols can be protected by acetalisation with 4-pentenal (Scheme 4). Deprotection requires in this case

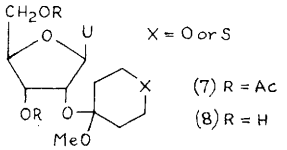


Reagents: i, ≈∿CHO, H^+; ii, NIS·H_2O; iii, Zn

(6)

Scheme 4

sequential treatment with N-bromosuccinimide and zinc powder and proceeds by way of an iodolactone (6).[14] An improved procedure for preparing 4-methoxytetrahydropyranyl ethers of nucleosides, e.g. (7), uses 4,4-dimethoxytetrahydro-4H-pyran (or the corresponding thiopyran) and trimethylsilyl chloride. Compounds



X = O or S

(7) R = Ac

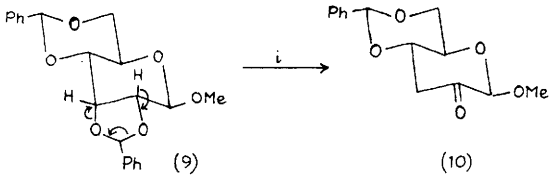
(8) R = H

(7) were readily deacetylated to give the selectively 2-O'-protected uridines (8).[15]

4 Reactions of Acetals

Butyl lithium in THF at temperatures ≤0°C cleaves benzylidene dioxolanes fused to methyl pyranosides or to 1,5-anhydroalditols while 6-membered benzylidene acetals are left intact (Scheme 5). The reaction involves preferential abstraction of a quasi-axial

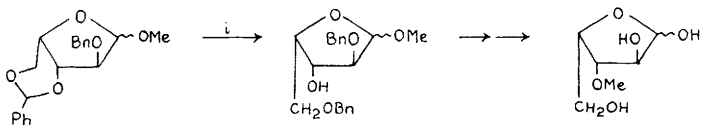
proton and expulsion of benzaldehyde and affords vicinal deoxyketones, e.g. (10), in high yields from starting compounds



Reagents: i, BuLi-THF (-30°)

Scheme 5

with rigid chair conformations e.g. the bis-acetal (9).[16] The reductive cleavage of a 6-membered benzylidene acetal fused to a furanose ring (Scheme 6) was a key step in the synthesis of 3-O-methyl-L-xylose.[17] 6-O-Tritylated 1,2-O-(1-cyanoethylidene)



Reagents: i, LAH-$AlCl_3$

Scheme 6

hexopyranose derivatives have been polymerized in the presence of trityl perchlorate to give homopolysaccharides and block-heteropolysaccharides.[18] Sodium dicyanoborohydride, a reducing agent useful for the preparation of alditols (see Chapter 18), cleaves benzylidene acetals but offers no advantage, in this respect, over sodium cyanoborohydride.[19] The photobromination of benzylidene acetals of pyranosides is covered in Chapter 8, and a conformational analysis of dioxolanes 1,2-fused to pyranose rings is referred to in Chapter 21.

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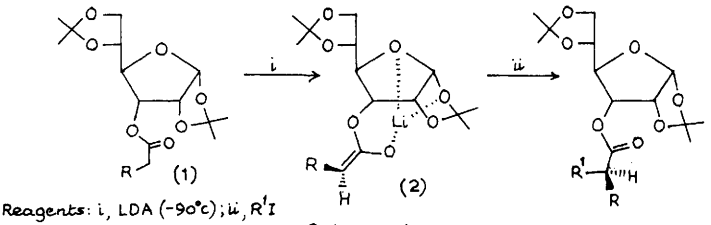
7
Esters

1 Carboxylic Esters

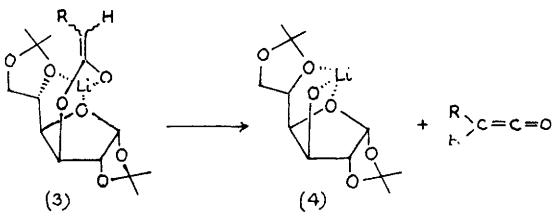
Some novel observations have been made on ester enolates during attempts to use them as chiral templates. Treatment of α-D-allofuranose esters (1, Scheme 1) with LDA gave Z-enolates (2);



Reagents: i, LDA (-90°C); ii, R^1I

Scheme 1

these could be alkylated at -90°C diastereoselectively and in good yield without activation by polar compounds such as HMPA. Alkylation was less successful with the corresponding D-gluco-enolates (3), which were obtained as Z/E - mixtures and were prone to decompose into the stable lithium alcoholate (4) and ketenes (Scheme 2). Ester enolates with strongly complexing ligands,

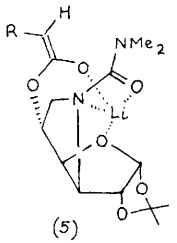


Scheme 2

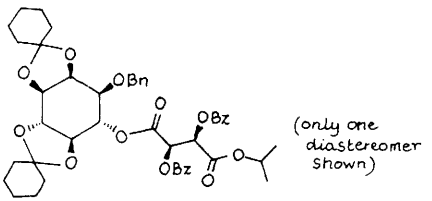
e.g., compound (5) were unreactive towards carbon electrophiles.[1] (±)1-O-Benzyl-myo-inositol has been resolved via the diastereomeric L-tartrates (6) which were separable by chromatography.[2] The synthesis of 4-O-formyl derivatives of pentopyranoses by 1,2-cleavage of hexopyranoses is described in Chapter 2.

Selective partial acylations and deacylations continue to be of interest. Exposure of hexopyranose peracetates to Bu_3SnOMe or

Bu_2SnO in methanol at 50°C for 2-3 h allowed hydrolysis at the anomeric centre preferentially. Prolonged reaction resulted in



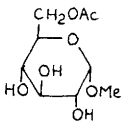
(5)



(6)

complete deacetylation, secondary acetate groups being removed before primary ones, so that during deprotection of methyl tetra-O-acetyl-α-D-glucopyranoside, for example, the monoacetate (7) was detected as a major intermediate by ^{1}H-n.m.r. spectroscopy.[3] Treatment of α-D-galactopyranose pentaacetate with aqueous trifluoroacetic acid at ambient temperature gave the 1,3,4,6-tetra-O-acetate in 70% yield, under similar conditions α-D-glucopyranose pentaacetate was hydrolysed at O-1 only, while the two corresponding 1,2-cis-related β-peracetates were unreactive.[4] Partially acetylated derivatives of D-glucose and of 2-amino-2-deoxy-D-glucose underwent acetyl migration from O-4 to O-6 on reaction with butyl lithium.[5] The partial deacetylation of sucrose octaacetate is referred to in Part 3 of this Chapter.

The selectivity of conventional pivaloylation (pivaloyl chloride - pyridine) of 2-acetamido-2-deoxy sugars has been studied. The order of reactivity of the hydroxyl groups for 2-acetamido-2-deoxy-D-glucose and its methyl pyranosides was HO-6 > HO-3 (>HO-1) > HO-4, rendering, for example, anomeric dipivaloates (8) available in 69% yield. From the methyl α-glycoside of N-acetylmuramate only the primary monopivaloate (9) could be



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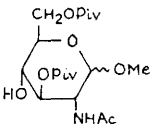
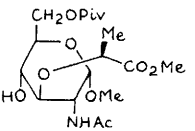


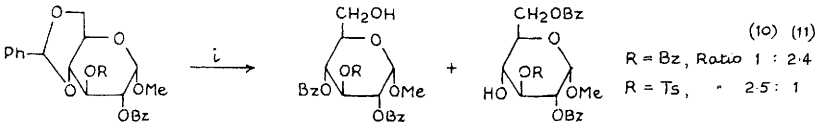
(8)



(9)

obtained, even under forcing conditions.[6] The partial methanolysis and hydrazinolysis of tri-O-butyryl- and tri-O-palmityl-1,6-anhydro-β-D-glucopyranose have been investigated[7] (See Vol. 18, p. 63 for similar work with the peracetyl and perbenzoyl analogues). 4,6-O-Benzylidene acetals of hexopyranoid compounds are cleaved oxidatively by tert-butylhydroperoxide to give

mixtures of the 4-O- and 6-O-monobenzoates. The product ratios depend on the nature and orientation of the substituent and C-3; examples are given in Scheme 3. Under the reaction conditions



(10) (11)

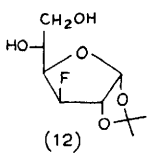
Scheme 3

benzyl ethers are oxidised to benzoates.[8] Regioselective benzoylation *via* stannylene intermediates has been achieved at the primary position of glucofuranose derivative (12)[9] and at O-4 of 1,6-anhydro-β-D-glucopyranose (See Chapter 17).

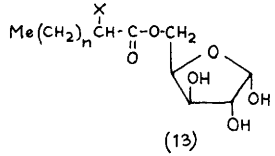
A number of selective acylations and deacylations catalysed by enzymes, especially by lipases in organic solvents, have been reported. Methyl pentofuranosides could be selectively acetylated at O-5 on a preparative scale by use of a lipase and 2,2,2-trifluoroethyl acetate as acyl donor in THF, while selective hydrolysis could be effected at the primary positions of peracetylated methyl pentofuranosides and hexopyranosides, and at the anomeric centres of peracetylated D-ribo- and D-xylo-furanoses and -pyranoses with lipases in aqueous DMF.[10] Methyl β-D-glucopyranoside, D-mannose, and 2-acetamido-2-deoxy-D-mannose were all substituted selectively at O-6 by lipase-mediated transesterification with vinyl acetate in pyridine.[11] Acyl exchange with 2,2,2-trichloroethyl butyrate under catalysis by subtilisin (a protease) in dry DMF led to preferential reaction at O-6 of glucose and at the primary hydroxy groups of the non-reducing terminal units of oligosaccharides (*e.g.*, maltose, maltotriose).[12] The 2,3-, 3,4-, and 2,4-diacetates of 1,6-anhydro-β-D-glucopyranose have been obtained in good yields from the triacetate by selective hydrolysis using pig liver esterase, a *Rhizopus javanicus* lipase and a wheat germ lipase, respectively.[13] Similar experiments have been carried out with 1,6-anhydro-tri-O-butyryl-β-D-glucopyranose. The enzyme-catalysed procedure is reported to be more regioselective than methanolysis or hydrazinolysis.[14]

Several penta-O-n-alkanoylglucopyranoses derived from long-chain acids have been synthesised in the usual way for use in phase-behaviour studies.[15] Xylose derivatives (13) have been prepared from 1,2-O-isopropylidene-α-D-xylofuranose by standard

methods in the course of a continuing investigation of surfactants.[16] Three 1-O-hydroxybenzoates of β-D-glucopyranose,



(12)



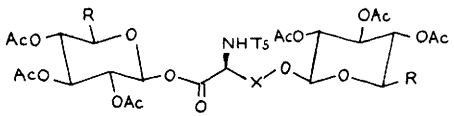
X = Br or SAc
n = 9, 11, or 13

(13)

required as reference standards in the g.c. and h.p.l.c. analysis of plant extracts, have been synthesised by reaction of the sodium salt of 4,6-O-benzylidene-D-glucose with the appropriate benzyloxybenzoyl chloride followed by hydrogenolysis.[17] The β-D-glucosides of six hydroxybenzoic acids prepared at the same time are referred to in Chapter 3.

A one-stage procedure involving sodium catalysed transesterification between raffinose undeca-acetate and methyl esters of long-chain fatty acids (derived, for example, from salad oil) has been employed to produce raffinose fatty acid polyesters in excellent yields (>96%); their physical properties are described as similar to those of analogous sucrose polyesters.[18] Certain carbohydrate esters of fatty acids, *e.g.*, sucrose monolaurate, -palmitate, and -stearate, have been found to enhance the activity of thiabendazole, a fungicide used against *Penicillium digitatum* infections of citrus fruit. The mechanism of this action remains to be clarified.[19]

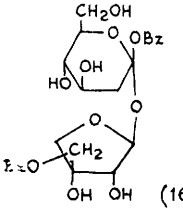
Glycosyl esters have been obtained by reaction of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide and 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide with the silver salts of N-tosylated amino acids (glycine, L-alanine, L-valine, L-leucine, and L-isoleucine).[20] Similar experiments with N-tosylserine and N-tosylglutamic acid gave, as expected, O-glycosidic glycosyl esters (14) and diglycosyl diesters (15), respectively.[21]



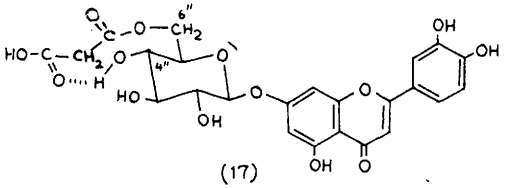
R = CH_2OAc or H
(14) X = CH_2
(15) X = CH_2CH_2CO

2,3-Di- and 1,2,3-tri-O-hexanoyl-α-D-glucopyranose were the principal components in the exudate from glandular trichomes of *Datura metel* (Solanaceae),[22] whereas the glandular trichomes of certain non-tuberous *Solanum* species furnished mainly 2-O-acetyl-3-O-isobutyryl-4-O-isocapryl-D-glucopyranose and similar 3,4-di- and 2,3,4-tri-O-acylated glucopyranoses, the ester at O-2 always

being acetate.[23] From the Bolivian wild potatoe, Solanum neocardenasii, 2,3,4,3′-tetra-O-acylsucroses (a new class of sucrose derivatives) have been isolated, for example 2-O-acetyl-3′-O-hexanoyl-3,4-di-O-isobutyrylsucrose.[24] The structure of 6-O-acetyl-2,3,4-tri-O-[(S)-3-methylpentanoyl]sucrose, a flavour precursor isolated from tobacco leaves (see Vol. 20, p. 74), has been confirmed by synthesis,[25] and that of 2-O-apiosyl-β-D-glucose dibenzoate (16), obtained from the Australian bush Daviesia latifolia, by 2D n.m.r. spectroscopy.[26] On the basis of ^{1}H-n.m.r. data, a 10-membered boat-chair-boat ring, formed by hydrogen bonding between 4″-OH and carboxylate oxygen has been postulated as the tertiary structure of luteolin 7-O-(6″-O-malonyl)-β-D-glucopyranoside (17) found in carrot foliage. Pyranoside (17) in

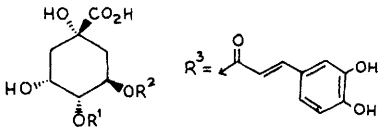


(16)



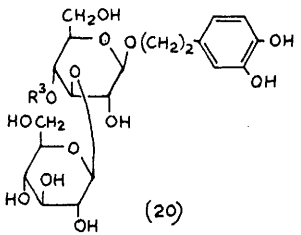
(17)

combination with trans-chlorogenic acid (18) acts as an oviposition stimulant for black swallow butterfly.[27] The biological activity of dicaffeoxy quinic acid (19) is referred to in Chapters 18 and 19. The disaccharide caffeic acid ester plantamajoside (20), extracted from a Plantago major subspecies,



(18) R^1 = H, R^2 = R^3

(19) R^1 = R^2 = R^3



(20)

showed antibacterial activity as do related disaccharides.[28] Acetyl-soyasaponins have been found to contain peracetylated β-D-xylo- and β-D-gluco-pyranosyl units. These are believed to be responsible for bitterness and astringency in soya beans. The corresponding deacetylated soyasaponins taste neither bitter nor astringent.[29,30] Tubeimoside I, a novel, cyclic oleanane saponin with a 3-hydroxy-3-methylglutarate bridge has been isolated from Bolbostemma paniculatum tubers. Full details are given on the isolation and structure determination of this and two related

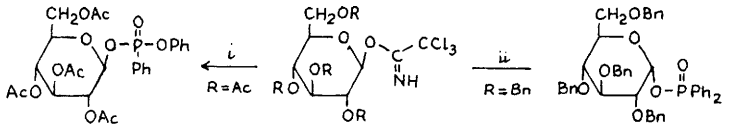
cyclic saponins.[31] Current ideas on the complexation between proteins and polyphenol (tannin, including gallic esters of glucose and related materials) have been reviewed.[32] The ^{13}C-n.m.r. signals of the D-glucose residues of hydrolysable tannins with unsubstituted anomeric hydroxyl groups have been assigned, and their utility in structure determination demonstrated,[33] and hydrolysable tannins containing glucopyranose cores in the unusual $^1C_4$ conformation and C-glycosidic acyclic glucose cores have been studied by 2D ^{13}C-n.m.r. spectroscopy.[34] A new class of gallotannins containing sucrose monoesterified by gallic acid at either O-2, O-6, O-1′, O-4′, or O-6′ have been isolated from Chinese and North Korean commercial rhubarb.[35] Complex tannins, *e.g.*, mongolicin B, in which hydrolysable tannin and flavonoid moieties are connected through a carbon-carbon linkage, continue to be discovered in the bark of *Quercus mongolica* species.[36,37]

2 Phosphates and Related Esters

A review on phosphorylation and cyclophosphorylation of carbohydrates has been published which includes sections on analogues of natural sugar phosphates and on OH-protection during reactions.[38] The degradation of sugar phosphates by hydroxyl radicals (Ti^{3+} - H_2O_2) has been investigated by e.s.r. spectroscopy. The complex spectra obtained indicated non-selective hydrogen abstraction from all carbon atoms of pyranoses and selective abstraction from the carbon atoms adjacent to the ring oxygen atom of furanose derivatives. The β-phosphate substituted radicals thus formed preferentially from D-fructose 6-phosphate, D-fructose 1,6-diphosphate, and D-ribose 5-phosphate underwent rapid rearrangement with loss of phosphate. These observations lend support to the idea that radiation-induced strand breakage of DNA involves hydrogen abstraction from C-4′ followed by rupture of the phosphate linkage.[39] From a spectrophotometric kinetic study of the oxidation of D-glucopyranose 1-phosphate by chromium(VI) and by vanadium(V) it was concluded that the mechanisms involved are different from those proposed for the corresponding oxidations of glucose and glucose 6-phosphate.[40] During the oxidation of glucose 1-phosphate to glucuronic acid 1-phosphate by oxygen over platinum on carbon strong catalyst deactivation was encountered due to complete coverage and distortion of the catalyst surface by excess of oxygen, thus blocking the adsorption of the sugar phosphate.

The problem has been overcome by use of a suitably structured carbon carrier with large particles which provide a built-in barrier for oxygen diffusion.[41,42]

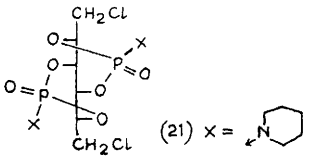
A new phosphorylating reagent, dibenzyl phosphorofluoridate, has been introduced. In the presence of caesium fluoride as base it reacts with primary and anomeric hydroxy groups preferentially. Secondary hydroxy groups, e.g., those of partially protected myo-inositol, can be phosphorylated after deprotection with butyl lithium.[43] 1,2-Di-phosphates were obtained in good to excellent yields by treatment of vicinal diols with diethyl phosphorochloridate and butyl lithium; there was no evidence of formation of cyclic phosphates, the predominant products when other bases are used.[44] O-Glycosylation of phosphonic and phosphinic acids has been achieved by the trichloroacetimidate method; examples are given in Scheme 4.[45]

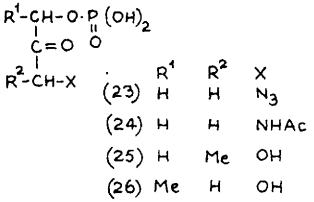


Reagents: i, HOP(O)(OPh)Ph ; ii, $HOP(O)Ph_2$

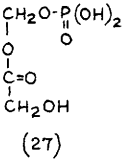
Scheme 4

The (R,S)-P-diastereomer of 2,4;3,5-bis(cyclicphosphoramidate) (21) was formed when the bis(cyclicphosphorochloridate) (22) was treated with piperidine and triethylamine.[46] The X-ray analysis of product (24) is referred to in Chapter 22. Analogues (23) - (27) of 1,3-dihydroxyacetone phosphate have been prepared as potential





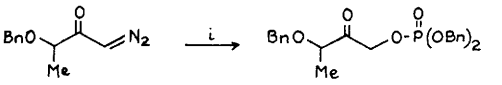
	R^1	R^2	X
(23)	H	H	N_3
(24)	H	H	NHAc
(25)	H	Me	OH
(26)	Me	H	OH



(27)

substrates for the synthesising aldolase which produces D-fructose 1,6-diphosphate. In the synthesis of compounds (25) and (26) a new method for generating α-hydroxyketone phosphates was applied, involving reaction of a diazoketone with dibenzyl phosphate, as illustrated in Scheme 5.[47] Analogues of D-fructose 1,6-diphosphate and D-fructose 2,6-diphosphate, the natural substrate and a natural inhibitor, respectively, of the enzyme D-fructose

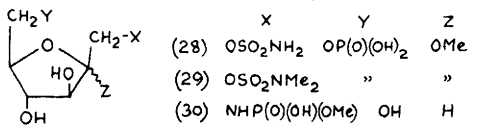
1,6-bisphosphatase were required during a program aimed at control of diabetes by suppression of "gluconeogensis". Compounds



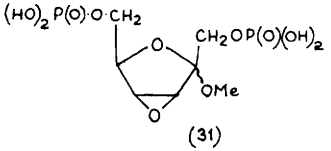
Reagent: i, $HOP(O)(OBn)_2$

Scheme 5

synthesised included D-arabino- and D-ribo-furanose 1,5-diphosphate, sulphamates (28) and (29), phosphoramidate (30), and epoxide (31). These were obtained by conventional procedures from

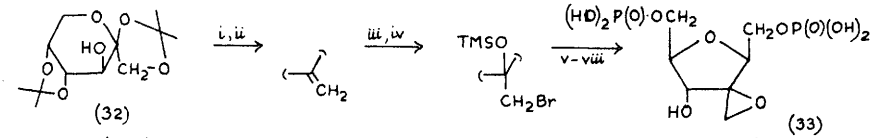


	X	Y	Z
(28)	OSO_2NH_2	$OP(O)(OH)_2$	OMe
(29)	OSO_2NMe_2	»	»
(30)	$NHP(O)(OH)(OMe)$	OH	H



(31)

known starting compounds, mostly as anomeric mixtures. A further analogue, the spiro-epoxide (33), was available from diacetone fructose (32) as illustrated in Scheme 6. The anomeric D-arabinofuranose 1,5-diphosphates and compounds (29) and (31) were



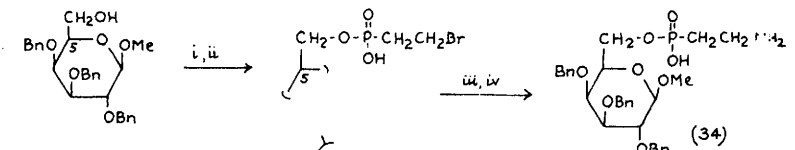
(32) (33)

Reagents: i, $(COCl)_2$-DMSO-TEA; ii, Ph_3PCH_2Br-LiBr; iii, MCPBA; iv, TMSBr-LiBr; v, MeOH-H^+; vi, $(PhO)_2P(O)Cl$-Py; vii, H_2-PtO_2; viii, Na_2CO_3

Scheme 6

strong inhibitors of the biphosphatase <u>in vitro</u>; however, no interference with gluconeogenesis was observed in isolated hepatocytes indicating an inability of anionic phosphates to cross cell membranes.[48]

α-D-Ribofuranose 1,2-cyclicphosphate-5-phosphate has been obtained by reaction of commercially available α-D-ribofuranose 5-phosphate-1-pyrophosphate with DCC. On alkaline hydrolysis it furnished the 1,5- and 2,5-diphosphates. Detailed n.m.r. and



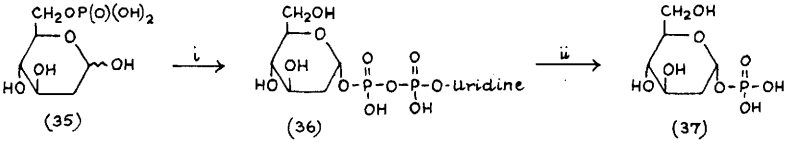
(34)

Reagents: i, $(HO)_2P(O)CH_2CH_2Br$-  -Py; ii, H_2O; iii, LiN_3-DMF; iv, H_2S-Py-H_2O

Scheme 7

molecular mechanics studies have been carried out on the novel

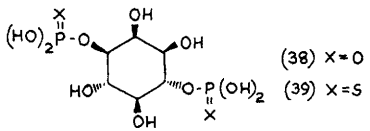
bicyclic ester and related molecules.[49] Two routes to methyl 6-O-(2′-aminoethylphosphonyl)-tri-O-benzyl-β-D-galactopyranoside (34) have been developed. One of these uses 2-bromoethylphosphonic acid, a new reagent, and is shown in Scheme 7. β-D-Galactose esterified at O-6 with 2-aminoethylphosphonic acid occurs in snail galactans.[50] Commercially available 2-deoxy-D-arabino-hexose 6-phosphate (35, Scheme 8) has been converted to the 1-phosphate (37) by an enzymatic process via the uridine diphosphate intermediate (36) which could be isolated and purified.[51]

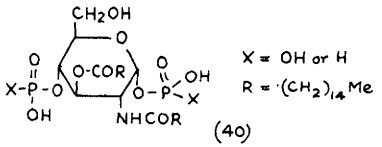


Reagents: i, Phosphoglucomutase-uridine diphosphoglucose pyrophosphorylase-uridine; ii, uridine diphosphoglucose pyrophosphorylase - $Na_4P_2O_7$

Scheme 8

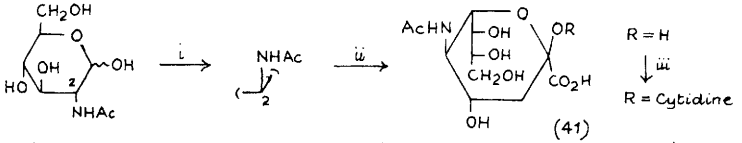
(±)-Myo-inositol 1,4-diphosphate (38), the racemate of a metabolite of second messenger myo-inositol 1,4,5-triphosphate and its diphosphorothioate analogue (39) have been synthesised from (±)-1,2,4,5-di-O-isopropylidene-myo-inositol by way of phosphite intermediates.[52] Similarly, (±)-myo-inositol 1,3,4-triphosphate has been obtained from (±)-2,4,5-tri-O-benzyl-myo-inositol.[53] Phosphite chemistry was also employed in the preparation of diphosphorylated and diphosphonylated Lipid A monosaccharide analogues (40).[54] Related Lipid A components are mentioned in Chapter 9. Methyl 3-deoxy-α-D-manno-oct-2-ulopyranosidonic acid 4-phosphate has been synthesised and its chemical stability studied.[55]





By a combination of chemical and enzymatic reaction steps, as shown in Scheme 9, cytidine N-acetylneuraminic acid 5′-phosphate (41) is available from 2-amino-2-deoxy-D-glucose on a multigram scale.[56] Phospholipase D catalyses the regiospecific transfer of alkylphosphoryl residues from alkylphosphorylcholines to primary carbohydrate hydroxy groups. This allowed the efficient, one-step synthesis of D-glucose 6-stearylphosphate and various nucleoside 5′-alkylphosphates from unprotected starting materials.[57] In the

preparation of agrocinopine A (42), a diglycosyl phosphate

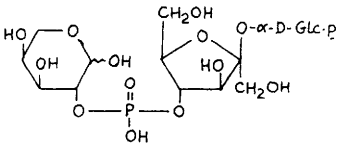


Reagents: i, NaOH ; ii, $MeCOCO_2Na$-neuraminic acid aldolase; iii, CTP- cytidine 5'-monophospho-N-acetyl-neuraminic acid synthetase

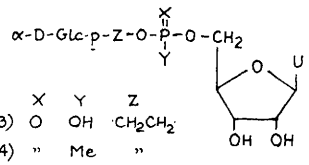
Scheme 9

produced by crown gall tumours of dicotyledonous plants, the phosphonate coupling method was used to link appropriately blocked derivatives of sucrose and of L-arabinose 2-phosphonate. The synthesis was completed by oxidation of the phosphonate to a phosphate and deprotection.[58]

Compounds (43) - (46) are analogues of the biological glucosyl donor uridine 5'-diphosphate glucose (UDPG) (47). Having

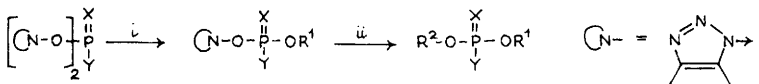


(42)



	X	Y	Z
(43)	O	OH	CH_2CH_2
(44)	"	Me	"
(45)	"	Ph	"
(46)	S	Me	"
(47)	O	OH	$O{\cdot}P(O)OH$

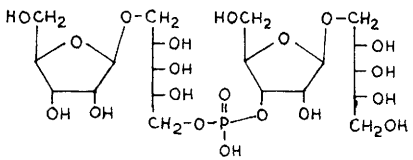
a bridge between the sugar and the nucleoside moiety of similar length and spatial arrangement to that of the natural pyrophosphate (47), but lacking the labile O-glycosidic linkage, they are potential inhibitors of glycolipid biosynthesis. Their preparation has been achieved by use of the hydroxybenzotriazole method which is outlined in Scheme 10.[59] Several approaches to



Reagents: i, Protected nucleoside (R^1OH)-Py ; ii, Protected anhydro-octitol (R^2OH)-methylimidazole-Py

Scheme 10

the synthesis of repeating units of the capsular polysaccharide of



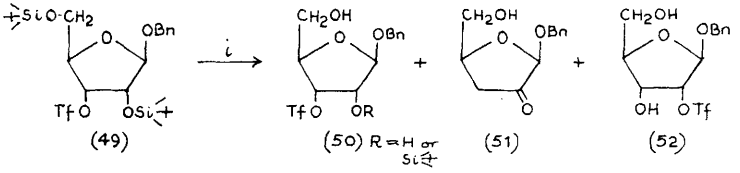
(48)

Haemophilus influenzae Type B, e.g., the dimeric fragment (48), have been published.[60,61] They are also referred to in Chapter 3.

3 Sulphonate Esters

The octamolar tosylation of sucrose has been reinvestigated.[62] In continuation of an on-going study, the partial tosylation of methyl α- and β-D-galactopyranoside has been reported (see Vol. 20, p. 69 for similar work with methyl α-D-mannopyranoside). The order of reactivity was found to be HO-6 > HO-2 > HO-3 > HO-4 and HO-6 > HO-3 > HO-2 > HO-4 for the α- and β-anomers, respectively.[63] 2,3,4,6,6′-Penta-O-acetylsucrose, the major product in the partial deacetylation of the octaacetate on exposure to Al_2O_3-K_2CO_3, was subjected to partial tosylation to give a mixture of mono- and di-tosylates, and in addition the 1′,3′,4′-tritosylate. These were converted to a large number of anhydrosucrose derivatives.[64] Detosylation by U.V. irradiation is reported to proceed with reasonable efficiency in the presence of electron transfer reagents such as dimethoxybenzenes. 1,2;5,6-Di-O-isopropylidene-α-D-allofuranose, for example, was obtained in 65% yield from the corresponding 3-O-tosylate.[65]

Triflyl migration has been observed during the desilylation of benzyl β-D-ribofuranoside derivative (49, Scheme 11). Apart

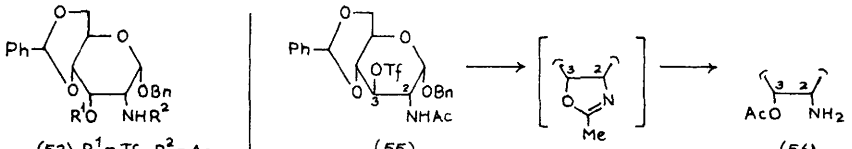


Reagents: i, HF-MeCN

Scheme 11

from moderate amounts of the desired products (50), ketone (51) and 2-O-triflate (52) were obtained in ca. 30 and 5% yield, respectively. This represents the second report of triflyl migration in a ribofuranose system[66] (see Vol. 20, p. 204). Conventional triflation of benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-allo- and -α-D-gluco-pyranosides gave in the first instance the expected products (53) and (55) respectively, which were however unstable. On standing in solution the allo-triflate (53) rearranged to the 3-O-acetyl-2-deoxy-2-trifluoromethylsulphonamido derivative (54), and the gluco-triflate (55) decomposed into a mixture of products. Among these

the 3-O-acetyl-2-amino-2-deoxy-D-allose derivative (56), formed presumably as shown in Scheme 12 via an oxazoline intermediate,



(53) R^1 = Tf, R^2 = Ac
(54) R^1 = Ac, R^2 = Tf

(55)

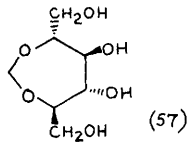
(56)

Scheme 12

could be identified.[67]

4 Other Esters

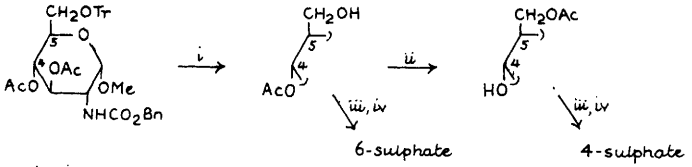
The protection of 1,2-diols as cyclic orthoesters has been briefly reviewed. Cyclic orthoesters are stable to base but are readily opened by acid to give monoformates which can then be hydrolysed by alkali. As an example, the protection/deprotection of vicinal diol (57) is mentioned, which proceeds cleanly without cleavage of



(57)

the methylene bridge between O-2 and O-5, due to the large difference in acid hydrolysis rates.[68]

The 2-, 3-, 4-, and 6-monosulphates of methyl α-D-galactopyranoside have been synthesised,[69] as have the 3-, 4-, and 6-monosulphates of methyl 2-amino-2-deoxy-α-D-glucopyranoside. In the preparation of the last two compounds acetyl migration from O-4 to O-6 was exploited, as shown in Scheme 13.[70] A mixture of



Reagents: i, HBr-HOAc ; ii, NaOH ; iii, Py-SO_3 ; iv, Deprotection

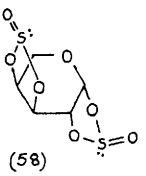
Scheme 13

four diastereomeric 1,2,3,4-bis(cyclic sulphites) was formed when L-arabinose was treated with thionyl chloride in pyridine, the major product being the exo-exo isomer (58). Attack by

nucleophiles (e.g., by NaN_3 in HMPA at 70°C) took place at C-1 preferentially affording 1,2-trans-glycosides unprotected at O-2. Under more forcing conditions (e.g., NaN_3 in DMA at 120°C) nucleophiles attacked also at C-3.[71] Cyclic sulphites have been used as intermediates in the synthesis of nucleosides.[72]

From the i.r. spectrum of a single crystal of methyl β-D-glucopyranoside 2,3,4,6-tetranitrate the intermolecular interactions of the nitrate groups have been calculated,[73] and i.r. data from the 400-800 cm^{-1} range have been used in the conformational analysis of, for example, methyl β-D-glucopyranose 2,3,6-trinitrate.[74] The i.r. spectra of several mono- and di-nitrates of methyl α- and β-D-glucopyranosides are referred to in Chapter 22.

Carbohydrate alcohols and diols reacted with two analogues (59) and (60) of Viehe's salt (61) to give the products corresponding to those obtained earlier with Viehe's salt itself, i.e., 1,2-trans-bromodeoxycarbamates, cyclic carbamates, or cyclic carbonates, depending on the reaction conditions. Free sugars gave glycosyl bromides.[75]



(58)

$R_2\overset{+}{N}=CX_2\ X^-$

(59) R = Me X = Br
(60) R = Et X = Br
(61) R = Me X = Cl

Complexes between pentoses and borate are covered in Chapter 17.

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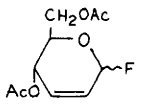
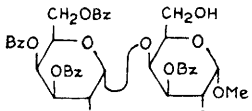
8
Halogeno-sugars

1 Fluoro-sugars

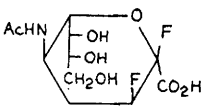
A review on deoxyfluorocarbohydrates covered membrane transport, enzymic and metabolic studies, particularly on 3-deoxy-3-fluoro- and 4-deoxy-4-fluoro-D-glucose.[1] Treatment of tri-O-acetyl-D-glucal with pyridinium poly (hydrogen fluoride) affords the allylically rearranged glycosyl fluoride (1). Other glycals with 3,4-trans-related esters underwent this reaction whereas the cis-compounds gave uncharacterised products.[2] Unprotected α-D-hexopyranosyl fluorides have been alkylated (DMF, alkyl halide, KOH or Ag_2O) to give the corresponding tetra-O-alkyl-α-D-hexopyranosyl fluorides. Hepta-O-benzyl-α-D-lactosyl fluoride and N-acetyl-2-amino-3,4,6-tri-O-benzyl-2-deoxy-α-D-glucopyranosyl fluoride were also prepared by this method.[3] Conversely the hydrogenolysis of benzyl ethers has been effected in the presence of a glycopyranosyl fluoride moiety.[4] The preparation of methyl(2,3,4-tri-O-acetyl-β-D-glucopyranosyl fluoride)uronate from the corresponding α-bromide and its use as a glycosylating agent have been reported.[5] Treatment of the disaccharide derivative (2) with DAST gave a mixture of the 6-O-methyl galactobiosyl fluorides by a reaction which involved migration of the C-1 methoxy group to C-6.[6]



(1)



(2)



(3)

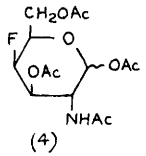
Evidence has been provided for a covalently bound intermediate in a β-glucosidase mediated glycosyl fluoride hydrolysis. 2-Deoxy-2-fluoro-β-D-glucopyranosyl fluoride becomes bound to the enzyme and then the 2-fluoro group considerably slows what is normally a fast hydrolysis step to regenerate the enzyme and produce the hydrolysed sugar. The adduct formed between 2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride and the enzyme was shown

by ^{19}F n.m.r. to have an α-linkage.[7] Similarly, the 3-deoxy-3-fluoro-glycosyl fluoride derivative (3) of neuraminic acid is reported to be a potent inhibitor of neuraminidase.[8]

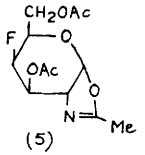
The reaction of gaseous [^{18}F] fluorine or [^{18}F] acetyl hypofluorite with tri-O-acetyl-D-galactal has allowed the synthesis of 2-deoxy-2[^{18}F]fluoro-D-galactose.[9] Nucleophilic displacements employing [^{18}F] fluoride ions on either methyl 3-O-benzyl-4,6-O-benzylidene-2-O-triflyl-β-D-mannopyranoside or 1,6-anhydro-3,4-di-O-benzyl-2-O-triflyl-β-D-mannopyranose have given access to 2-deoxy-2-[^{18}F]fluoro-D-glucose.[10]

Methyl 6′-deoxy-6′-fluoro-α-sophoroside and -α-laminaribioside as well as methyl 6′-deoxy-6′-fluoro-α-kojibioside and -α-nigeroside have been synthesized by standard methods.[11] N-Acetyl-9-deoxy-9-fluoroneuraminic acid has been prepared by DAST treatment of an appropriately protected mono-ol.[12] The preparation of methyl 6-deoxy-6-fluoro-β-D-galactobioside has been reported,[13] as has that of 6-deoxy-6-fluorosucrose.[14] Benzyl 2-acetamido-6-O-benzyl-2,4-dideoxy-4-fluoro-α-D-glucopyranoside has been prepared by DAST treatment of an appropriately protected galactosamine derivative, and after coupling with tetra-O-acetyl-α-D-galactopyranosyl bromide the product was deprotected to give 2-acetamido-2,4-dideoxy-4-fluoro-3-O-(β-D-galactopyranosyl)-D-glucopyranose.[15] The synthesis of some di- and tri-saccharides with primary fluoride groups is covered in chapters 3 and 4, and the formation of a 6,6-difluorogalactose derivative is mentioned in chapter 15.

Treatment of benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-4-O-mesyl-α-D-glucopyranoside with fluoride ion followed by protecting group manipulation afforded the 4-fluorogalactosamine derivative (4), which after exposure to trimethylsilyl triflate gave the oxazoline (5). This was phosphorylated at C-1 and then coupled with a uridine 5′-monophosphate derivative to give a uridine diphosphate-N-acetyl-galactosamine analogue. Similar treatment of the 6-fluoride (6) afforded a uridine diphosphate-N-acetyl-glucosamine analogue.[16] The synthesis of the C-4 epimer of compound (5) and its utility as a good glycosylating agent is mentioned in chapter 9.



(4)



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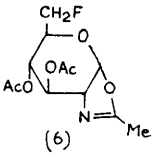

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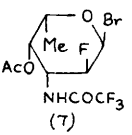
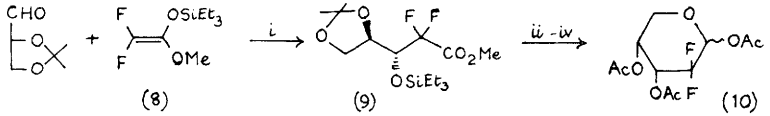


(7)

The 2-fluoro-daunosamine derivative (7) has been coupled to daunomycinone to give, after deprotection, (S)-2'-fluorodaunorubicin.[17] Treatment of 2,3-O-isopropylidene-D-glyceraldehyde with difluoroketene acetal (8) afforded ester (9) with good selectivity (Scheme 1). This was converted into the

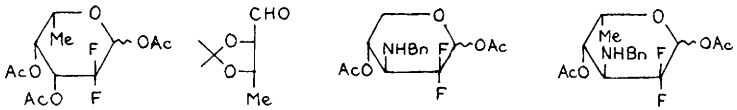


(8) (9) (10)

Reagents: i, ZnI_2, MeCN; ii, DIBAH; iii, TFA-H_2O; iv, Ac_2O-Py

Scheme 1

difluoropentose derivative (10). Similarly the 6-deoxy-L-arabino-hexose analogue (11) was obtained from aldehyde (12).[18] When this procedure was extended to the N-benzylimine derivatives of the two aldehydes employed above, the products were obtained with opposite stereoselectivity. Thus the major 2,3-dideoxy-2,2-difluoro-3-aminosugars produced were compounds (13) and (14). It was



(11) (12) (13) (14)

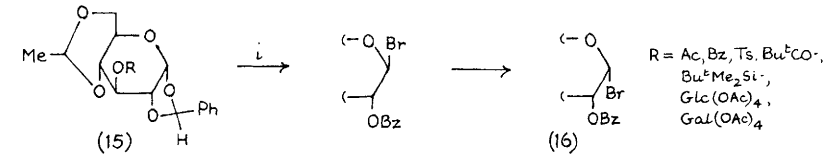
postulated that a Felkin-type transition state was operating for the aldehydes, but an α-chelation for the imines due to the increased basicity of the nitrogen.[19]

The metabolic interconversion of 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-mannose (and their 6-phosphates) in tumour cells was investigated by ^{19}F - NMR spectroscopy, and a mannose: glucose equilibrium ratio of ~4:1 was observed.[20] The conversion of 2-deoxy-2-fluoro-D-galactose into its gluco-isomer via the action of a UDP-galactose epimerase has been observed *in vivo* in mice by use of ^{19}F - NMR spectroscopy.[21]

2 Chloro-, Bromo-, and Iodo-sugars

Photobromination (hν, Hg lamp/Cl_3CBr) of 1,2-O-benzylidene-α-D-glucopyranose derivatives (15) gave initially the β-glycosyl bromides which isomerised readily to the α-bromides (16) (Scheme 2). Similar reaction occurred with NBS as reagent but the products were less clean. Galacto-analogues behaved similarly with the β→α isomerisation being more rapid.[22] Methyl

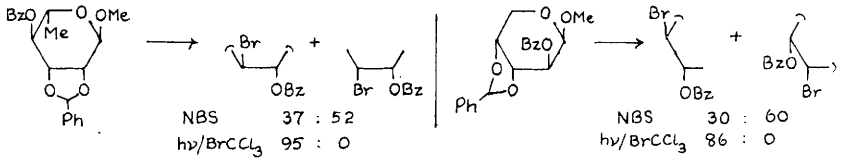
glycopyranosides have been transformed directly into the corresponding glycosyl halides by use of excess of acyl halide



Scheme 2

(e.g. acetyl bromide) and a lewis acid (e.g. zinc bromide).[23] A stereoselective C-glycoside synthesis from glycosyl bromides is mentioned in chapter 3. A study of the reaction of partially protected carbohydrates with analogues of Viehe's salt such as $Me_2N^+=CBr_2$ Br^- and $Et_2N^+=CBr_2$ Br^- has shown they reacted in an analogous manner to Viehe's salt itself, i.e. diols gave bromodeoxy sugars, cyclic carbonates or carbamates and free sugars gave glycosyl bromides.[24]

2,3-, 3,4-, and 4,6-O-Benzylidene acetals on pyranosides undergo photobromination upon u.v. irradiation in bromotrichloromethane to yield bromodeoxy benzoates in analogous fashion to the NBS method. However neighbouring acyl group participation is not encountered, rendering some reactions (e.g. Scheme 3) stereo- or regiospecific.[25] Some 5-chloro-5-deoxy- and



Scheme 3

6-chloro-6-deoxy-L-idofuranose derivatives have been prepared by chloride ion displacement of mesylate or chlorosulphonate groups.[26] Similar displacement of a chlorosulphonate group at C-3 in L-ido- and D-xylofuranose derivatives by chloride have been reported.[27] A number of 2-acylamino-2,6-dideoxy-6-iodo-D-glucopyranoses have been prepared by standard iodide displacements of the corresponding 6-tosylates.[28] The conversion of some pent-3-enofuranoses into halogenated aldulose derivatives is covered in chapter 15. Some radical chain extension reactions of deoxyiodo-sugar derivatives employing tributyltin hydride are mentioned in

chapter 16, as are some reactions of bromodeoxy aldonolactones. The formation of a number of 6,6′-dithiosucrose compounds from 6,6′-dideoxy-6,6′-diiodo-(or dibromo-)sucrose hexa-acetate is noted in chapter 11.

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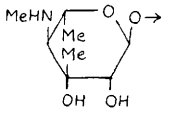
9
Amino-sugars

1 Natural Products

Suggestions on the nomenclature of and abbreviations for sialic acids have been made. A sialic acid is any natural or synthetic derivative of neuraminic acid (5-amino-3,5-dideoxy-D-glycero-D-galacto-nonulosonic acid).[1] The biosynthesis of 2-amino-2-deoxy-D-glucose and its incorporation into streptothricin F has been studied.[2] Full details on the identification of galactostatin as 5-amino-5-deoxy-D-galactopyranose (Vol.21, p.82), and its conversion to the corresponding lactam and 1-deoxy-analogue, have appeared.[3] Amino-sugars to have been identified as components of antibiotic substances include 2-deoxy-2-methylamino-D-xylopyranose and 3-amino-3-deoxy-D-mannopyranose,[4] 4-amino-4,6-dideoxy-D-galactopyranose[5] and its N-methyl-derivative,[6] the branched-chain amino-sugar (1)[7,8] and 4-epi-L-vancosamine (2).[9,10] Greater detail on these antibiotics is given in Chapter 19.

2 Synthesis

Syntheses of L-daunosamine have been reviewed.[11] Other syntheses covered in this section are grouped according to the methods used for introducing the amino-functionality.



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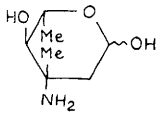

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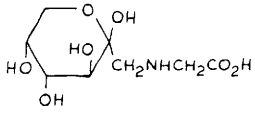
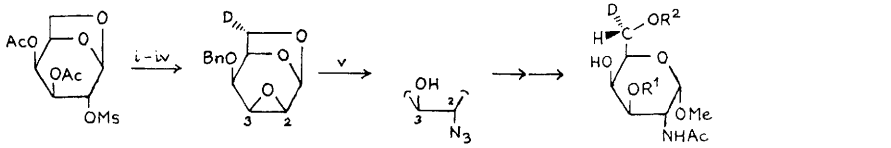


(3)

The synthesis and mutagenic effect upon Salmonella typhimurium of 1-deoxy-1-(p-tolylamino)-D-fructose, nine related glycosylamines, and their N-nitroso derivatives have been reported. It was suggested that mutagenicity was associated with production of the arenediazonium cation.[12] The Amadori reaction between D-glucose and glycine led to the expected fructose-glycine condensation product which was shown to exist mainly in the

β-pyranose form (3) accompanied by lesser amounts of the α- and β-furanose and α-pyranose forms.[13]

The mono-, di- and tri-saccharides (4)-(6), in which the 6-pro-S proton of the sugar at the reducing terminus is selectively replaced by deuterium, have been synthesized as model mucin oligosaccharides by conventional procedures from the ^{2}H-labelled anhydro-sugar (7). Their solution conformations were studied by ^{1}H-n.m.r. spectroscopy. The deuterium label was introduced by a photobromination - radical dehalogenation sequence, and the azido-functionality by opening of 2,3-epoxide (8) with azide (Scheme 1).[14] Several carbohydrate epoxides have been converted to amino-sugar derivatives through neighbouring group participation by a

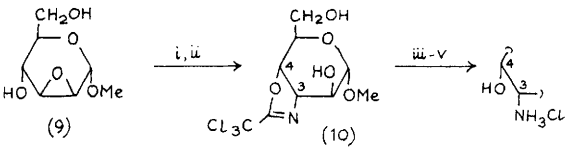


(8) (7) (4) $R^1=R^2=H$; (5) $R^1=\beta$-D-Gal p, $R^2=H$; (6) $R^1=\beta$-D-Gal p; $R^2=\beta$-D-GlcNAc p

Reagents: i, NBS-hν; ii, Bu_3SnD; iii, MeONa, MeOH; iv, NaH-BnBr; v, NaN_3

Scheme 1

trichloroacetimidoyl group, although the yields varied from good, e.g., 89% for the conversion (9) to (10) shown in Scheme 2, to moderate.[15] Coupling of an aminocyclitol and a trisaccharide

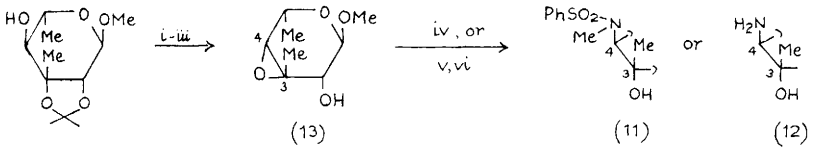


(9) (10)

Reagents: i, Cl_3CCN-NaH; ii, MeONa-MeOH; iii, $CF_3CO_2H-H_2O$; iv, Resin (OH^-); v, HCl

Scheme 2

epoxide was the key step in the first complete synthesis of acarbose which is further detailed in Chapter 18.[16] Known



(13) (11) (12)

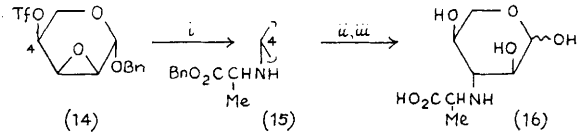
Reagents: i, MsCl-Py; ii, HCl-MeOH; iii, KOH-MeOH; iv, $PhSO_2\bar{N}Me\,Na^+$; v, $Et_4\overset{+}{N}N_3^-$; vi, H_2-Pd/C

Scheme 3

precursors (11) and (12) of the branched-chain amino-sugars L-sibirosamine and N-acylkansosamine, respectively, were obtained

from the common epoxide (13) by trans-diequatorial ring opening reactions (Scheme 3).[17]

Several deoxypentoses linked through C-3 or C-4 to L-alanine residues have been synthesized from epoxy-triflates. As exemplified in Scheme 4, the β-L-ribo-derivative (14) underwent initial triflate displacement to epoxide (15). Irreversible isomerization of this 2,3-epoxide to a 3,4-epimine and subsequent hydrolysis of this gave predominantly the 3-amino-3-deoxy-L-xylose derivative (16).[18,19]

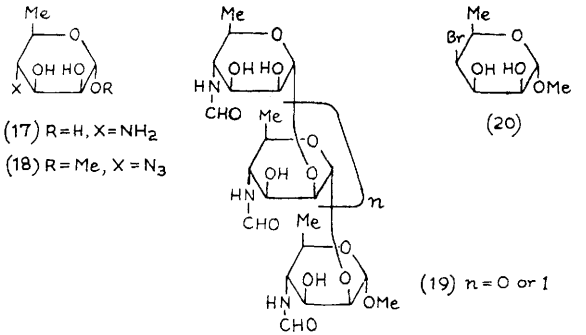


(14) (15) (16)

Reagents: i, $BnO_2CCH(Me)NH_2$; ii, H_3O^+; iii, H_2-Pd

Scheme 4

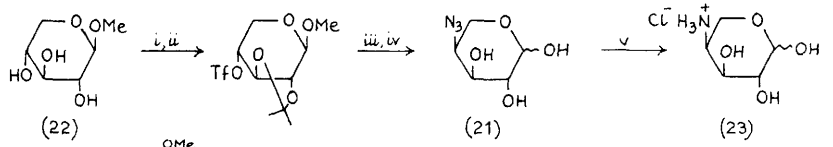
Many amino-sugar syntheses have employed sulphonate displacements to introduce the amino-functionality, the combination of triflate displacement with azide ion as nucleophile being especially favoured. A variety of heterocyclic bases[20] (e.g., piperidine, morpholine, and indoline) and alkaloids[21] (e.g., harmine and ephedrine) have been coupled to C-6 of D-galactose through their condensation with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-triflate. Eis and Ganem obtained D-perosamine (17), from D-mannose by a multistep



synthesis involving: a) 6-deoxygenation ($LiAlH_4$ on a 6-tosylate); b) inversion at C-4 via an oxidation-reduction sequence and c) displacement of a 4-sulphonyloxy group by azide.[22] Bundle and co-workers employed an identical strategy to obtain the azide (18) in good yield on a multigram scale, and used a novel reagent system (KN_3 - 18-crown-6 - DMF) for the final displacement of a 4-

triflate. Azide (18) served as a common precursor for the synthesis of the N-formylated di- and tri-saccharides (19; n=0 or 1) which were potent inhibitors of the binding of Brucella O-polysaccharide by Brucella-specific monoclonal antibodies.[23] Kenne and co-workers obtained the azide (18), and thence various N-acylated methyl 4-amino-4,6-dideoxy-α-D-mannopyranosides for use in a ^{1}H- and ^{13}C-n.m.r. study, by the action of sodium azide on the known 4-bromide (20).[24]

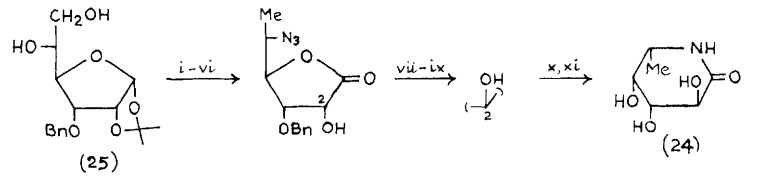
4-Azido-4-deoxy-L-arabinose (21) was obtained from methyl β-D-xyloside (22) by triflate displacement as shown in Scheme 5;



Reagents: i, HCl-  ; ii, Tf_2O-Py; iii, NaN_3; iv, H_3O^+; v, H_2-Pd/C-6M HCl

Scheme 5

reduction in strong acid led to the 4-amine hydrochloride (23), whereas reduction in weaker acid (0.1 M HCl) led to 1,4-dideoxy-1,4-imino-L-arabinitol.[25] The synthesis and chemistry of other cyclic iminoalditols is covered in Chapter 18. The sixteen step synthesis of "L-fuconic-δ-lactam" (24) from D-glucose via the D-allose derivative (25) involved inversion at C-2 and C-3, introduction of azide at C-5 with inversion, and C-1 oxidation (Scheme 6). Lactam (24) was a weak but specific inhibitor of α-L-furcosidases.[26] Shing[27] and Fleet and co-workers[28] employed the

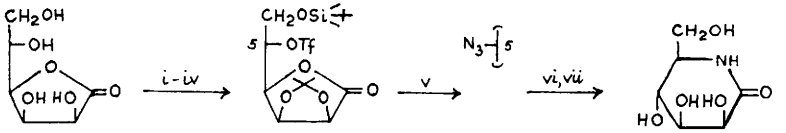


Reagents: i, TsCl-Py; ii, $LiEt_3BH$; iii, MsCl-Py; iv, NaN_3; v, H_3O^+; vi, Br_2-H_2O-$BaCO_3$; vii, Tf_2O-Py; viii, CF_3CO_2Na-DMF; ix, MeOH-H_2O; x, H_2-Pd/C; xi, H_2-Pd-H^+

Scheme 6

same approach to synthesise "D-mannono-1,4-lactam" (26) from Vitamin C via L-gulono-1,4-lactone (27) (Scheme 7). The latter group similarly prepared the L-enantiomeric lactam from D-gulono-1,4-lactone, and converted a protected form of lactam (26) into 1-deoxy-D-mannojirimycin. The synthesis of the potent neuraminidase inhibitor siastatin B (28) from L-ribose via the azide (29) provided proof of the absolute configuration of the natural

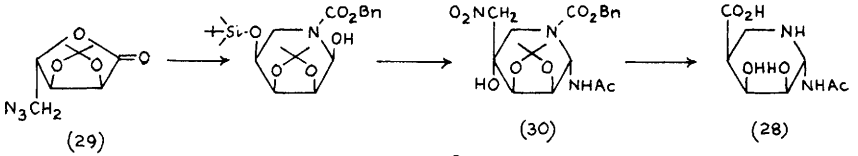
product (Scheme 8). Deoxygenation of the tertiary alcohol (30)



Reagents: i, Me_2CO-H^+; ii, AcOH-H_2O; iii, Bu^tMe_2SiCl-Py; iv, Tf_2O-Py; v, Bu_4NN_3; vi, H_2-$Pd(OH)_2$-EtOAc; vii, CF_3CO_2H-H_2O

Scheme 7

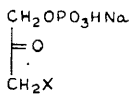
was effected by an elimination-hydrogenation sequence.[29] The



Scheme 8

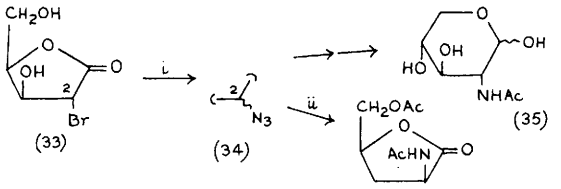
azido- and acetamido-analogues, (31) and (32) respectively, of 1,3-dihydroxyacetone phosphate have been synthesized by conventional means as potential substrates for the synthesising aldolase which produces D-fructose 1,6-diphosphate.[30]

A variety of α-amino-polyhydroxy-tetronic and pentonic acids have been synthesized from bromodeoxyaldonolactones. Typically, the 2-bromo-2-deoxy-D-xylonolactone (33) gave the epimeric azides (34) as a 1:1 mixture; after isolation by chromatography, the D-xylo-azide could be converted to 2-acetamido-2-deoxy-D-xylose (35)



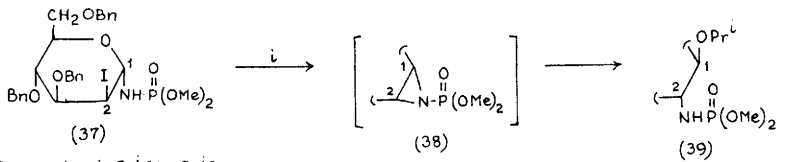
(31) X = N_3

(32) X = NHAc



Scheme 9

(Scheme 9). The mixed azides (34) were also converted to the 3-deoxy-lactone (36) via a 2,3-ene.[31] Treatment of 1,2-trans-2-

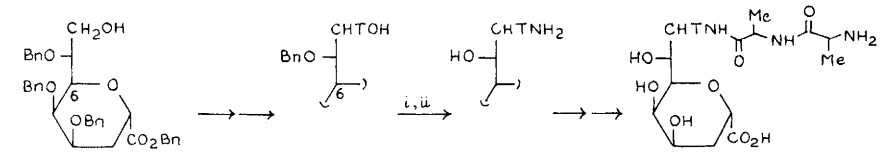


Reagents: i, Pr^iOH-Pr^iONa

Scheme 10

deoxy-2-iodo-glycopyranosyl phosphoramidates, e.g., α-D-manno-compound (37), with base in the presence of an alcohol led, via an aziridine, e.g., (38), to the corresponding 1,2-trans-2-deoxy-2-phosphoramido-glycopyranosides with inversion of configuration at both C-1 and C-2, e.g., (39), Scheme 10.[32] A further example of halogen displacement for the introduction of nitrogen functionality is covered earlier in this chapter (ref. 24).

Reagent systems involving triphenylphosphine have been employed to activate primary hydroxyl groups for displacement with nitrogen nucleophiles. A ^{3}H-labelled form (40) of an inhibitor of lipopolysaccharide biosynthesis has been synthesized from the 2-deoxy-β-KDO derivative (41), a redox sequence being used to introduce the ^{3}H-label (Scheme 11).[33] Mitsunobu conditions

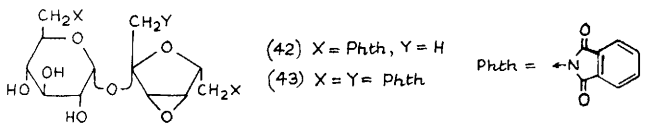


(41) (40)

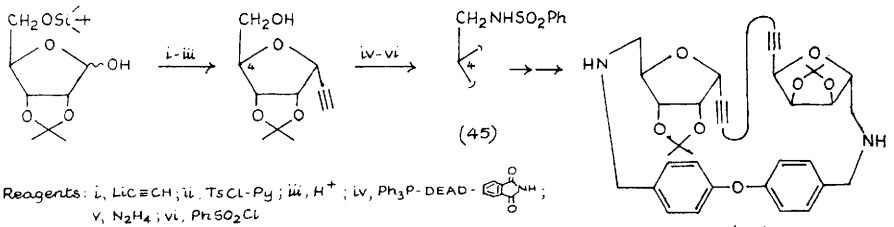
Reagents: i, LiN_3-CBr_4-Ph_3P; ii, Ph_3P-BnOH

Scheme 11

(Ph_3P - phthalimide - diisopropyl azodicarboxylate) were used to convert sucrose selectively into the di- or tri-phthalimido-tagato-epoxides (42) and (43), by reaction for 2.5 or 48 hours, respectively. Each of these products was isolated in 70% yield by



direct crystallisation and converted into the corresponding aminodeoxy sucroses by hydrazinolysis.[34] The "glycophane" (44), a chiral water-soluble cyclophane, was synthesised by coupling the



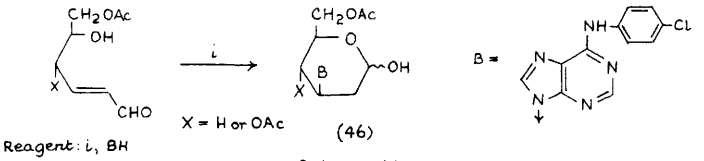
Reagents: i, LiC≡CH; ii, TsCl-Py; iii, H^+; iv, Ph_3P-DEAD-; v, N_2H_4; vi, $PhSO_2Cl$

(44)

Scheme 12

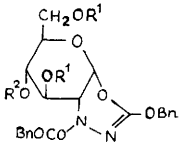
sugar-derived C-glycosidic acetylene (45) and an appropriate biphenyl ether derivative, the required amino-function being introduced using the Mitsunobu reaction (Scheme 12).[35]

Hirama has reviewed the application of intramolecular conjugate additions of γ- and δ-carbamoyloxy-α,β-unsaturated esters (c.f., Vol.21, p.89) in the synthesis of a variety of aminodeoxy-sugars.[36] Further anomalously coupled nucleosides, e.g., isonucleosides (46), have been obtained by Michael-type addition of purines to unsaturated aldehydes (Scheme 13).[37] Complex amino-disaccharides have been synthesized by employing the cycloadducts



Scheme 13

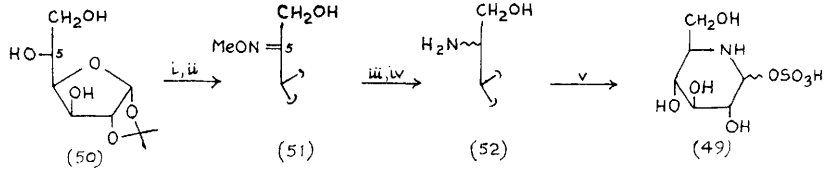
(47) and (48) formed from dibenzyl azodicarboxylate with O-protected D-glucal or D-lactal, respectively, as glycosylating agents in the presence of an acid catalyst (see also Chapter 3).[38]



(47) $R^1 = R^2 =$ Si⟨ or Ac

(48) $R^1 =$ Si⟨ ; $R^2 = \beta$-D-Galp-(Si⟨)$_4$

Nojirimycin, as its bisulphite adduct (49), has been synthesised from 1,2-O-isopropylidene-α-D-glucofuranose (50) in 50% overall yield without recourse to chromatography. Selective oxidation at C-5 was achieved by employing a stannylidene derivative. Reduction of the derived O-methyloxime (51) yielded the D-gluco- and L-ido-amines (52) in a 2:1 ratio (Scheme 14).[39]

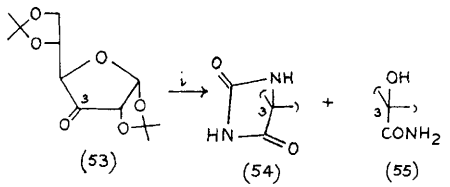


Reagents: i, $(Bu_3Sn)_2O \cdot Br_2$; ii, $MeONH_2$; iii, TsOH; iv, LAH; v, $SO_2 \cdot H_2O$

Scheme 14

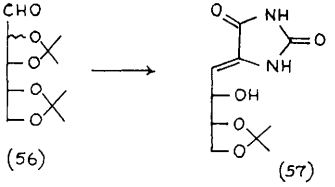
An α-lactosamine derivative has been synthesised (48% overall yield) in a similar reaction sequence. Oxidation (Br_2 - Bu_3SnOMe - MeCN) of the dibutylstannylene derivative of methyl 3′,4′-O-isopropylidene-α-lactoside led specifically to a 2-keto-

derivative, the O-benzyloxime of which was reduced (H_2 - Pd/C - NH_2NH_2), and the resulting free amine was acetylated.[40] Application of the Bucherer reaction to aldulose (53) gave predominantly the expected branched-chain amino-sugar (54) accompanied by compound (55) (Scheme 15). Both epimers of aldehydo-sugar (56), however, underwent elimination to yield the same alkene (57) under these conditions (Scheme 16).[41] The major



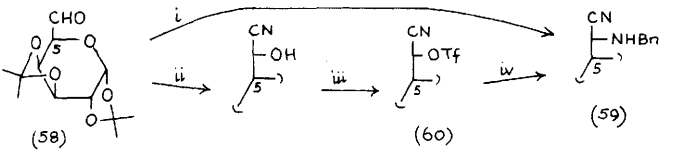
Reagents: i, KCN-$(NH_4)_2CO_3$-H_2O-EtOH

Scheme 15



Scheme 16

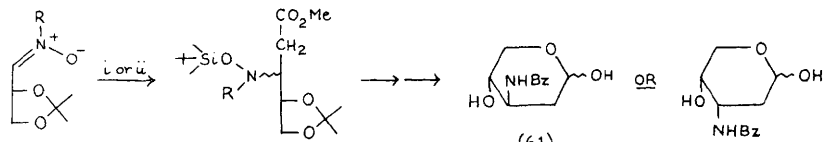
α-aminonitriles formed on co-addition of cyanide and various non-tertiary amines to the aldehyde (58) had the configuration at C-6 shown for the benzylamino-derivative (59), which is the opposite of that desired for construction of lincosamine derivatives. A greater proportion of the epimeric product was obtained by use of the triflate (60) but again the product (59), with retained stereochemistry, was found to be the major isomer (Scheme 17).[42]



Reagents: i, $NaHSO_3$ - NaCN-$BnNH_2$; ii, NaCN-NH_4Cl-H_2O ; iii, Tf_2O ; iv, $BnNH_2$

Scheme 17

The synthesis of amino-sugars from smaller chiral starting materials has again featured in several reports. 3-Benzamido-2,3-



(63) R = Bn

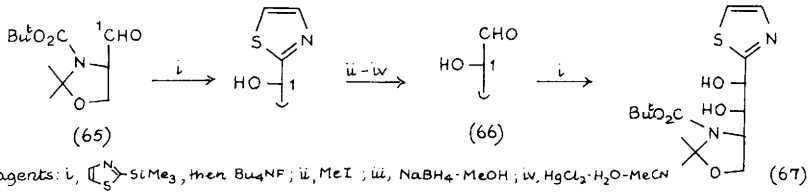
(64) R = $CHPh_2$

Reagents: i, ii,

Scheme 18

dideoxypentoses (61) and (62) have been obtained from syn- or anti-selective dipolar cycloadditions of ketene acetals with

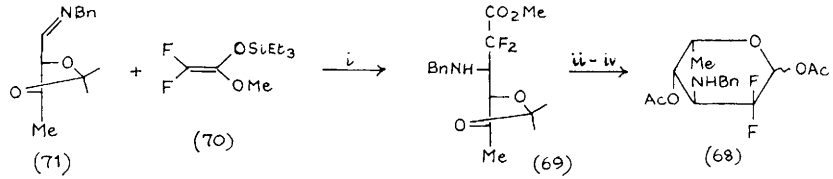
nitrones (63) and (64), respectively, derived from 2,3-O-isopropylidene-D-glyceraldehyde (Scheme 18). The enantiomer of compound (61) was obtained similarly from an L-glyceraldehyde derived nitrone.[43] The L-serine derived aldehyde (65) has been chain extended to give the 3-amino-3-deoxy-L-erythrose derivative (66) and thence the 4-amino-4-deoxy-L-ribose derivative (67) through two anti-selective additions of 2-trimethylsilylthiazole (Scheme 19).[44] The 3-amino-2,3-dideoxy-2,2-difluoro-sugar (68)



Reagents: i, -SiMe$_3$, then Bu$_4$NF; ii, MeI; iii, NaBH$_4$-MeOH; iv, HgCl$_2$-H$_2$O-MeCN

Scheme 19

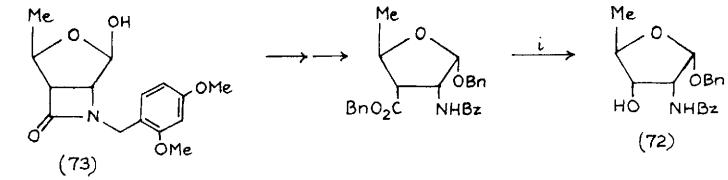
has been synthesised from the major adduct (69) obtained on chelation controlled addition of the difluoroketene acetal (70) to the tartrate-derived imine (71) (Scheme 20). Similarly, addition



Reagents: i, ZnBr$_2$; ii, Bu$^i_2$AlH; iii, CF$_3$CO$_2$H; iv, Ac$_2$O-py

Scheme 20

of acetal (70) to an imine derived from 2,3-O-isopropylidene-D-glyceraldehyde provided the analogous pentose derivative.[45] Benzyl 2-benzamido-2,5-dideoxy-α-D-ribofuranoside (72) has been synthesised, albeit in very low yield, from the bicyclic β-lactam (73) (Scheme 21), which was available from D-allo-threonine by a



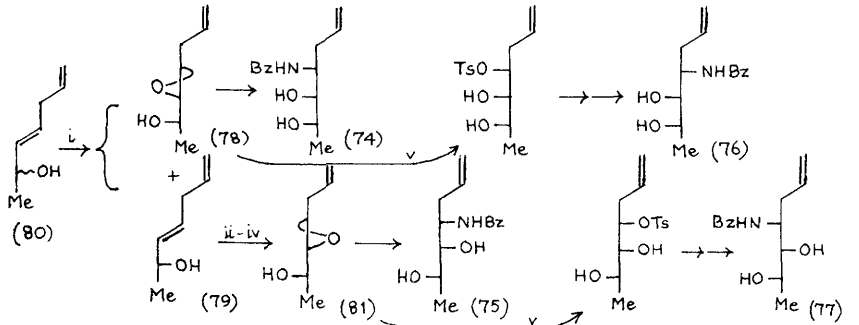
Reagents: i, MCPBA-DCC

Scheme 21

multistep procedure (Shiozaki et al., Tetrahedron, 1983, 39, 2399).[46] The synthesis of eight isomeric 2-C-methyl-2,3,6-trideoxy-3-amino-L-hexose derivatives from four carbon chiral

sulfenimines is covered in Chapter 14.

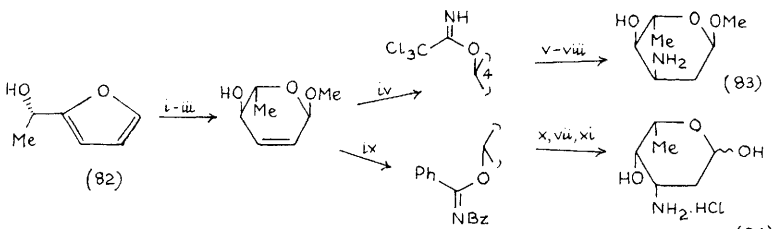
Chiral auxiliaries have been employed in syntheses of amino-sugars. Precursors (74)-(77) of all the isomers of 3-amino-2,3,6-trideoxy-L-hexose have been synthesised as shown in Scheme 22



Reagents: i, $But O_2H$ - Di-Pr^i L-Tartrate-$Ti(OPr^i)_4$; ii, $But O_2H$ - Di-Pr^i D-Tartrate - $Ti(OPr^i)_4$; iii, 4-$NO_2 \cdot C_6H_4CO_2H$ - DEAD - Ph_3P; iv, MeONa - MeOH; v, TsOH - 2,6-Lutidine. TsOH

Scheme 22

either from the chiral epoxyalcohol (78) or the selectively unreacted diene alcohol enantiomer (79) obtained on Sharpless epoxidation of racemic diene alcohol (80). The L-epoxide (81) was synthesised from the D-alcohol (79) by sequential epoxidation and Mitsunobu epimerization of the secondary alcohol. The precursors (74) and (75) with the stereochemistry required for L-ristosamine and L-daunosamine were obtained exclusively upon ring opening of epoxides (78) and (81), respectively, in methanolic ammonia. The precursors (76) and (77) with the stereochemistry required for L-acosamine and 3-<u>epi</u>-L-daunosamine, respectively, were obtained via a double inversion sequence involving reaction of the above epoxides with 2,6-lutidinium tosylate. These precursor alkenes can be converted to the requisite aminosugars by ozonolysis.[47]



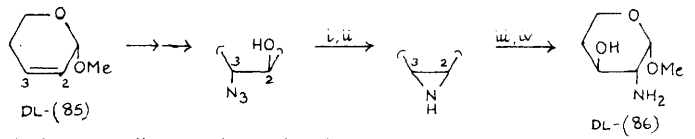
Reagents: i, Br_2 - MeOH; ii, HCO_2H - MeOH; iii, $NaBH_4$; iv, Cl_3CCN - NaH; v, NIS; vi, H_2 - Pd/C; vii, Bu_3SnH; viii, NaOH; ix, Bz_2NH - DEAD - TPP; x, NBS; xi, HCl - MeOH - H_2O.

Scheme 23

Asymmetric reduction [$LiBH_4$ in the presence of (<u>S</u>,<u>S</u>)-<u>N</u>,<u>N</u>′-dibenzoylcystine] of 2-acetylfuran provided the (<u>S</u>)-alcohol (82)

from which the glycosides (83) and (84) of L-daunosamine and L-ristosamine, respectively, were obtained in 98% ee as detailed in Scheme 23.[48] The synthesis of 2-amino-2-deoxy-4-C-methylpentonic acids using an organometallic cyclo-dipeptide reagent is covered in Chapter 14.

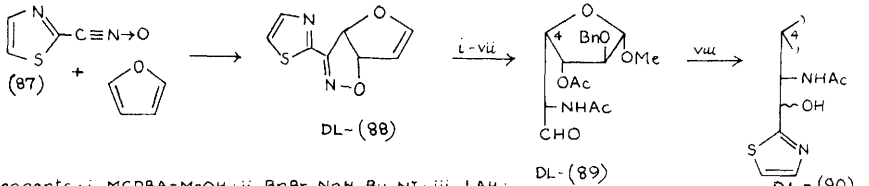
A variety of racemic aminodideoxypentopyranoses have been synthesised from 2-methoxy-5,6-dihydro-2H-pyran (85), primarily by manipulating the known products of epoxidation - azide ring opening as exemplified in Scheme 24 for the synthesis of the 2-amino-2,4-dideoxy-DL-threo-pentoside (86). These amino-sugars



Reagents: i, MsCl-Et_3N; ii, LAH; iii, $(CF_3CO)_2O$; iv, MeOH-NH_3

Scheme 24

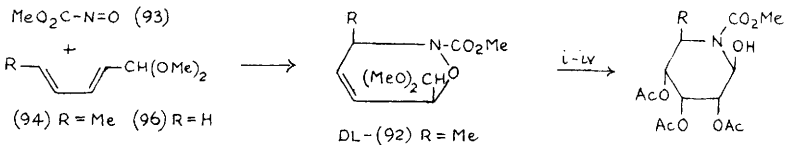
were converted into the corresponding ureido-derivatives by reaction with 2-chloroethyl isocyanate.[49] Dipolar cycloaddition of the nitrile oxide (87) with furan, in close analogy with the methodology of Jager et al. (Vol.19, p.93), provided the single adduct (88) from which the racemic extended-chain amino-sugar (89) and thence (90) could be elaborated (Scheme 25). The thiazole



Reagents: i, MCPBA-MeOH; ii, BnBr-NaH-Bu_4NI; iii, LAH; iv, AcCl-Et_3N; v, MeI; vi, $NaBH_4$; vii, $HgCl_2$-H_2O; viii, 

Scheme 25

moiety is employed as a masked aldehyde function.[50] The racemic 5-amino-5,6-dideoxy-allose derivative (91) has been synthesised



Reagents: i, OsO_4; ii, H_2-Raney Ni; iii, Ac_2O; iv, HCO_2H-H_2O

Scheme 26

from the adduct (92) formed by condensation of nitroso derivative

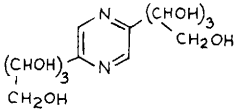
(93) with the diene (94) (Scheme 26). The racemic 5-amino-5-deoxy-ribose (95) was similarly obtained from the diene (96).[51]

3 Reactions

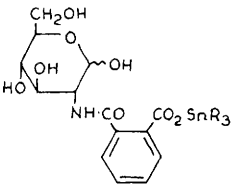
The major product formed from 2-amino-2-deoxy-D-glucose and lysine under physiological conditions (pH 7.4, 37°C, 1 week) has been identified as the 2,5-bis(tetrahydroxylbutyl)pyrazine (97) incorporating two molecules of the amino-sugar.[52]

Organotin derivatives such as (98) have been synthesised by phthalation of 2-amino-2-deoxy-D-glucose and 1-deoxy-1-methylamino-D-glucitol followed by replacement of the acidic proton by the organotin moiety.[53] 2-Amino-2-deoxy-sugars have been *N*-acylated with phenylalkanoic acids and amino-acids and the products have been tested for antitumor activity.[54] Direct *N*-acylation of 2-amino-2-deoxy-D-glucose has been effected using mixed anhydrides of dimethylphosphinothioic and carboxylic acids [*i.e.*, $Me_2P(S)OC(O)R$].[55]

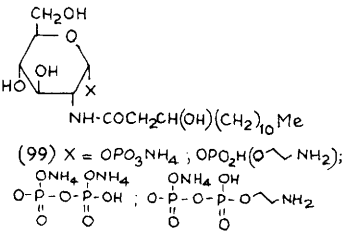
Reductive dephthalimidation, originally developed by Ganem for use with amino-acids, has proved to be a mild, efficient method for deprotection of *N*-phthalimido-sugars. The method is better than hydrazinolysis; both *O*- and *S*-glycosidic linkages are stable to the conditions ($NaBH_4$ - Pr^iOH - H_2O then HOAC, pH 4.5, 80°C), and isolated yields of the amino-sugars after *N*-acetylation were 70-80% for several tri- and oligo-saccharide examples.[56,57] Oligosaccharides containing *N*-acetamido-groups (exemplified with penta- and hexa-saccharides) can be quantitatively de-*N*-acetylated using calcium in liquid ammonia, but polysaccharides were only partially deprotected.[58]



(97)



(98) R = Bu, Ph

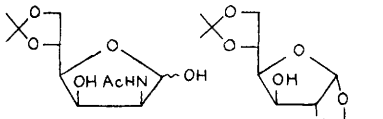


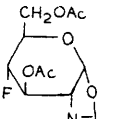
(99) X = OPO_3NH_4 ; $OPO_2H(O\text{-}C_6H_{10}\text{-}NH_2)$;

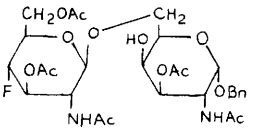
Benzyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranosides bearing a 3-*O*- or 6-*O*-octanoyl, -lauroyl, or -palmitoyl moiety have been synthesised and transformed into the corresponding 3- or 6-*O*-acylated-2-(3-carboxypropanoyl)amino-2-deoxy-D-glucoses by

hydrogenolysis in the presence of succinic anhydride.[59] The 2-acylamido-2-deoxy-D-glucosyl phosphates and pyrophosphates (99), related to components of lipid A, have been synthesised.[60] Other analogues of lipid A are covered in Chapters 3, 4 and 7, and the selective pivaloylation of 2-acetamido-2-deoxy-sugars is referred to in Chapter 7.

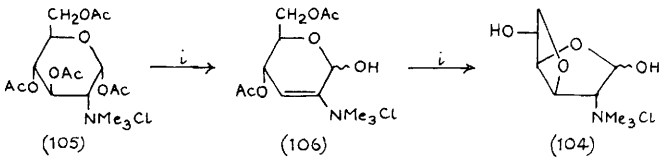
The 2-acetamido-2-deoxy-D-mannofuranose derivative (100) has been synthesised from 2-acetamido-2-deoxy-D-glucose. Reaction of the latter with acetone in the presence of a Lewis acid (*e.g.*, $FeCl_3$) yielded the oxazoline (101). Cleavage of the oxazoline ring upon mild acid hydrolysis was followed by epimerization at C-2 on exposure to a weakly basic anion-exchange resin.[61] The fluorinated oxazoline (102) has been obtained from 2-acetamido-1,3,6-tri-*O*-acetyl-2,4-dideoxy-4-fluoro-D-glucopyranose by reaction with trimethylsilyl triflate, and its utility as a glycosylating agent demonstrated, as in the synthesis of disaccharide (103).[62] The synthesis of fluorinated oxazolines and their application in the synthesis of fluorinated analogues of UDP-GlcNAc and UDP-GalNAc is covered in Chapter 8.







The 3,6-anhydro-sugar (104) was the unexpected product from alkaline hydrolysis of the quaternary ammonium sugar derivative (105), the reaction occurring by way of the isolable unsaturated intermediate (106) (Scheme 27).[63]



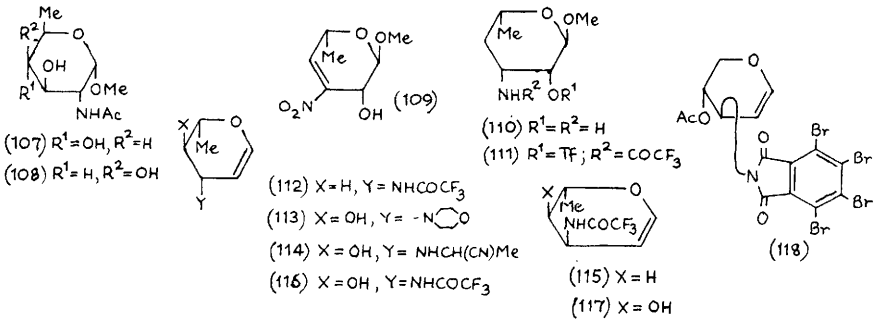
Reagents: i, NaOH-H_2O-MeOH

Scheme 27

The methyl glycosides (107) and (108) of D-quinovosamine and D-fucosamine have been synthesised in several steps from 2-acetamido-2-deoxy-D-glucose and -D-galactose, respectively. The required 6-deoxygenations were effected by reduction ($LiAlH_4$) of 6-tosylates.[64] The known unsaturated nitro-sugar (109) has been reduced ($NaBH_4$ then H_2 - Pt - HCl) to the 3-amino-3,4,6-trideoxy-α-

L-lyxo-hexoside (110), and a new preparation of the C-2 epimer of compound (110) has been detailed; these products are analogues of daunosamine in which the hydroxy group is transposed from C-4 to C-2. Attempts to introduce a fluorine at C-2 were unsuccessful, the triflate (111) yielding a 2,3-alkene.[65]

Conventional syntheses of acyl derivatives of 2-acetamido- and 2-benzamido-2-deoxy-D-glucose and their conversion to the corresponding glucopyranosyluronic acid and its benzyl α-glycoside have been described.[66,67] Six naturally occurring sialic acids (e.g., Neu5Ac, Neu5,9Ac$_2$, Neu5Ac9Lac, Neu5Gc, and Neu9Ac,5Gc where Gc = glycolyl) have been synthesised by coupling multigram amounts of 2-amino-2-deoxy-D-mannosamines with pyruvate using an agarose-immobilised acylneuraminate pyruvate lyase.[68] The synthesis of N-acetyl-3-fluoro-neuraminic acids is covered in Chapter 8.



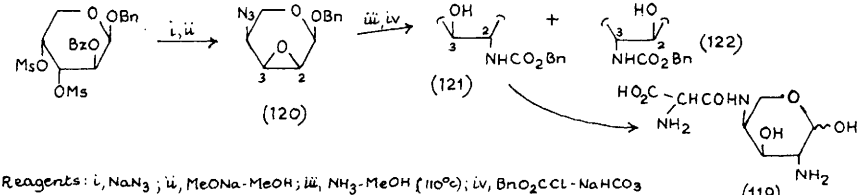
The aminoglycal derivatives (112) - (115) have been synthesised as potential glycosylating reagents from the precursors (116) or (117), the modifications being those which are effective in eliciting antitumor activity when applied to the daunosamine residue of anthracyclines.[69] The glycal (118) has been synthesised from the corresponding 2-deoxy-glycosyl acetates.[70] Reactions of 2-acylamino-2-deoxy-4,6-O-ethylidene-D-glucose with Wittig reagents is covered in Chapter 13, while the removal of a D-desosamine residue from the macrolide antibiotic oleandomycin, involving Cope elimination of the N-oxide of its dimethylamino-moiety, is covered in Chapter 19.

Desosamine's basic dimethylamino-group interferes with many standard glycosylating procedures, but a successful synthesis of its β-glycosides has been effected using the glycosyl fluoride (see Chapter 3). The constructions of other glycosides and oligosaccharides containing amino-sugar residues are covered in Chapters 3 and 4, respectively, and mass spectral studies of

certain amino-sugar derivatives are reported in Chapter 22.

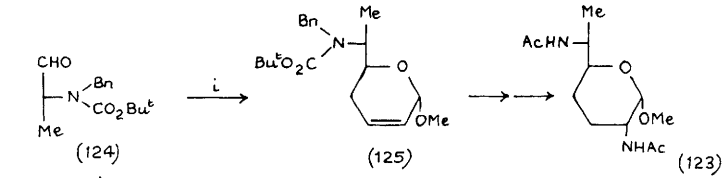
4 Diamino-sugars

The antifungal agent prumycin (119) has been synthesised from D-arabinose in 13 steps and 28% overall yield, by amination of the epoxide (120) which yielded similar amounts of the 2,4- and 3,4-diamino-sugar derivatives (121) and (122), respectively (Scheme 28).[71]



Scheme 28

Methyl 2,6-di-*N*-acetyl-α-D-purpurosaminide (123) has been synthesised from D-alanine via high-pressure [4+2]cycloaddition of aldehyde (124) with 1-methoxybutadiene (Scheme 29). The major



Scheme 29

adduct (125) was converted to diamino-sugar (123) by a hydroboration - sulphonate displacement sequence.[72] The synthesis of "nitrogen-in-the-ring" anhydro-diamino-aldonic acids, potential sialidase inhibitors, is covered in Chapter 16.

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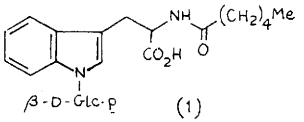
10
Miscellaneous Nitrogen Derivatives

1 Glycosylamines

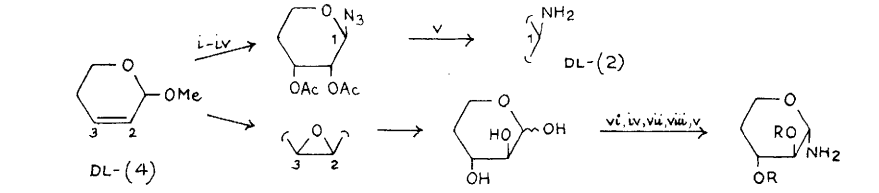
The N-glucosylated tryptophan derivative (1) has been isolated from the flowers of Pueraria lobata, material used as an oriental crude drug.[1]



(1)

N-(3-Ethylindolyl)-D-xylopyranosylamine, eight N-(substituted-phenyl)pentopyranosylamines, and their N-nitroso-derivatives have been synthesized and their mutagenicities reported.[2] The synthesis and antitumour activity of quaternary ellipticine N-glycosides is covered in Chapter 19, and the e.i.-m.s. fragmentation of per-O-acetylated N-(4-substituted-phenyl)glycopyranosylamines in Chapter 22.

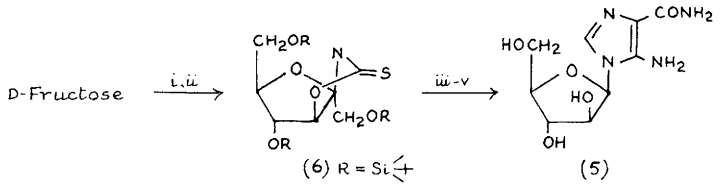
The racemic 4-deoxy-pentopyranosylamines derivatives (2) and (3) have been synthesized from 2-methoxy-5,6-dihydro-2H-pyran (4) (Scheme 1) and converted into their ureido-derivatives by reaction



Scheme 1

with 2-chloroethyl isocyanate.[3] 5-Amino-1-β-D-fructofuranosyl-imidazole-4-carboxamide (5) has been synthesized in 5 steps from D-fructose, the intermediate oxazolidine-2-thione derivative (6) being obtained in 40% yield (Scheme 2).[4] An anomeric mixture of N-(glycosyl oxime)pyrazoles (7) was obtained on reaction of 2-nitrosoglycosyl chloride (8) with pyrazole at room temperature,

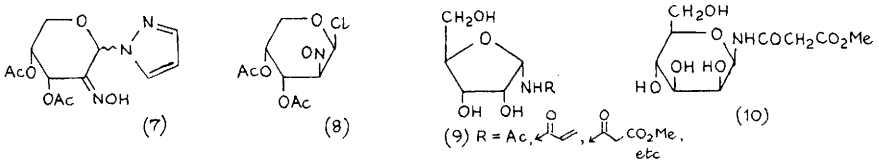
whereas at 80°C only the α-anomer was obtained.[5]



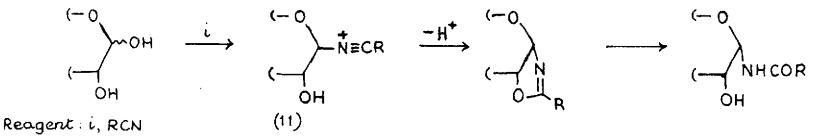
Reagents: i, KSCN-H_3O^+; ii, Si Cl-DMF; iii, Raney Ni; iv, $NCCH(NH_2)CONH_2$; v, HCl-MeOH.

Scheme 2

N-Acyl-glycosylamines were the products from reactions of free sugars with nitriles in liquid hydrogen fluoride followed by an aqueous treatment. D-Ribose gave 1,2-cis-furanosylamines, e.g., (9) as did D-arabinose and D-glucose. D-Mannose gave β-pyranosylamines, e.g., (10), as did L-rhamnose. D-Xylose gave

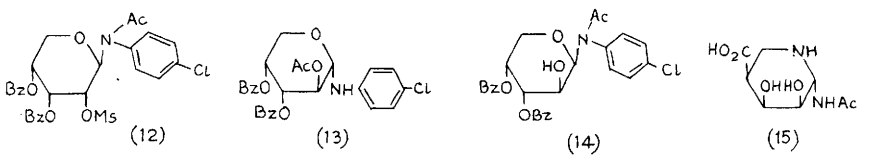


both α-pyranosylamine and β-furanosylamine products. The mechanism of the reaction appears to involve formation, cyclization and subsequent hydrolysis of glycosyl nitrilium species (11) (Scheme 3).[6] Attempted azide displacement of the N-acetyl-N-(4-chlorophenyl)-β-D-ribopyranosylamine 2-mesylate (12) in



Scheme 3

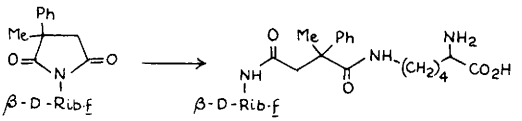
dimethylformamide led rather to the α-D-arabinopyranosylamine (13) through solvolysis with participation by the N-acetyl group. In acetonitrile a 1:1 mixture of α-(13) and β-(14) was obtained. The mesylate derivative of (14) did not react under these conditions,



but the regioisomeric 3-mesylate underwent the expected S_N2 displacement with azide.[7] Synthesis of the potent neuraminidase

inhibitor siastatin B (15) is covered in Chapter 9.

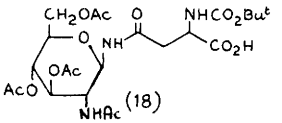
The synthesis, and ring-opening with ammonia, of N-(β-D-ribofuranosyl)-succinimide, -maleimide, and their analogues has been investigated. The possibility of glycosylsuccinoylation of protein amino-groups in biological systems was demonstrated by ring-opening of the 3-methyl-3-phenylsuccinimide derivative (16) with lysine to give adduct (17).[8]



(16) (17)

2,3,4-Tri-O-benzoyl-β-D-ribopyranosylamine has been synthesized from D-ribosylamine via the corresponding hydrobromide tribenzoate. Reaction of this amine with thiophosgene in alkaline medium yielded the corresponding β-glycosyl isothiocyanate accompanied by a small amount of its α-anomer. Various thiourea and related derivatives were prepared from these isothiocyanates.[9]

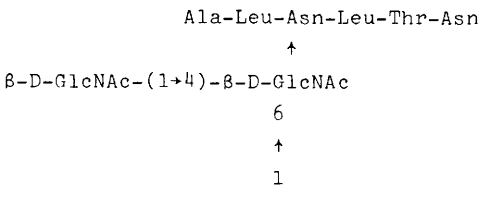
The construction of N-linked glycopeptides has attracted increasing attention. N-(L-Aspart-4-oyl)-β-D-xylopyranosylamine has been synthesized by dicyclohexylcarbodiimide-induced coupling of partially protected amino-acid and O-protected glycosylamine derivatives.[10] The same strategy was used to obtain an O,N-protected N-(glutam-5-oyl)-β-D-glucopyranosylamine.[11] This and the related 2-amino-2-deoxy-β-D-glucopyranosylamine derivative (18) have been converted to the corresponding glycopeptides by conventional peptide chain extension.[11-13] The fucosyl-chitobiose glycopeptide (19) was similarly elaborated from a trisaccharide glycosylamine.[14] A heptasaccharide isolated from urine of



(18)

swainsonine-intoxicated sheep has been converted into the oligoglycosyl-aspartate (20), the peracetylated heptasaccharide sequentially being transformed into an oxazoline derivative, a glycosyl azide, and a glycosylamine, then coupled to an aspartate moiety.[15]

Kunz and co-workers have employed 2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosylamine (21) as a chiral auxiliary in a diastereoselective Ugi reaction for the synthesis of optically



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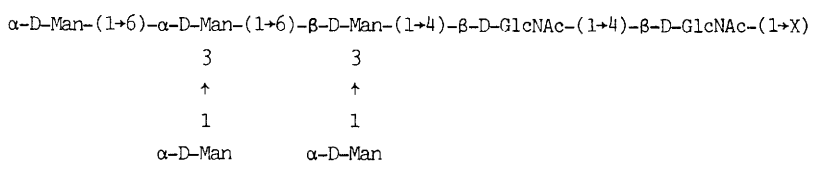
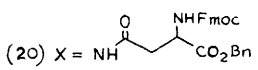
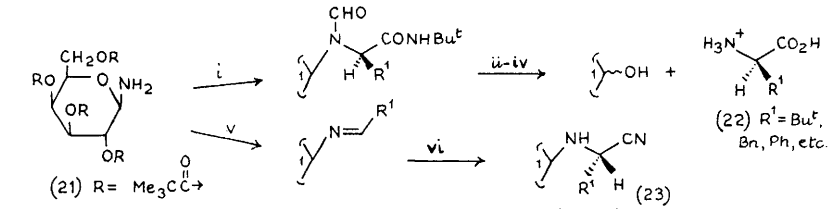




active (R)-amino-acids (22),[16,17] and in the Strecker synthesis which yielded predominantly the (S)-α-aminonitriles (23) when chloroform was the solvent (Scheme 4);[18] the (R)-isomer predominates in isopropanol (*c.f.*, Vol.21, p.101).



Reagents: i, R^1CHO-$Bu^tN{\equiv}C$-$ZnCl_2$-HCO_2H; ii, HCl-MeOH; iii, H_2O; iv, H_3O^+; v, R^1CHO; vi, Me_3SiCN-$ZnCl_2$-HCl.

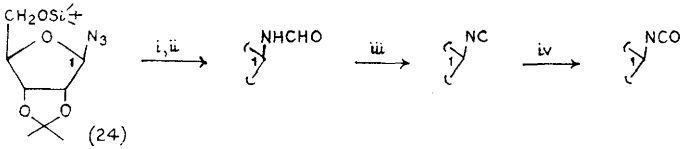
Scheme 4

Further studies on the Maillard reaction have been reported. The rate constants for the first five steps in the condensation of glucose with valine have been measured, intermediates have been identified by ^{13}C-n.m.r. spectroscopy and FAB-m.s. (+ve and -ve ion modes), and a mechanism was proposed. Thermal degradation of these intermediates in acidic medium was followed by ^1H-n.m.r. spectroscopy. A CIDNP effect at 130° indicated the operation of a

radical degradation.[19] The reactions of D-glucose with glycine, DL-alanine, and DL-phenylalanine, and the resulting Amadori products, have been subjected to differential thermal analysis, with the loss of carbohydrate and amino-acid components being determined by h.p.l.c. analysis. The results indicated the existence of three temperature dependent reaction phases.[20]

2 Azido-, Azi- and Diazo-sugars

The conformations of the α- and β-anomers of 2,3,4-tri-O-acetyl-D-arabinopyranosyl azide have been predicted from semi-empirical quantum chemical calculations.[21] Neutral Raney nickel has been used to convert a glycosyl azide to the corresponding glycosylamine in the presence of O-benzyl protecting groups.[14]



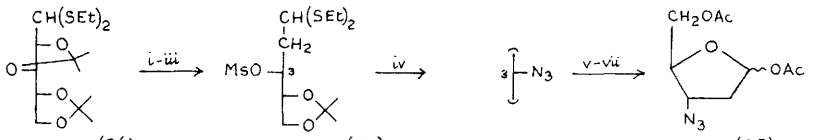
(24)

Reagents: i, Ph_3P; ii, HCO_2COMe; iii, $POCl_3$-Pr^i_2NH; iv, $Pb(OAc)_4$

Scheme 5

Glycosyl azides, such as the β-D-ribosyl derivative (24), have been converted to the corresponding formamide, isocyanide, and isocyanate derivatives as indicated in Scheme 5.[22]

The 3-azido-2,3-dideoxy-D-erythro-pentose diacetate (25), a synthon for the anti-AIDS nucleoside AZT, has been synthesized in an efficient 9-step procedure from D-xylose. The D-xylose dithioacetal (26) was converted into mesylate (27) by a modification of a known synthesis of 2-deoxyribose (Vol.12, p.99).

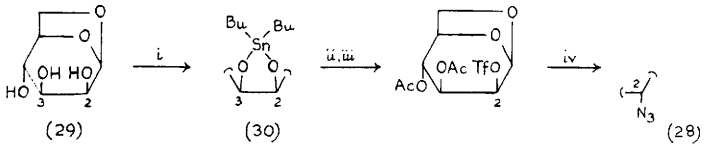


(26) (27) (25)

Reagents: i, BuLi; ii, LAH; iii, MsCl-Py; iv, NaN_3-DMF; v, HgO-$HgCl_2$-MeOH; vi, H_3O^+; vii, Ac_2O-Py

Scheme 6

The azido-group was introduced by sulphonate displacement (Scheme 6).[23,24] A facile preparation of the 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose derivative (28) from 1,6-anhydro-β-D-mannopyranose (29) in 49% yield involved selective 2-O-triflation of the 2,3-O-stannylidene intermediate (30) (Scheme 7).[25]

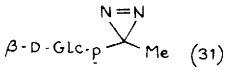


(29) (30) (28)

Reagents: i, Bu_2SnO; ii, CF_3SO_2Cl; iii, Ac_2O-Py; iv, NaN_3-DMF

Scheme 7

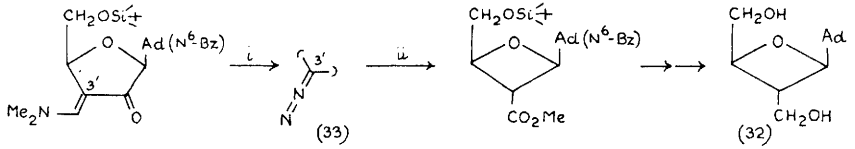
3,7-Anhydro-2-azi-1,2-dideoxy-D-glycero-D-gulo-octitol (31) has been synthesized from the corresponding 1-C-acetyl-1-deoxy-D-glucose tetraacetate, and elaborated into its malto-oligosaccharide analogues (DP 1-5) by cyclodextranase catalysed



(31)

glucosyl transfer from α-cyclodextrin. These azi-compounds inhibited uptake of maltose via the maltose-binding protein-dependent transport system in E. coli. The radiolabelled trisaccharide analogue was used to photolabel the protein's binding site.[26]

Synthesis of oxetanocin (32), an anti-AIDS drug, relied upon the synthesis, and Wolff rearrangement on photolysis of, the diazo-ketone (33) (Scheme 8).[27] Tronchet and co-workers have developed their earlier work on the synthesis of gem-azoacetates

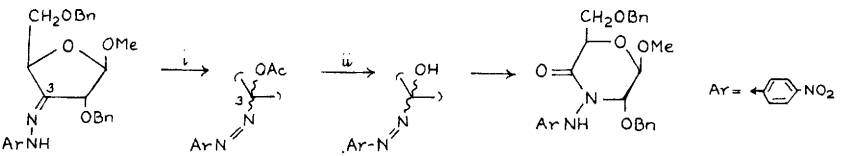


(33) (32)

Reagents: i, $CF_3SO_2N_3$; ii, hν(>280nm)-MeOH

Scheme 8

and the ring expansion of the derived gem-azoalcohols (c.f., Vol.8, p.82) as exemplified in Scheme 9. Earlier examples had



Reagents: i, $Pb(OAc)_4$; ii, NaOMe; iii, KOBu^t

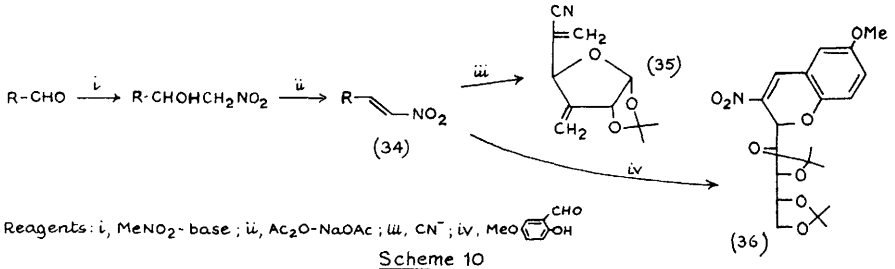
Scheme 9

isopropylidene groups adjacent to the reaction centre, and in such cases the azoacetate formation was stereospecific, the azoalcohols

were more stable, and the rearrangement proceeded better.[28]

3 Nitro-sugars

New antiviral compounds have been identified amongst the electrophilic sugar compounds, i.e., unsaturated nitro-sugars (34) in which R is any of twelve sugar moieties, mostly furano-4-yl derivatives, and their adducts, e.g., compounds (35) and (36) (Scheme 10) which were produced from a pentodialdose and an

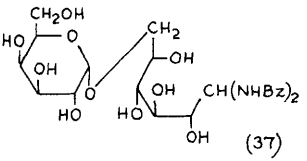


Scheme 10

acyclic pentose derivative, respectively.[29] The synthesis of branched nitro-sugars is covered in Chapter 14.

4 Nitriles, Oximes and Hydroxylamines

The preparation of the octa-O-benzoyl-aldobiononitriles of cellobiose, gentiobiose, lactose, and maltose from the unprotected oximes has been effected by treatment with benzoyl chloride in pyridine at 90°C.[30] Reaction of melibiononitrile perbenzoate with methanolic ammonia yielded the 1,1-dibenzamido-derivative (37) as the major product, isolated in 38% yield.[31] The erythro- and threo-cyanohydrins (38) were obtained in a 4:1 ratio from 2,3-O-isopropylidene-D-glyceraldehyde on reaction with trimethylsilyl cyanide, and were converted to the four carbon lactone synthons (39).[32] The chiral hexane-1,6-dinitrile (40) has been synthesized



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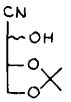

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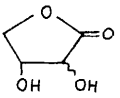
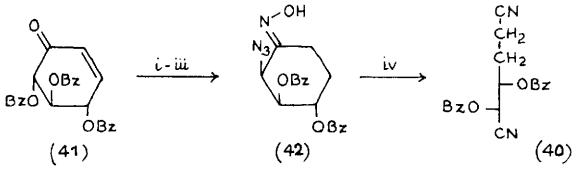


(39)

from D-glucose via the known cyclohexenone (41) which was available from a Ferrier carbocyclization reaction. The α-azido-oxime (42) formed stereospecifically in 50% yield, and underwent

C-C cleavage under the conditions of the kind used for Beckmann rearrangement (Scheme 11).[33]

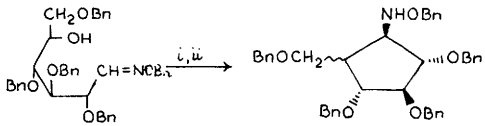


(41) (42) (40)

Reagents: i, H_2-Pd/C ; ii, $NH_2OH.HCl$-Py ; iii, Bu_4NN_3-Et_3N ; iv, $POCl_3$-Py

Scheme 11

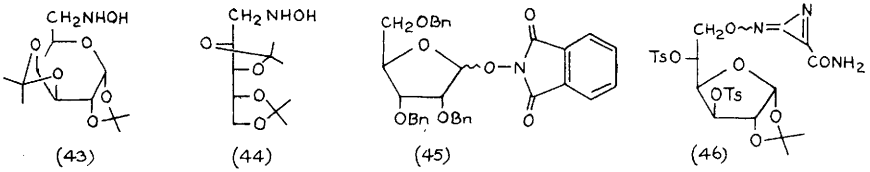
Aminocyclitols have been obtained from sugar oxime derivatives by a radical cyclization procedure, as exemplified in Scheme 12.[34]



Reagents: i, PhOC(S)Cl ; ii, Bu_3SnH

Scheme 12

A variety of terminal deoxy-hydroxylamino-sugars, e.g., compounds (43) and (44), have been synthesized from the corresponding oximes by reduction ($NaBH_3CN$ at pH 3). They were reasonably stable, but oxidized in air to give nitroxide radicals



(43) (44) (45) (46)

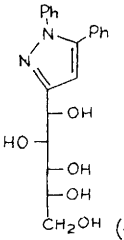
which were studied by e.s.r. spectroscopy.[35] Five N-glycosyloxy-phthalimides, e.g., ribosyl derivatives (45), have been obtained as anomeric mixtures from 1-OH unprotected monosaccharide derivatives by application of the Mitsunobu reaction (Ph_3P-DEAD-N-hydroxyphthalimide).[36] The azirineimine (46) has been obtained in 15% yield by displacement of a 6-tosylate (with KCN-CH_3NO_2-Bu_4NCl-H_2O). Isotope experiments demonstrated that the azirine ring carbons derive from the nitromethane, and the carboxamide group carbon atom comes from the cyanide ion, but the mechanism of the reaction remains obscure.[37]

5 Hydrazones, Osazones, Formazans, and Related Heterocycles

Pentahydroxypentylpyrazoles, e.g., diphenyl-derivative (47), have been prepared by condensation of D-galactose phenylhydrazones with various β-nitrostyrenes, and were converted to pyrazole-3-carboxylic acids.[38,39] Cyclization (by use of Ac_2O) of per-O-acetylated pentose and hexose benzoylhydrazones yielded diastereomeric 2,3-dihydro-1,3,4-oxadiazole derivatives, e.g., the epimeric D-arabinitol-1-yl compounds (48). A correlation between the optical rotations and the stereochemistry of the products was established.[40]

In a study of the deacetylation of acetylated sugar osazones it has been shown that under alkaline conditions and depending upon the substrate, either an external nucleophile (e.g., N_3^-, MeO^-, NH_3) can be incorporated at C-3 or a 3,6-anhydride can be formed. The 3-methoxy-epimers (49) were thus formed from the L-erythro-pentose osazone triacetate presumably by formation and 1,4-addition to a phenylazo-ene intermediate.[41] The 2-acetoxy group of aldose diphenylformazan peracetates is also readily displaced. 2-Deoxy-D-arabino-hexose diphenylformazan (50) was thus formed when penta-O-acetyl-D-glucose or -D-mannose N,N'-diphenylformazan was treated with sodium borohydride.[42]

The regioselective formation of arylhydrazones at position 2 of dehydro-L-ascorbic acid has been effected with acetone hydrazone in aqueous medium.[43] The synthesis and heterocyclization of 2- and 2,3-bis-(P-fluorophenyl)hydrazones of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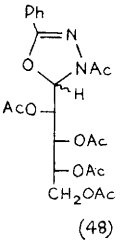
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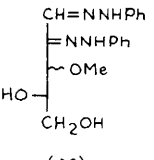
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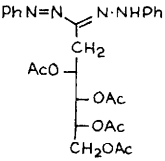
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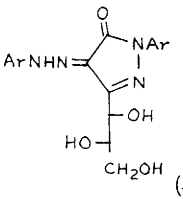
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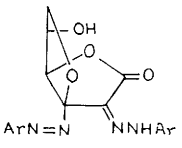
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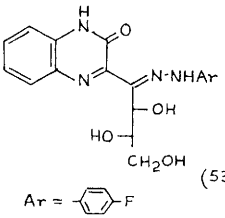
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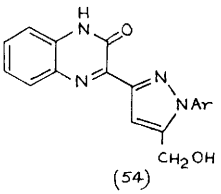
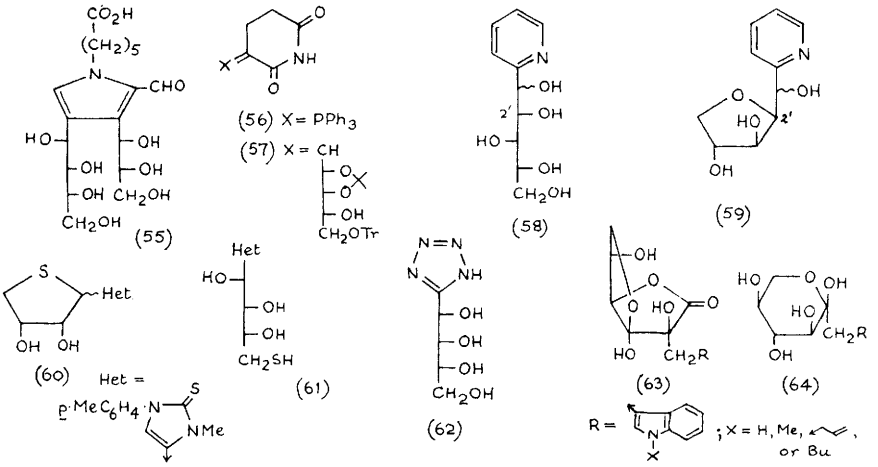

(54)

dehydro-L-ascorbic acid, and some reaction of the products have been reported. The 2,3-bishydrazone gave the pyrazoline-4,5-dione (51) (with NaOH then AcOH) and the 3,6-anhydride (52) (with $CuCl_2$).[44] The quinoxalinone (53) has been obtained from sequential reaction of dehydro-L-ascorbic acid with *o*-phenylenediamine then P-fluorophenylhydrazine, and converted into the pyrazolyl-quinoxaline (54).[45] Studies have been reported on the isopropylidenation of L-threo-glycerol units,[46] and the benzylidenation of L-threo- and D-threo- glycerol units,[47] attached to heterocycles.

6 Other Heterocyclic Derivatives

Sulphite inhibition of the Maillard reaction of glucose and 6-aminohexanoic acid has been shown to be dependent upon the formation of compounds such as pyrrole (55).[48] Three carbohydrate aldehydes/hemiacetals have been treated with the Wittig reagent (56) to produce 2-substituted glutarimides, such as (57).[49] The use of compound (57) to make C-nucleosides is covered in Chapter 20. The formation and cyclization of 2-(pentitol-1-yl)pyridines has been examined. Addition of 2-trimethylsilylpyridine to 2,3,4,5-tetra-O-acetyl-aldehydo-D-xylose gave, after deacetylation, a mixture (58) of D-gulo- and D-ido-isomers, which were independently cyclized (H_2SO_4-Pr^iOH) to the epimeric anhydrides (59) in which the C-2′ stereochemistry was retained.[50]



The synthesis of new glycoheptofurano[2,1-d]imidazoline-2-thiones from the reaction of 2-amino-2-deoxy-heptoses and aryl

isothiocyanates, and the conversion of such products to 4-(pentitol-1-yl)-4-imidazolidine-2-thiones, has been further detailed (c.f., Vol.21, p.103).[51] The thio-C-nucleosides (60) have been obtained by acid-catalyzed dehydration of the imidazolidine-2-thione (61).[52]

D-Ribose oxime has been converted into the tetrazole (62) by condensation of the derived D-ribononitrile tetrabenzoate with azide ion.[53]

Treatment of the ascorbigens (63) with base (pH 11-12, 20°, 12 h) gave C-1 substituted L-sorbopyranoses (64) by ring-cleavage of the lactone, decarboxylation, and rearrangement.[54]

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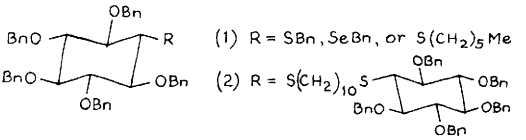
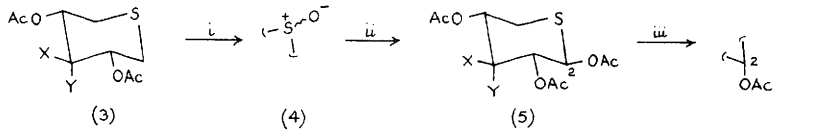
11
Thio- and Seleno-sugars

A review on the synthesis and application of sugar thio- and seleno-phosphates has appeared.[1] The di-n-alkyl (e.g. di-n-octyl) dithioacetals of D-glucose, D-galactose, D-mannose, D-arabinose, D-lyxose, D-xylose, and L-rhamnose have been investigated by optical microscopy and differential scanning calorimetry; all except the L-rhamnose dithioacetals showed complex melting behaviour and thermotropic liquid crystal behaviour, the derivatives of D-xylose exhibiting the characteristic at room temperature. The relationship of these properties to chemical structure is discussed.[2,3] Liquid crystalline behaviour has also been reported for monothio- (and a monoseleno-) scillitol ethers (1) and for the bis-thioether (2) with a C_{10} spacer, which displayed a novel type of metaphase.[4]



3-Deoxy-6-thio-D-manno-2-octulosonic acid (6-thio-KDO), a potential inhibitor of CMP-KDO synthetase, has been prepared. Its ammonium salt failed however to inhibit this enzyme.[5] 3-Deoxy-5-thiopentopyranoses with branch-points at C-3 have been synthesized from non-carbohydrate precursors (3) (see Vol 20, p 148 for their preparation) as shown in Scheme 1. The Pummerer rearrangement of



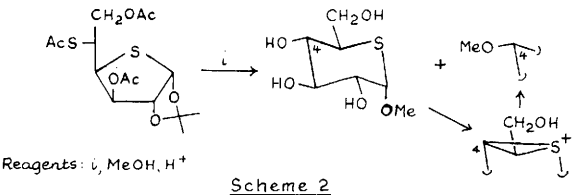
Reagents: i, MCPBA; ii, Ac_2O-p-TsOH-CH_2Cl_2; iii, $HClO_4$-Ac_2O-AcOH

X, Y = Electron-withdrawing groups, e.g. CO_2Et, CN, NO_2

Scheme 1

sulphoxides (4) produced β-anomers (5) stereospecifically; these could be isomerised to the α-anomers by exposure to perchloric

acid.[6] Participation of the ring sulphur atom has been encountered in the conversion of 5-thio-D-glucofuranose derivatives to 5-thiopyranosides outlined in Scheme 2; several

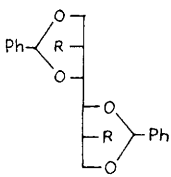


Reagents: i, MeOH, H^+

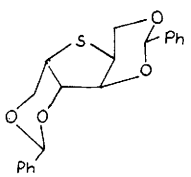
Scheme 2

related rearrangements via episulphonium ions are also described.[7] Radical deoxygenation of the 2,5-bis(S-methylthiocarbonyl)-D-mannitol derivative (6) gave unexpectedly the thiolane (7) in 80% yield, as is also mentioned in Chapter 18.[8]

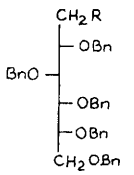
The 1-thio-D-glucitol derivative (9) has been obtained in three steps from 2,3,4,6-tetra-O-benzyl-D-glucose by way of the tosylate (8). Mono- and di-sulphide bridged dimers (10) and (11)



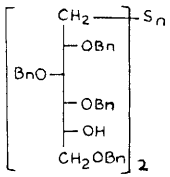
(6)



(7)

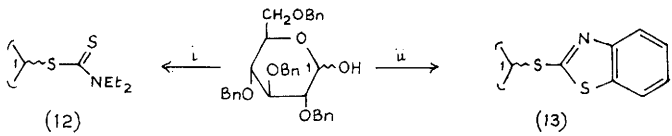


(8) R = OTs
(9) R = SH



(10) n = 1
(11) n = 2

were then formed by use of thiol (9) in the displacement of the tosylate group of compound (8) and by hydroperoxide oxidation of thiol (9), respectively. The benzyl protecting groups could be removed by subsequent acetolysis and transesterification.[9] For the preparation of thioglycosyl N,N-diethyl dithiocarbamates such as (12) and thioglycosyl benzothiazoles such as (13) from protected reducing monosaccharides a one-pot, phase-transfer method involving intermediate glycosyl tosylates has been developed. Examples are given in Scheme 3. The procedure is

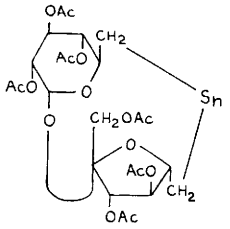


(12) (13)

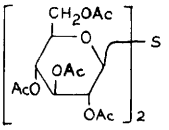
Reagents: i, Et_2NCS_2Na - p.TsCl - NBu_4Cl - C_6H_6, NaOH (50% aq.); ii,  - SH - pTsCl - Bu_4NCl, C_6H_6 - NaOH (50% aq.)

Scheme 3

compatible with acid labile protecting groups and gives, in general, high yields of anomeric product mixtures.[10,11] The syntheses of an aryl thioglycoside of sialic acid and of a 3′-thiothymidine derivative by nucleophilic substitution are covered in Chapters 3 and 20, respectively. Attempts to make 6,6′-dithiosucrose derivatives from 6,6′-dibromo-6,6′-dideoxysucrose hexaacetate by double displacement were successful when, for example, thioacetate or thiocyanate were employed as nucleophiles. However, use of O-ethyl dithiocarbonate or of thiourea followed by metabisulphite led to formation of S-bridged compounds (14) and (15) in mediocre yields.[12] Symmetrical S-bridged disaccharides, e.g. (16), are readily available from glycosyl bromides and sodium



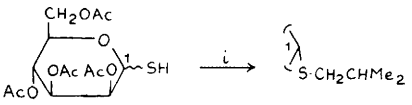
(14) n = 1
(15) n = 2



(16)

sulphide under phase-transfer conditions. Unsymmetrical analogues resulted from reaction between glycosyl halides and protected or unprotected 1-thio-D-glucose.[13] S-Linked trisaccharides are mentioned in Chapter 4.

Radical addition of a 1-thiosugar to an alkene has been used in the preparation of a number of thioglycosides as exemplified in Scheme 4; with regard to the anomeric configuration of the

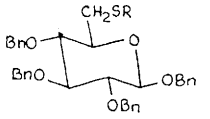


Reagents: i, $CH_2{=}CMe_2$ - AIBN

Scheme 4

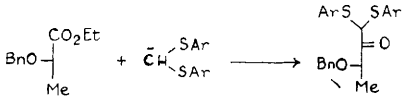
products the "trans-rule" seems to apply.[14] 1-Thiohex-2-enopyranoses have been synthesized from glycal ethers and esters by treatment with TMS-thiols and BF_3 etherate, a procedure which does not yield the thermodynamic 3-substituted products; details are given of the compatibilities of this reaction.[15] Addition of O,O-dialkylphosphorodithionic acids to peracylated glycals is treated in Chapters 3 and 12. 6-Thio-β-D-glucose derivatives (17)-(20) have been obtained by treatment of the parent thiol with

PhNCO, PhNCS, 4-$BrC_6H_4COCH_2Br$, and $ClCH_2CO_2Et$ respectively, and the sulphides (19) and (20) were then oxidised to the corresponding sulphones.[16]



(17) R = PhNHCO·
(18) R = PhNHCS·
(19) R = Br-C$_6$H$_4$-CH$_2$·
(20) R = EtO_2C-CH_2·

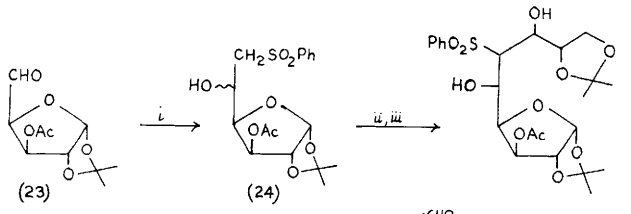
4-Deoxy-L-threose and -erythrose derivatives are available from ethyl O-benzyl-L-lactate by chain elongation with the formyl anion equivalent (21) and subsequent reduction of ketone (22) (Scheme 5).[17] The anion of methyl phenyl sulphone has been added



(21) (22)

Scheme 5

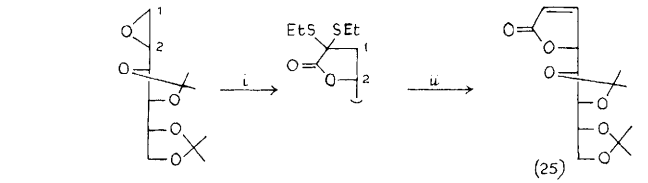
to dialdose derivative (23), as shown in Scheme 6, to give a 73:27 mixture of D-gluco- and L-ido-β-hydroxysulphones (24). From the gluco-isomer higher carbon sugars have been synthesized by



(23) (24)

Scheme 6

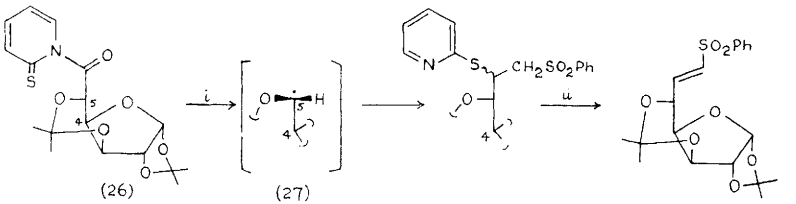
deprotonation and addition (Scheme 6) of the resulting carbohydrate dianion to aldehydes (e.g. isopropylidene-D-glyceraldehyde).[18] A new synthesis of 3-deoxy-D-manno-2-octulosonic acid enol lactone (25) involves epoxide opening by a sulphur stabilised carbon nucleophile (Scheme 7).[19] Similar experiments in the L-gulo-series have also been reported.[20] The reaction of lithium dithiane with a 6-deoxy-6-iodo-D-galactopyranose derivative is referred to in Chapter 13. Chain extension by addition of carbohydrate-derived radicals to electron-poor alkenes has been reported. For example, radical (27) generated from 1,2,3,5-di-O-isopropylidene-β-D-



Reagents i, $(EtS)_2CHCO_2H$ · BuLi ; ii, NBS

Scheme 7

galactofuranuronic acid via the 2-thiopyridone ester (26) added to phenyl vinyl sulphone with retention of configuration at the radical centre. The addition product was further transformed as detailed in Scheme 8. This method has been applied to uronic

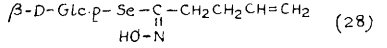


Reagents: i, hν, $CH_2=CHSO_2Ph$; ii, MCPBA · PhMe (reflux)

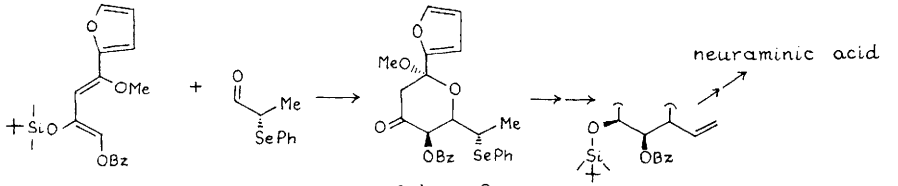
Scheme 8

acids derived from methyl pentofuranosides and from D-ribonucleosides and is also mentioned in Chapter 13.[21]

The desulphoselenoinolate (28) has been prepared from 1-selenoglucose for use as analytical reference in a search for



naturally occurring compounds of this kind.[22] In a new total synthesis of neuraminic acid outlined in Scheme 9 the dihydropyrone (31) was formed regio- and stereo-selectively by



Scheme 9

cyclocondensation of diene (29) with (S)-(phenylseleno)aldehyde (30) which is available in two steps from methyl (R)-lactate. In a later reaction step oxidative elimination of the seleno function furnished a terminal alkene suitable for elaboration of the

hydroxylated side chain. A new total synthesis of KDO was achieved by use of a similar strategy involving the enantiomer of pyrone (31). These reactions are also referred to in Chapters 3 and 16.[23]

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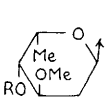
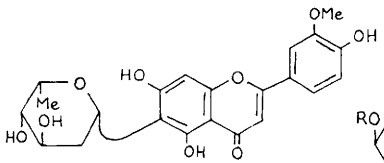
12
Deoxy-sugars

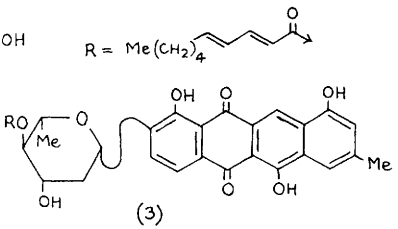
L-Sarmentose (2,6-dideoxy-3-O-methyl-L-xylo-hexose) has been found as the α-glycosidic sugar component (1) in pregnane glycosides from the plant Trachelospermum asiaticum,[1] the D-enantiomer having been encountered in related materials. The new sugar, 3-deoxy-D-lyxo-heptulosonic acid, has been found as a glycosidically bound component in the ubiquitous plant cell wall polysaccharide rhamnogalacturonan II.[2] The first two examples of naturally occurring flavonoid C-dideoxyglycosides have been reported. Alternanthin (2) from Alternanthera philoxeroides contains a C-β-L-boivinopyranoside moiety,[3] while the benzanthraquinone C-glycoside (3) from a Streptomyces strain contains an isomeric deoxy-sugar of



(1)
R = H or Ac



(2)



(3)

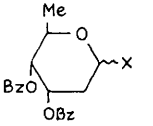
undetermined absolute configuration.[4] The occurrence of deoxy-sugar residues in antibiotic substances is covered in Chapter 19.

Evidence has been presented that the biosynthesis of 3,6-dideoxyhexoses may proceed via a radical reduction process at C-3.[5] A study of the anomerisation of 5-deoxy-L-pentoses is covered in Chapter 21.

2-Deoxy-D-arabino-hexose has been converted into its [6-^{13}C]-labelled analogue by cleavage and reconstruction of the C5-C6 bond. Cleavage was effected by periodate treatment of the methyl 2-deoxy-α-D-arabino-hexofuranoside, formed in good yield from the free sugar (with 1% CF_3CO_2H in MeOH). The resulting 5-aldehyde was converted to a mixture of cyanohydrins with labelled cyanide ion to reconstruct the hexose skeleton.[6]

2,6-Dideoxy-β-D-ribo-hexopyranose tribenzoate (4) has been prepared in 72% yield from digitoxin, a naturally occurring

terpenoid digitoxose trisaccharide, by a hydrolysis-benzoylation sequence. It was converted to the glycosylating agents (5), and to the tert-butyl glycosides (6), starting materials for the



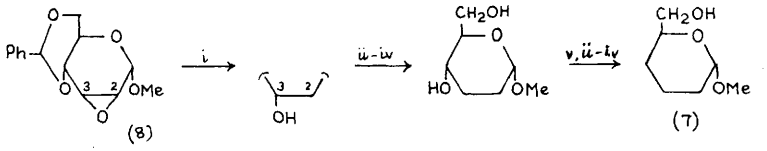
(4) X = β-OBz
(5) X = α-Cl; α-Br; α,β-SEt
(6) X = α,β-OBu^t

preparation of other 2,6-dideoxy-sugars. The anomeric deprotected glycosides (6) were more easily separated chromatographically than other glycosides of this sugar.[7]

A report has appeared on the enzymatic hydrolysis of α,α-trehalose and various deoxy- and dideoxy-analogues.[8] In a study on the biosynthesis of sucrose, mono-deoxy-glucose analogues of UDP-glucose have been shown to act as donors, but more slowly than UDP-glucose itself.[9] The synthesis of, and conformations adopted by, a variety of methyl β-D-galabiose analogues (1,4-α-linked disaccharides) including the 2-, 3- and 6-deoxy-derivatives, has been reported.[10,11] The 2- and 6-deoxygenation was effected by radical and catalytic reduction of a 2-xanthate and a 6-iodide, respectively.

The absolute stereochemistry of oleandrose and digitoxose, which can co-occur as glycosidic units in natural products, can be determined by h.p.l.c. on a chiral-phase column [(S)-1-(α-naphthyl)ethylamine residues on aminopropylsilica], the oleandroses as their methyl glycoside O-3,5-dinitrophenylcarbamate derivatives,[12] and the digitoxoses as their 3,4-O-isopropylidene-1-O-(3,5-dinitrophenylcarbamates).[13]

Trideoxy-glycoside (7), a potential chiral synthon, has been obtained from epoxide (8) by three sequential deoxygenation steps (Scheme 1).[14]

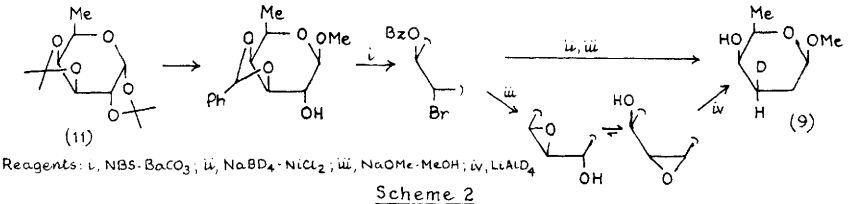


Reagents: i, LAH; ii, NaH-CS_2-MeI; iii, Bu_3SnH; iv, H_3O^+; v, TrCl-Py

Scheme 1

Specifically deuterated abequosides (3,6-dideoxy-L-xylo-hexosides) (9) and (10) have been synthesised for use in biosynthesis studies. The 6-deoxy starting materials (11) and (12), shown in Schemes 2 and 3, were obtained from D-galactose and

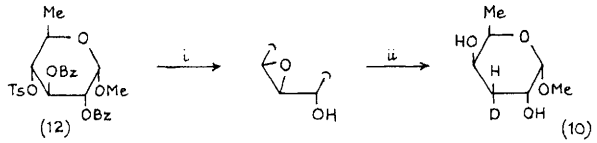
methyl α-D-glucoside (in 9 steps), respectively.[15]



Reagents: i, NBS-$BaCO_3$; ii, $NaBD_4$-$NiCl_2$; iii, NaOMe-MeOH; iv, $LiAlD_4$

Scheme 2

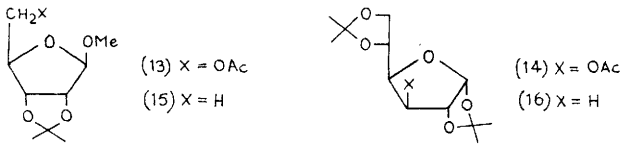
A new reagent system (Ph_3SiH - $Bu^tO_2Bu^t$, 140°C) has been used to convert five acetylated sugars, e.g., (13) and (14), into



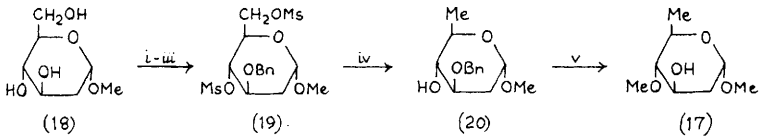
Reagents: i, NaOMe-MeOH; ii, $LiAlD_4$

Scheme 3

the corresponding deoxy-sugars, e.g., (15) and (16) which were obtained in 71 and 66% yield, respectively.[16]



Methyl 2,6-dideoxy-4-O-methyl-α-D-arabino-hexopyranoside (17) (see also ref. 30) has been synthesised in 7 steps, 33% overall yield from the 2-deoxy-glycoside (18) (Scheme 4).



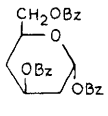
Reagents: i, $PhCH(OMe)_2$-TsOH; ii, BnBr-NaH; iii, H_3O^+; iv, MsCl-Py; v, LAH, vi, MeI - NaH, vii, Na-NH_3(l);

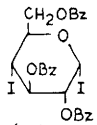
Scheme 4

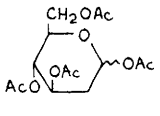
Treatment of the 4,6-dimesylate (19) with lithium aluminium hydride resulted in C-O cleavage at C-6, and O-S cleavage of the sulphonyloxy group at C-4. An alternative route to intermediate (20), involving the reaction of a 4,6-O-benzylidene derivative with N-bromosuccinimide, was also reported.[17] Reductive cleavage ($LiAlH_4$) of a 6-tosylate has also been employed in the synthesis

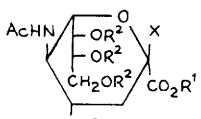
of D-quinovosamine and the methyl glycoside of D-fucosamine from D-glucosamine and D-galactosamine, respectively.[18]

Radical reduction (with Bu_3SnH) of thioacylated sugars and bromo-sugars continues to be a popular means of access to deoxy-sugars. A number of 2′-deoxy-β-D-threo-pentofuranosyl nucleosides have been obtained by Barton deoxygenation of the protected 2′-O-(phenoxythiocarbonyl)-D-xylofuranosyl nucleoside precursors.[19] Further details on these and related syntheses can be found in Chapter 20. Giese and co-workers have published in full[20] and extended[21] their work on the production of 2-deoxy-sugars through a novel radical rearrangement reaction which occurs during the reduction of peracylated glycosyl halides and phenylselenides (c.f., Vol.21, p.121). The 2,4-dideoxy-sugar (21) was obtained in 50% yield on treatment (Bu_3SnH - AIBN) of the 1,4-diiodide (22) under conditions of high dilution. While tetra-O-acetyl-α-D-glucopyranosyl bromide gave the α-acetate (23), acetobromomannose

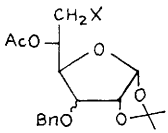
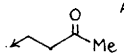

(21)


(22)

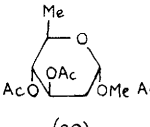

(23) α-
(24) β-

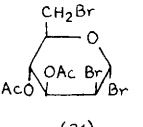

(25) X = R¹ = R² = H
(26) X = Cl, R¹ = Me, R² = Ac

gave the β-acetate (24). The "β-anomer" (25) of 2-deoxy-N-acetylneuraminic acid has been synthesised from the glycosyl chloride (26) via tributyltin hydride reduction, and from a 2,3-ene by catalytic reduction ($Pd/C-H_2$).[22] The "α-anomer" of (25) was the major product of catalytic reduction of chloride (26).[22,23] Higher carbon deoxy-sugars, e.g., (27), have been synthesised in moderate yield by trapping the radicals generated from the 6-iodides (28) with methyl vinyl ketone or other electron-deficient alkenes. The D-allo-iodide in addition gave the 6-deoxy-3-O-(1-phenylalkyl)-derivatives (29) in 15% yield following a 1,6-hydrogen shift undergone by the initial radical.[24]


(27) X = 
(28) X = I

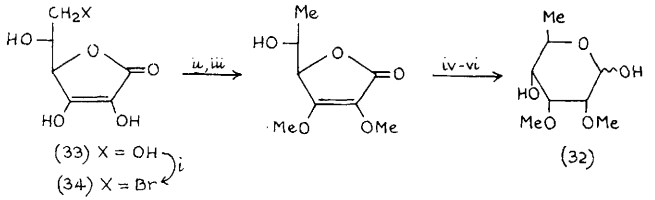
(29)


(30)


(31)

Methyl 3,4-di-O-acetyl-2,6-dideoxy-D-arabino-hexopyranoside (30) has been synthesised from the known tribromide (31) in two steps (i, MeOH-H_2SO_4; ii, H_2-Pd/C). Glycosylations with (31)

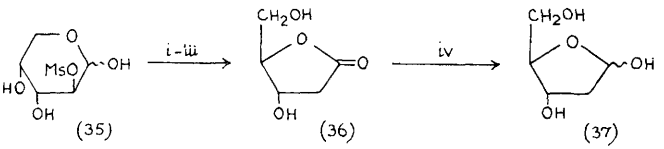
promoted by halide ions or mercury(II) iodide give α-glycosides in good yield, so that the above appears to be a general route to α-glycosides of 2,6-dideoxy-D-arabino-hexopyranose.[25] D-Mycinose (32) has been synthesised from isoascorbic acid (33) via the known 6-bromide (34) (Scheme 5).[26] Deoxy-derivatives of certain sugar lactones are covered in Chapter 16.



Reagents: i, HBr-HOAc; ii, CH_2N_2; iii, H_2-Pd/C-Et_3N-MeOH; iv, Rh(Diphos-4)(norbornadiene)$^+BF_4^-$-H_2 (1850psi); v, Bu^i_2AlH; vi, H_3O^+

Scheme 5

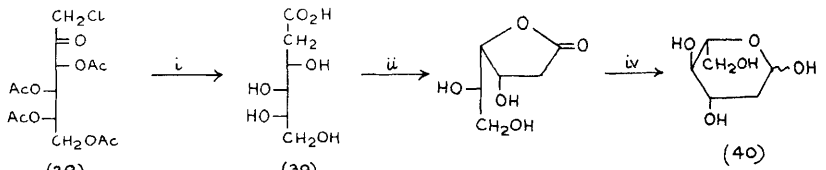
Gakhokidze and co-workers have reported further applications of an unusual lead(II) hydroxide induced redox rearrangement wherein aldoses and ketoses bearing a leaving group α- to the anomeric centre are transformed into 2-deoxy-aldonic acids (c.f., Vol.21, p.154). The D-arabinose 2-mesylate (35), or the corresponding 2-tosylate, thus gave lactone (36) from which 2-deoxy-D-erythro pentose (37) was obtained on reduction (Scheme 6).[27] 1-Chloro-1-deoxy-L-fructose tetraacetate (38) gave 2-deoxy-L-gluconic acid (39) from which 2-deoxy-L-glucose (40) was



Reagents: i, $Pb(OH)_2$-H_2O; ii, H^+; iii, Δ - H_2O; iv, $NaBH_4$ (pH 4)

Scheme 6

obtained (Scheme 7). 1-Chloro-1-deoxy-D-glucoheptulose pentaacetate similarly gave 2-deoxy-D-gluco-heptonic acid. The

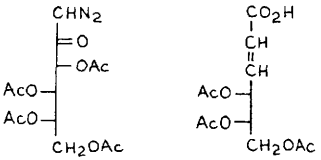


Reagents as in Scheme 6

Scheme 7

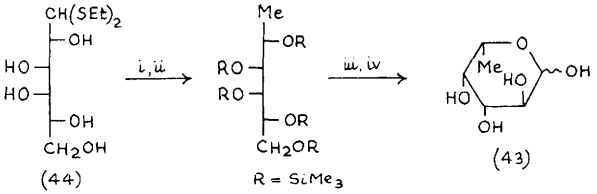
starting 1-chloro-ketoses were available from L-arabinose and D-

glucose, respectively, via 1-diazo-ketoses. The 1-deoxy-1-diazo-L-fructose derivative (41) gave the hex-2-enoic acid (42) in the presence of silver oxide as catalyst.[28]



(41) (42)

An efficient synthesis of L-fucose (43) in 54% overall yield from D-galactose dithioacetal (44) utilized a recently developed selective Collins oxidation of the primary centres in pertrimethylsilylated sugars (step iii, Scheme 8).[29]

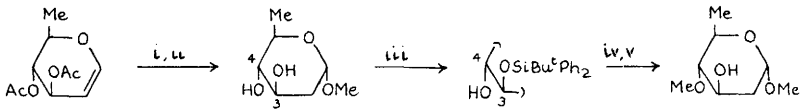


(44) R = $SiMe_3$ (43)

Reagents: i, Raney Ni ; ii, Me_3SiCl - HMDS - Py ; iii, CrO_3 - Py ; iv, Resin(H^+) - C_6H_6 - H_2O

Scheme 8

Another synthesis of methyl 2,6-dideoxy-4-O-methyl-α-D-arabino-hexopyranoside (17) (c.f., ref. 17), this time from di-O-acetyl-6-deoxy-D-glucal (45) (Scheme 9), confirmed the identity of the sugar at the non-reducing terminus of the tetrasaccharide moiety in the major phenol glycolipid of Mycobacterium kansasii.



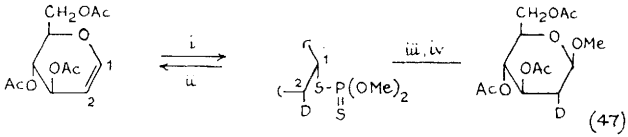
(45) (46) (17)

Reagents: i, $Hg(OAc)_2$ - MeOH ; ii, $NaBH_4$; iii, Bu^tPh_2SiCl - imidazole - DMF ; iv, MeOTf - BuLi ; v, Bu_4NF

Scheme 9

The enantiomer of (17) was synthesised from L-rhamnal by an analogous procedure. Methylation at O-4 of the monosilyl ether (46) with butyl lithium - methyl iodide was unsatisfactory due to desilylation, but a good yield (60-70%) of the desired product was obtained with one equivalent of methyl triflate and base (either BuLi or 2,6-di-tert-butylpyridine).[30] Further details have been published on the cis-addition of O,O-dialkylphosphorodithioic acids to peracetylated glycals, and the conversion of the products into 2-deoxy-glycosides (c.f., Vol.20, p.21). By using the

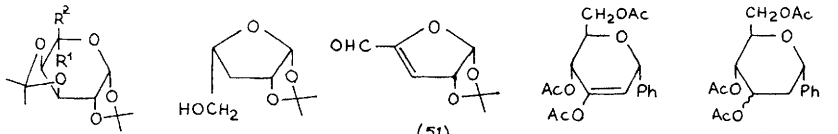
S-deuterated phosphorodithioic acid, the specifically deuterated β-glycoside (47) was synthesised (Scheme 10).[31]



Reagents: i, $(MeO)_2P(S)SD$; ii, Δ, MeCN-K_2CO_3; iii, MeONa-NaOH; iv, Ac_2O-Py.

Scheme 10

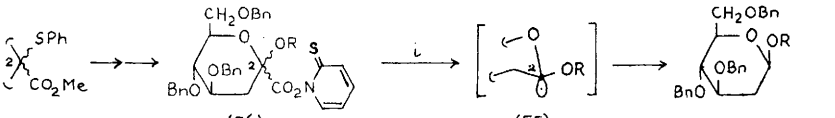
The 6-deoxy-β-L-altropyranose derivative (48) was obtained by stereoselective hydrosilylation (Me_2PhSiH - [Rh(norbornadien)Cl]$_2$) of the 5,6-ene (49) followed by protodesilylation (Bu_4NF).[32] The stereocontrolled synthesis of 3-deoxy-1,2-O-isopropylidene-β-L-threo-pentofuranose (50) from diacetoneglucose involved reduction of the known enal (51) first with sodium borohydride then with nickel boride.[33] Only moderate stereoselectivity was attained in the reduction [with KBH_4, $LiAlH_4$ or $NaAlH_2(OCH_2CH_2OMe)_2$] of the α-D-erythro-enol ester (52) or its α-D-threo-epimer, C-3 epimeric mixtures of 2-deoxy-C-glycosides e.g., (53), resulting in both cases.[34]



(48) R^1 = Me, R^2 = H
(49) R^1, R^2 = CH_2

(50) (51) (52) (53)

A novel synthesis of 2-deoxy-β-D-glucosides (54) (Scheme 11) has used Barton's O-acylthiohydroxamate methodology, good β-stereoselectivity being assured by the requirement that the 1-alkoxyglucos-1-yl radicals (55) generated by radical



(56) (55) (54) R = Me, p-Tolyl, 3β-Cholestanyl

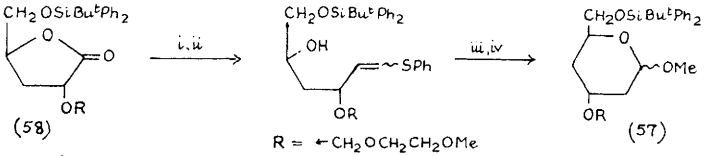
Reagents: i, hν (tungsten lamp) - $Me(CH_2)_8CMe_2SH$

Scheme 11

decarboxylation of ulosonic acid glycosides (56) will react by way of the lone electron in the axial position. Yields were in the 36-50% range, with β:α ratios of 10:1 or higher.[35]

The 2,4-dideoxysugar (57), a key intermediate in mevinic

acid synthesis, has been obtained by application of a novel one carbon expansion of lactone (58) using an alkoxymercuration - demercuration sequence (Scheme 12).[36]

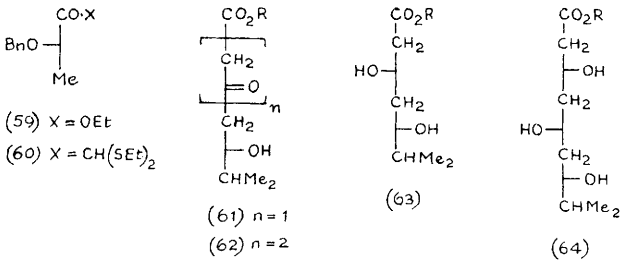


Reagents: i, Bu^i_2AlH; ii, $Ph_3P{=}CHSPh$; iii, $Hg(OAc)_2$-HgO-MeOH; iv, $NaBH_4$

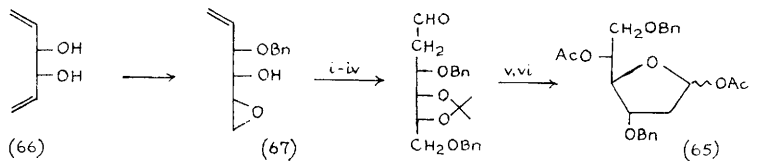
Scheme 12

Benzyl 2,4-di-O-benzyl-6-deoxy-α-L-talopyranoside has been obtained from benzyl 2,3-O-isopropylidene-α-L-rhamnopyranoside by an improved procedure involving inversion at C-4 using an oxidation-reduction sequence, and it was utilised in a trisaccharide synthesis (Chapter 4).[37]

Deoxy-sugars have also been constructed from non-carbohydrate starting materials. One-carbon extension of the L-lactate derivative (59) gave dithioacetal (60) from which various 4-deoxy-L-threose and -erythrose derivatives were synthesised.[38] Tetramethylammonium triacetoxyborohydride has been used to selectively reduce β-hydroxy-ketones to anti-1,3-diols, as in the conversion of ketones (61) and (62) to diol (63) and triol (64),



respectively. The reductions proceed by intramolecular hydride delivery.[39] The 2-deoxy-D-arabino-hexofuranose derivative (65)



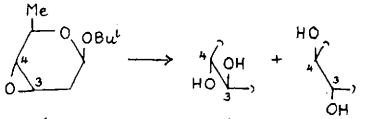
Reagents: i, $Ti(OBn)_4$; ii, Me_2CO-$CuSO_4$; iii, BH_3SMe_2, then H_2O_2-NaOH; iv, PCC; v, HOAc-H_2O; vi, Ac_2O-Py

Scheme 13

has been obtained with its β-pyranose isomer from meso-divinylglycol (66) via the known D-epoxide (67) (Vol.20, p.127)

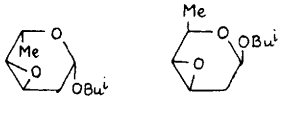
(Scheme 13).[40]

Enzymic hydrolysis of the racemic mixture of β-D-ribo-epoxide (68) and its L-enantiomer (69) using microsomal epoxide hydrolase ('MEH') was found to be enantioselective, but not regiospecific. Thus the D-epoxide gave the D-arabino- and D-xylo-diols (70) and (71) in an 88:12 ratio (Scheme 14), while the L-epoxide (69) remained unreacted.[41] In reviewing earlier work on



(68) (70) (71)

Scheme 14



(69) (72)

the enzymic hydrolysis of the corresponding β-DL-lyxo-epoxide (Vol.20, p.128), an incorrect structure for the unhydrolysed epoxide was shown; it should be (72).

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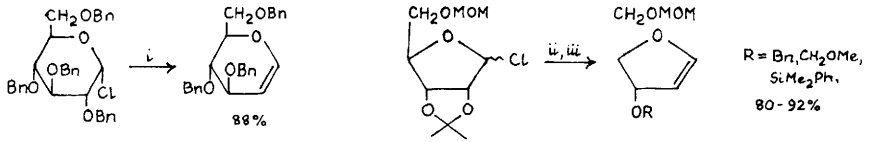
13
Unsaturated Derivatives

1 Glycals

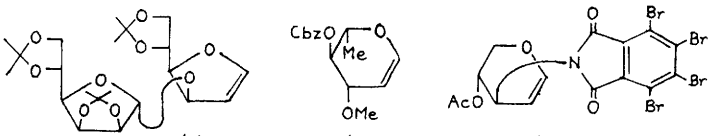
An apparently useful new means of converting tetra-O-acetyl-α-D-glucopyranosyl bromide into tri-O-acetyl-D-glucal involves the use of aluminium amalgam in aqueous tetrahydrofuran; an 85% yield is claimed.[1] Potassium-graphite laminate, (C_8K) readily prepared from potassium and graphite melt, in tetrahydrofuran, has proved to be a simple reagent for the conversion of glycosyl halides carrying O-2 alkyl or acetal substituents into glycals. Yields in excess of 80% are reported and the reaction can be applied in the furanoid or pyranoid series (Scheme 1). Again it looks to have



Reagents: i, C_8K; ii, C_8K (2 mol.); iii, RX (halide)

Scheme 1

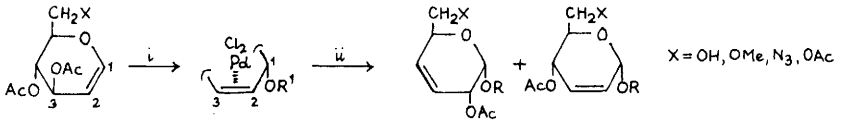
considerable potential value and notably was applied to the efficient synthesis of the disaccharide glycal derivative (1).[2] The glycal derivatives (2)[3] and (3)[4] were prepared by elimination reactions from the corresponding 2-deoxyglycopyranosyl chlorides.



(1) (2) (3)

Other 3-amino-3-deoxyglycal derivatives, precursors of modified anthracycline components, are reported in Chapter 9.

On treatment with palladium chloride in the presence of an alcohol several D-glucal derivatives are converted into glycosidic palladium(II) π-complexes which, on reduction, afford mainly 3,4-unsaturated products formed by allylic rearrangement together with much smaller proportions of the 2,3-alkenes (Scheme 2). The

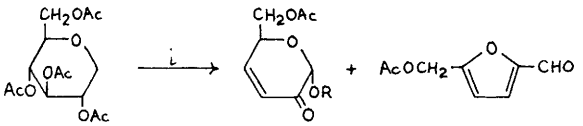


Reagents: i, $PdCl_2$-ROH ; ii, $NaBH_3CN$

Scheme 2

reaction did not proceed in the presence of phenylthio- or N-acetylamino-groups at C-6, and in the cases of D-xylal and L-rhamnal compounds hex-2-enopyranosides were the only products, suggesting that some co-ordination involving the C-6 substituent is necessary for allylic rearrangement to occur.[5]

In the area of 2-substituted glycals it has been shown that chiral pyranones are available directly by treatment with alcohols and Lewis acids, but some furans are formed concurrently (Scheme 3). Presumably the main products are derived by nucleophilic

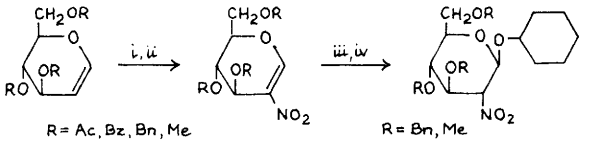


Reagents : i, ROH, $SnCl_4$ (0°c)

Scheme 3

attack by the alcohols at C-1 with concurrent displacement of the C-3 oxygenated substituent followed by selective hydrolysis of the vinyl ester at C-2 and β-elimination of the acyloxy group at C-4.[6]

2-Nitroglycal derivatives can be made from the corresponding unsubstituted glycals and are subject to stereo-selective additions of alcohols (Scheme 4).[7] Deprotonation of compound (4)

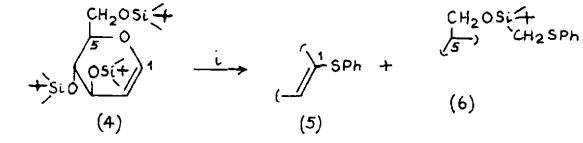


Reagents: i, $NO_2^+BF_4^-$; ii, Et_3N ; iii,  -OH, TLOEt ; iv, $(Me_2NCH_2)_2$

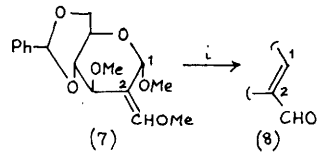
Scheme 4

with t-butyllithium and quenching with diphenyldisulphide gave only 15% of the desired product (5) together with 19% of compound (6) derived following deprotonation of a silyl-bound methyl group (Scheme 5).[8]

The 2-formylglycal derivative (8) was prepared from a 2-uloside by way of the Horner-Wittig product (7)[9] (Scheme 6; see Chapter 14 for references to related branched-chain glycals).



Scheme 5

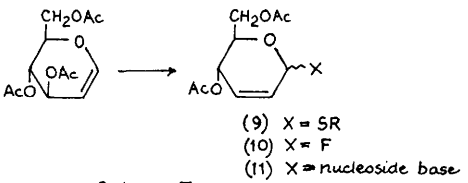


Scheme 6

Attempts to use appropriate glycal derivatives with carbomethoxy or acetoxymethyl groups at C-1 and the N-iodosuccinimide procedure for the synthesis of neuraminic acid glycosides and disaccharides were successful only when simple alcohols were used (Chapter 3).

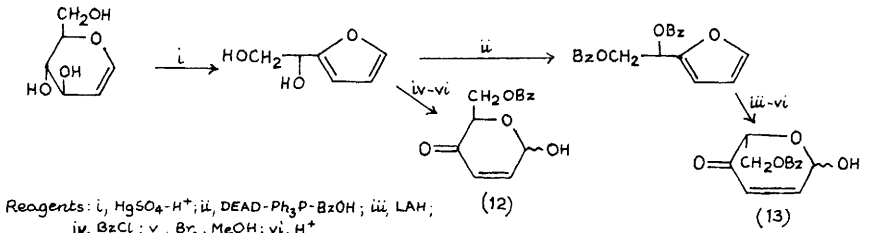
2 Other Unsaturated Derivatives

The rearrangement of glycal derivatives to 1-substituted 2-enose derivatives has been applied to the preparation of: i) 2,3-dideoxy-1-thiohex-2-enopyranosides (9, trimethylsilylated thiols and boron trifluoride; details of the complexities of the reaction are reported);[10] ii) 2,3-dideoxyhex-2-enopyranosyl fluorides [10, pyridine poly(hydrogen fluoride)];[11] iii) 2′,3′-unsaturated nucleosides (11, purine or pyrimidine derivatives with trityl perchlorate)[12] (Scheme 7).



Scheme 7

D-Glucal has also been used as a source of the epimeric hex-2-en-4-ulose epimers (12) and (13) (Scheme 8), and the latter gives access to hexose compounds of the L-series.[13] The exocyclic 2,3-unsaturated compound (14) was prepared from a 1-C-acetyl



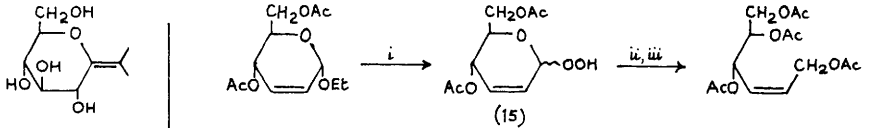
Reagents: i, $HgSO_4$-H^+; ii, DEAD-Ph_3P-BzOH; iii, LAH; iv, BzCl; v, Br_2, MeOH; vi, H^+

Scheme 8

analogue by reduction of the carbonyl group with labelled hydride, tosylation of the alcohol and base-catalysed elimination. The product was required as a probe for investigating stereochemical aspects of glycosylase catalysis.[14]

Reference is made to 2,3-unsaturated 1,6-anhydrohexofuranose compounds in Chapter 5.

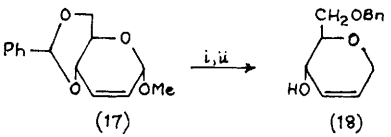
The formation of the hydroperoxide (15) and its reductive ring opening provides means of obtaining the cis-alkene (16) (Scheme 9).[15] Selective reduction of the well known alkene (17)



Reagents: i, H_2O_2-MoO_3; ii, $NaBH_4$; iii, Ac_2O-Py

Scheme 9

gives efficient access to the D-erythro-dihydropyran compound (18) (Scheme 10).[16]

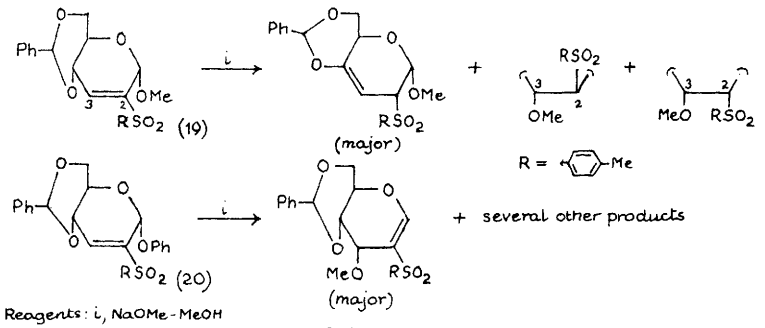


Reagents: i, $NaBH_3CN$; ii, HCl

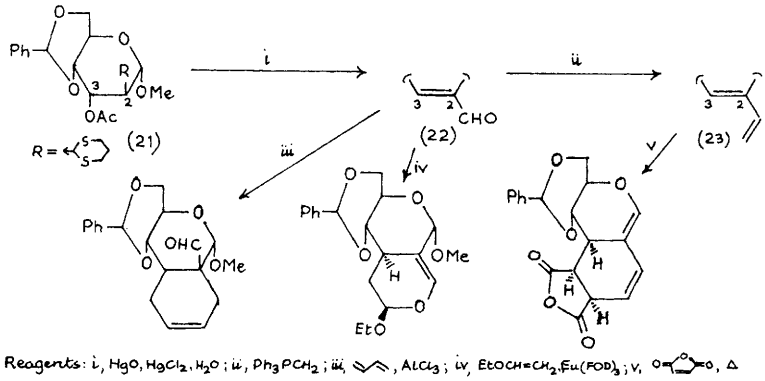
Scheme 10

In the area of 2-enes carrying substituent groups on the double bonds, Michael-like additions have been attempted on the sulphones (19) and (20) with the consequences illustrated in Scheme 11.[17]

Deprotection of the 1,3-dithianyl compound (21) gives access to the enal (22) which has been elaborated to the diene (23). These branched-chain compounds take part in cycloaddition reactions as illustrated in Scheme 12, and parallel work has been

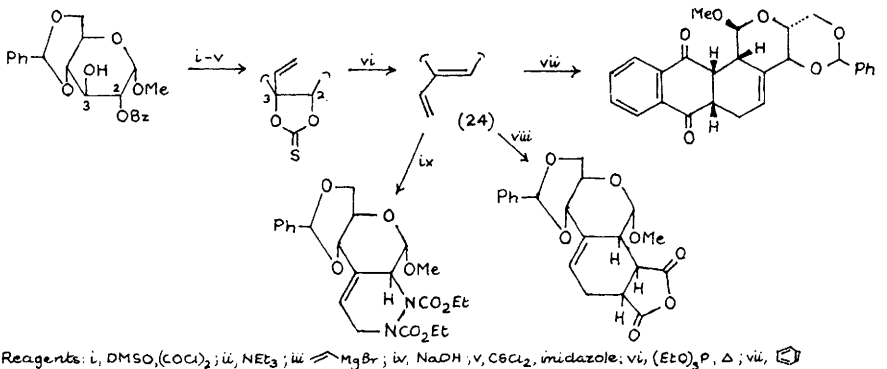


Scheme 11



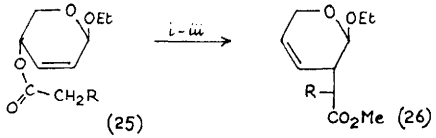
Scheme 12

carried out starting from a 3-branched analogue of the protected aldehyde (21).[18,19] The diene (24), produced in the course of this latter work, has also been made and used in Diels-Alder reactions as indicated in Scheme (13).[20]



Scheme 13

Application of the "Ireland-Claisen" rearrangement to the D-xylal derived (25) has given access to compounds (26) which have been used (Scheme 14) in novel syntheses of iridoid aglycones



(25) (26)

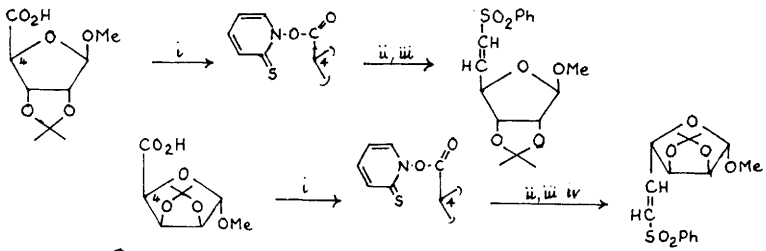
Reagents: i, $LiN(TMS)_2$; ii TBDMSiCl; iii, K_2CO_3 - MeOH

Scheme 14

(Chapter 24),[21] and 3- and 4-C-formyl hex-3-enopyranoside derivatives have been made from 3- and 4-ulosides by use of the methodology illustrated in Scheme 6.[9] A Diels-Alder addition of o-xylylene to the hex-3-en-2-ulose derivative "levoglucosenone", giving access to pyranonaphthoquinones, is noted in Chapter 24.

A one-pot, high yielding procedure involving nucleophilic displacement with iodide followed by elimination of hydrogen iodide using DBU in DMSO has been used to prepare 6-deoxyhex-5-enopyranoside derivatives from corresponding 6-bromo-compounds or 6-tosylates.[22] The conversion of alkenes of this type into 2-deoxyinososes, previously known to occur in the presence of mercury(II) salts in aqueous media, has now been shown also to take place under the influence of palladium salts and dilute acid.[23]

Useful new access is provided to furanoid 5-enes by a procedure involving the trapping of radicals derived by photolysis of carboxylic acid 2-thiopyridone derivatives. Very high stereoselectivity is observed in cases such as those illustrated in Scheme 15, and the reaction was shown to be applicable in the purine and pyrimidine nucleoside series.[24]

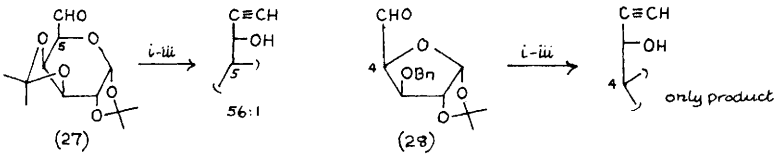


Reagents: i,  , DCC, DMAP; ii, HO. CH_2=CH SO_2Ph; iii, oxidation; iv, elimination.

Scheme 15

Several reports have appeared on alkenes derived by chain

extension from C-6 of hexose derivatives. Chelation control provides complete or very high selectivity in silyl Grignard reactions of aldehydes (27) and (28) (Scheme 16),[25] and a further



Reagents: i, TMSC≡CMgBr, $MgBr_2$, Et_2O; ii, $AgNO_3$, EtOH-H_2O; iii, KCN

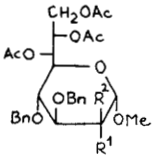
Scheme 16

report describes the use of the former in the preparation of several hept-6-enes and the parent hept-6-yne and related compounds.[26]

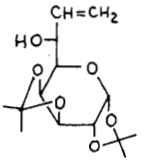
Brimacombe and his group have continued their work on the synthesis of extended chain sugars and have reported on the trans-6,7-diols produced from trans-oct-6-enopyranose derivatives of the α-D-gluco- and α-D-manno-configuration. X-Ray diffraction analyses have been reported for compounds (29) and (30).[27] Attempts by this group to obtain the C-6 epimer of compound (31) by use of the Mitsunobu procedure (DEAD, Ph_3P, BzOH) led to the 6-en-8-benzoate, but ultimately the desired product was obtained by way of a 6,7-anhydro-8-deoxy-8-iodide.[28] They have reported on the stereochemistry of the osmium tetraoxide oxidation of allylic alcohols from which extended chain sugars can be made and find that addition generally takes place anti- to the ring oxygen atom in accord with Kishi's empirical rule.[29]

Several acyclic unsaturated compounds have been reported following the treatment of carbohydrate hemiacetals with Wittig reagents: 1,2,4,5-tetradeoxyhept-4-en-3-uloses from 2,3-isopropylidene-D-glyceraldehyde;[30] Z- and E-isomers of 2,3-unsaturated heptonic acids, the ratios of products being examined in relationship to the structures of the pentofuranose derivatives used (2,3-O-isopropylidene-D-ribose compounds give predominantly 2-alkenes which D-lyxo-isomers afford mainly E-products);[31] hept-1-ynitol compounds by treatment of e.g. 2,3;4,6-di-O-isopropylidene-D-glucose with a chloromethylene Wittig reagent followed by base-catalysed elimination of hydrogen chloride;[32] the acyclic compounds (32) and (33) from 2-N-acetylamido-2-deoxy-4,6-O-ethylidene-D-glucose. The former was produced by use of a stabilised benzal ylid and by ozonolysis gave compound (32a) which is a useful acyclic derivative, the latter was formed in 70% yield

by application of a strongly basic ylid which caused retroaldol cleavage prior to the Wittig olefination.[33]



(29) R^1=OBn, R^2=H
(30) R^1=H, R^2=OBn



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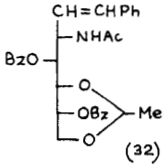

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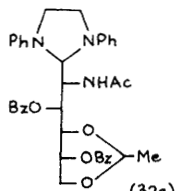
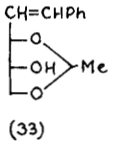


(32a)



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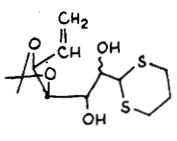

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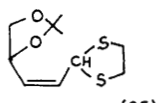
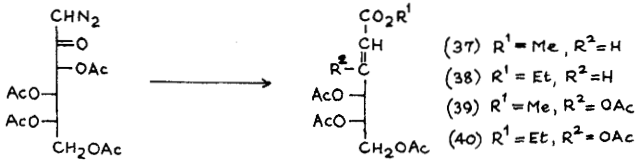


(35)

The sulphur-containing compounds (34, mainly L-gluco) and (35) have been produced, respectively, by treatment of 6-deoxy-6-iodo-1,2:3,4-O-isopropylidene-α-D-galactose with 1,3-dithian-2-yl lithium,[34] and methyl 5-O-benzoyl-2,3-dideoxy-β-D-glycero-pent-2-enoside (derived from D-ribose) with ethane dithiol followed by acetonation.[35]

Diels-Alder reaction of penta-O-acetyl-1,2-dideoxy-1-nitro-D-hept-1-enitols with cyclopentadiene afforded a mixture of 5-nitro-6-(penta-O-acetylpentitol-1-yl)norbornenes the 5-exo-nitro-6-endo-(D-manno-pentitol) and 5-endo-6-exo-isomers of which were characterised by X-ray diffraction analysis.[36]

Heating of the diazoketone (36) in methanol or ethanol in the presence of silver oxide gave the 2,3-dideoxyalkenes (37, 38) instead of the expected products of Wolff rearrangement (39, 40) (Scheme 17).[37]



(36)

(37) R^1 = Me, R^2 = H
(38) R^1 = Et, R^2 = H
(39) R^1 = Me, R^2 = OAc
(40) R^1 = Et, R^2 = OAc

Scheme 17

A route to 2,3-dideoxyald-2-enitols from 2,3-unsaturated glycosides by way of glycosyl hydroperoxides is illustrated in Scheme 9.

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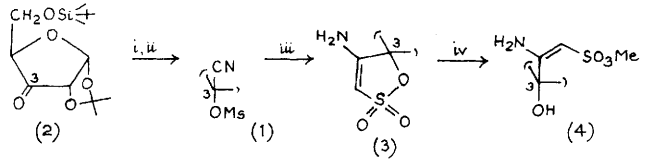
14
Branched-chain Sugars

1 Compounds with an R-C-O Branch

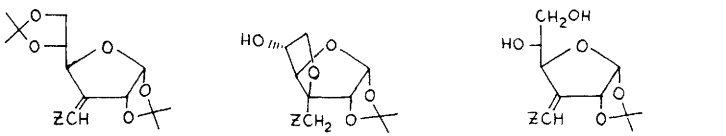
The stereochemistry of the products of nucleophilic addition of phenylacetic acid dianion to 1,2:5,6-di-O-cyclohexylidene-α-D-ribo-hexofuranos-3-ulose has been determined - partly by use of circular dichroism.[1] Base treatment of the O-mesylcyanohydrin (1) of the furanos-3-ulose (2) afforded spiro-oxathiole-2,2-dioxide (3) which cleaved with methoxide anion to give the branched-chain sugar derivative (4) (Scheme 1). Similar results were obtained



Reagents: i, NaCN-$NaHCO_3$; ii, MsCl-Py; iii, DBU; iv, NaOMe-MeOH

Scheme 1

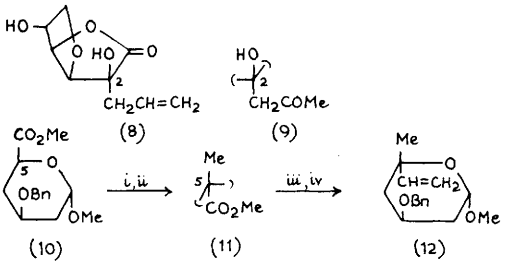
with the C-3 epimer of the cyanomesylate (1), and with D-glucose-derived C-3 epimeric cyanohydrins.[2] Some 3-deoxy-3-substituted-methylene derivatives of D-glucose have been observed to undergo intramolecular cyclisation reactions which are catalysed by acidic ion-exchange resins. Thus in this way alkenes (5) Z = CN or $pO_2NC_6H_4$ afforded the tricyclic species (6) whereas the analogues (5), with the non-electron withdrawing substituents Z = $pMeOC_6H_4$ and Ph, the diols (7) were obtained.[3] The Michael addition of L-ascorbic acid to enones has been extended to 2-cyclohexen-1-one



(5) Z = CN, p-$C_6H_4NO_2$, Ph, C_6H_4OMe (6) Z = CN, p-$C_6H_4NO_2$ (7) Z = p-C_6H_4OMe, Ph

and 2-cyclopenten-1-one and dramatic acid catalytic effects were observed.[4] The C-alkylation of potassium ascorbate with allylic

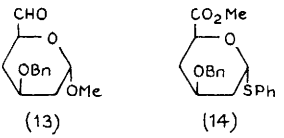
or propargylic halides gives the corresponding C-2 alkyl derivatives, e.g., (8), which was converted to the methyl ketone (9).[5] Methylation at C-5 of the hexopyranuronate (10) afforded the branched product (11) which was converted into olefin (12) required as a starting material for a forskolin synthesis (Scheme 2). Similar attempted alkylations of the aldehyde (13) and the



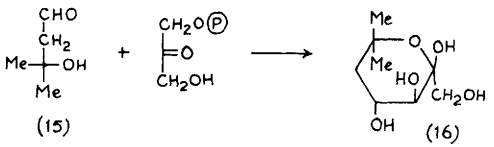
Reagents: i, LDA ; ii, MeI ; iii, DIBAL ; iv, $Ph_3P{=}CH_2$

Scheme 2

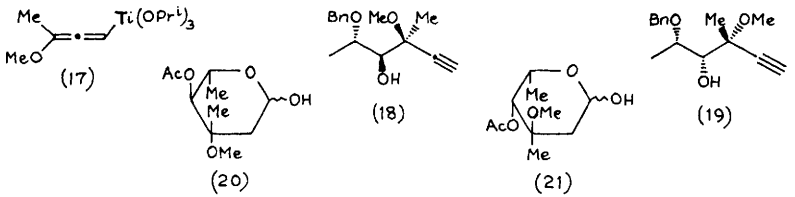
thioglycoside (14) were unsuccessful under a range of conditions.[6]



D-Fructose 1,6-diphosphate aldolase has been used to catalyse aldol condensations on some branched-chain sugar derivatives. For example the deoxytetrose (15) afforded the

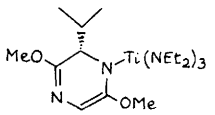


branched-chain heptulose (16).[7] The titanium reagent (17) reacted regioselectively with 2-benzyloxypropionaldehyde to generate predominantly the (racemic) products (18) and (19) with the



arabino- and xylo-stereochemistry, respectively. These were

converted into the racemic 2,6-dideoxy-3-C-methyl-3-O-methyl-hexoses (20) and (21), respectively.[8] The chiral titanated bislactim ether (22), when exposed to α,β-unsaturated aldehydes, afforded single products; e.g., with compound (23) it gave the adduct (24). Epoxidation of this alkene and subsequent hydrolysis gave the branched-chain amino acid derivative (25).[9]



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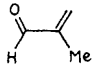

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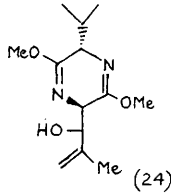

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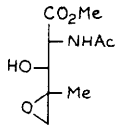
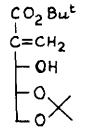


(25)

The syntheses of L-nogalose[10] and L-vinelose[11] from L-rhamnose have been described. Catalytic osmylation of α,β-unsaturated esters (26) and (27), followed by hydrolysis or hydrogenolysis, has produced the branched-chain lactones (28) and (29), respectively.[12] A racemic synthesis of some branched-chain lactones started with an unusual reaction of some oxetanes. For example, compound (30), when treated with DIBAL, afforded the



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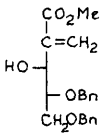

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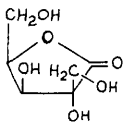

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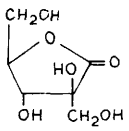

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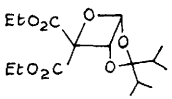

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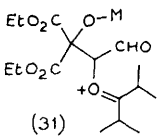

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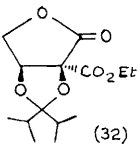

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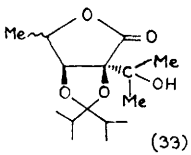

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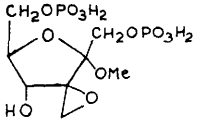
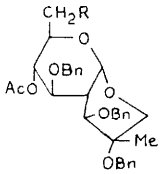


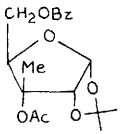
(34)

lactone (32) via the postulated intermediate (31). Similarly, when DIBAL was replaced by trimethylaluminium in the reaction, the same intermediate (31) was proposed to give rise to the lactone (33).[13] A Darzens condensation of chloromethyl p-tolylsulphone applied to some carbohydrate ketone derivatives afforded α,β-epoxy-sulphones.[14] Epoxide (34) has been synthesised as a potential inhibitor of the enzyme fructose 1,6-bisphosphatase.[15] Attempts

to convert bicyclic acetal (35a) to an acyclic compound by mercaptolysis, acetolysis or hydrolysis were plagued by multiple side reactions. The transformation was eventually effected by way of a reductive elimination of the iodide (35b).[16] Acetolysis of the D-ribose derivative (36) caused partial epimerisation at C-2;



(35a) R = OAc
(35b) R = I



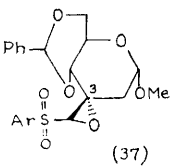
(36)

the products were converted into α-arabino- and β-ribo-nucleosides.[17]

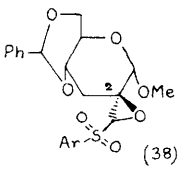
Two new antibiotics containing a branched-chain sugar are reported in Chapter 19. The synthesis of some 2′-C-methyl and 3′-C-methyl nucleosides is covered in Chapter 20. The assignment of the resonances of the ^{1}H and ^{13}C n.m.r. spectra of novobiocin is referred to in Chapter 21.

2 Compounds with an R-C-N Branch

Methanolysis of the glycopeptides of antibiotic A 82846 gave 4-epi-vancosamine in the first isolation of this compound from a natural product.[18] Treatment of epoxy-sulphones (37) and (38) with sodium azide afforded the azoaldehydes (39) and (40) respectively.[14] Condensation of 2,3-O-isopropylidene-D-glyceraldehyde with the 3-nitrobutanal derivative (41) in the



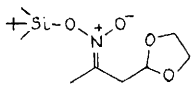
(37)



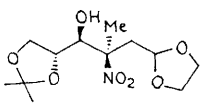
(38)

(39)

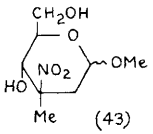
(40)



(41)



(42)

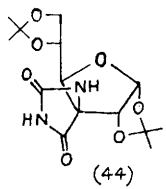


(43)

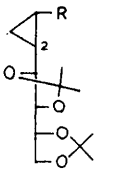
presence of tetrabutylammonium fluoride gave predominantly the nitro-sugar (42) which was transformed into the nitroglycosides (43).[19] The Bucherer reaction [KCN, $(NH_4)_2CO_3$, aq EtOH], when applied to 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexos-3-ulose

generated the expected bis-amide (44).[20]

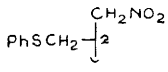
Some reactions of the cyclopropyl compound (45) have been studied. Hydrogenation followed by acetylation gave the N-acetate



(44)



(45) R = NO_2
(46) R = NHAc

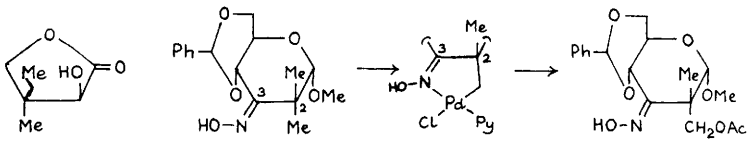


(47)

(46), whereas treatment with phenylthiolate ion afforded the ring opened derivative (47).[21]

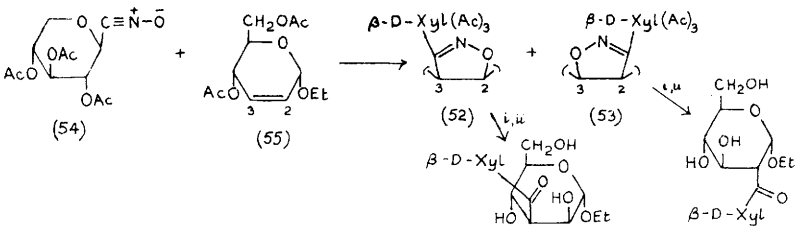
3 Compounds with an R-C-H, R-C-R, or C=R Branch

A novel route to 2-deoxy-2-C-alkyl-erythro-pentoses has been devised by way of aldol reaction of ketene acetals such as 1-tert-butyldimethylsilyloxy-1-methoxyprop-1-ene with 2,3-O-isopropylidene-D-glyceraldehyde.[22] The absolute configuration of the lactone (48), isolated from Marshallia tenuifolia, has been confirmed by its enantiospecific synthesis.[23] The gem-dimethylated oxime (49) has been specifically functionalised by a cyclopalladation - oxidation sequence giving, by way of the characterised organopalladium intermediate (50), the acetate (51).[24] A study of the conformations of 3-deoxy-3-C-methyl- and



(48) (49) (50) (51)

3-deoxy-3-C-ethyl-galactobiose derivatives by n.m.r. spectroscopic and computational methods is mentioned in Chapter 21.



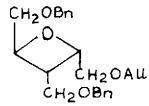
(54) (55) (52) (53) (56) (57)

Reagents: i, KCN-MeOH; ii, Pd/C-$B(OH)_3$-MeOH-H_2O

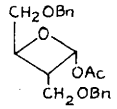
Scheme 3

Isoxazolines (52) and (53) were obtained from coupling of the xylose nitrile oxide (54) with the alkene (55) (Scheme 3). Reductive hydrolysis of these products gave the carbon-carbon linked disaccharides (56) and (57), the latter by way of a C-2 epimerisation during the reaction.[25]

In a synthesis of compounds related to oxetanocin, 5-O-benzyl-3-C-benzyloxymethyl-3-deoxy-1,2-O-isopropylidene-α-D-ribo-pentofuranose was converted into oxetanes (58) and (59).[26]

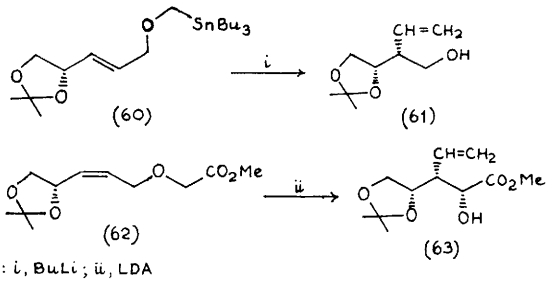


(58)



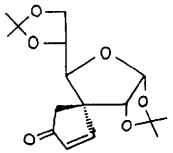
(59)

The base-promoted rearrangements of alkenes (60) and (62) has selectively afforded branched-chain derivatives (61) and (63) (Scheme 4).[27] A route to pyranoside conjugated enals is mentioned



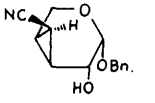
Scheme 4

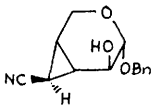
in Chapter 13. The synthesis of methyl 2,4-dideoxy-2,4-di-C-methyl-α-D-ido- and talopyranosides and their enantiomers from methyl α-D-mannopyranoside and its enantiomer, by way of epoxide intermediates, has been reported. The products are intended for use in the synthesis of propionate-derived natural products.[28] The synthesis of the spiro-carbocyclic derivative (64) has been described.[29]

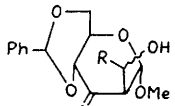

(64)

Treatment of benzyl 2,3-anhydro-4-O-trifluoromethanesulphonyl-α-D-ribopyranoside and benzyl 2,3-anhydro-4-O-trifluoromethanesulphonyl-β-L-ribopyranoside with

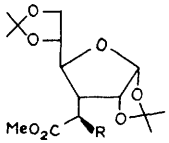
lithiated acetonitrile followed by further base yielded the first examples of 3,4-cyclopropanated sugars (65) and (66) respectively.[30] The enolate derived from methyl 4,6-O-benzylidene-2-deoxy-α-D-glucopyranosid-3-ulose when treated with acetaldehyde or propionaldehyde gave exclusively axial C-2 adducts (67) as a mixture of isomers.[31] The use of Claisen rearrangements


(65)

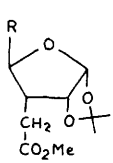

(66)

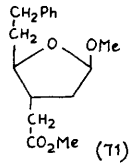

(67) R = Me, Et

on some pent-2-enopyranoside derivatives as part of an approach to iridoid aglycones is described in Chapter 24. Treatment of the ester (68) with LDA and then with alkyl halides or benzaldehyde has afforded alkylated products (69) with >99% diastereoselectivity. Because esters (70) showed undiminished selectivity, and the deoxy-analogue (71) had only slightly reduced


(68) R = H

(69) R = Me, Et, Allyl, Bn, PhCH(OH)·


(70) R = Bu^n, ·(CH$_2$)$_2$Ph

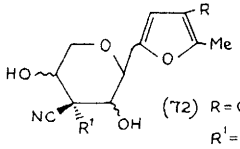

(71)

selectivity in the reaction, chelation was ruled out as the dominant contributing factor for the diastereoselectivity.[32] Condensation of some 1,5-dialdehydes with active methylene compounds has afforded C-glycopyranosylfurans (72) branched at C-3.[33]

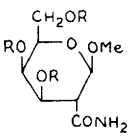
A range of reagents and conditions have been chosen which permit the selection of means for the preferential formation of 2-deoxy-2-C-methyl and 3-deoxy-3-C-methyl-pentopyranosides by the opening of 2,3-anhydropentopyranosides with various methylmetallic reagents.[34] The synthesis of eight isomeric 2-C-methyl-2,3,6-trideoxy-3-amino-L-hexose derivatives has been reported by the addition of crotyl organometallic reagents to two four-carbon chiral sulphenimines, which are available from cinnamaldehyde by microbial transformation.[35] Treatment of some unsaturated 4,5-anhydrohexitols with methyl cuprate reagents has afforded products of SN_2' addition.[36]

The cycloaddition of trichloroacetyl isocyanate to some protected glycals, followed by methanolysis of the products, has afforded predominantly 2-aminocarbonyl-2-deoxy-glycosides, e.g.,

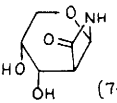
amide (73) from the corresponding galactal.[37] In another case the intermediate cycloaddition products were treated with benzylamine and then deprotected to give lactams such as (74).[38] The



(72) $R = CO_2Et, CO_2Me, COMe$; $R' = CN, CO_2Et$

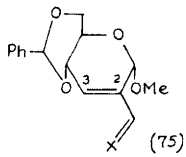


(73) R = Bn

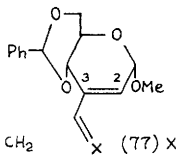


(74)

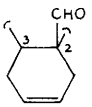
carbohydrate dienes (75) and (77) synthesised by standard procedures,[39] underwent the Diels-Alder reaction with standard dienophiles giving products of exclusively endo-addition from the β-face of the molecules. The enals (76) and (78), with butadiene, afforded cycloaddition products (79) and (80) respectively, the



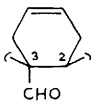
(75) X = CH_2
(76) X = O



(77) X = CH_2
(78) X = O

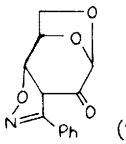


(79)

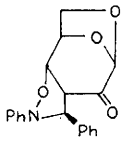


(80)

latter resulting from butadiene addition to the α-face of the molecule.[40] An alternative synthesis of diene (77) and studies of its reactivity in various Diels-Alder reactions has been reported in model studies for anthraquinone synthesis.[41] The total synthesis of some branched-chain sugars via the cycloaddition of a substituted enone with 1-ethoxypropene has been accomplished.[42] The 1,3-dipolar cycloadditions of benzonitrile oxide and C,N-diphenylnitrone to levoglucosenone were highly regio- and face-selective giving essentially the single products (81) and (82) respectively.[43]



(81)

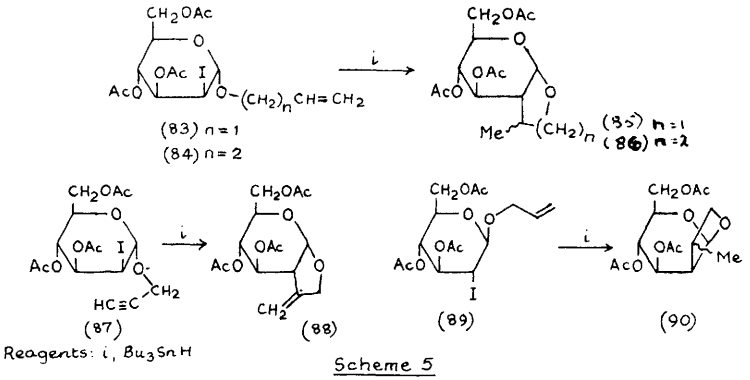


(82)

The optimum conditions for the production of methyl 4,6-dideoxy-2,3-O-isopropylidene-4-C-methyl-α-L-mannopyranoside by hydrogenation of the corresponding exocyclic olefin, methyl 4,6-dideoxy-2,3-O-isopropylidene-4-C-methylene-α-L-mannopyranoside, involved use of Raney Nickel in benzene solution. The product is an intermediate in the synthesis of a segment of amphotericin B.[44,45] Hydrogenation of 3,5,6-trideoxy-1,2-O-isopropylidene-3-C-

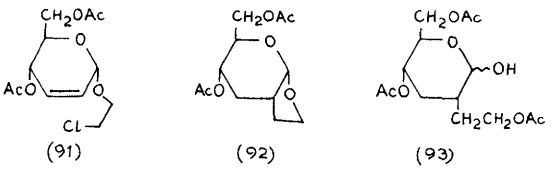
methyl-α-D-glycero-hex-3,5-dienofuranose gave 3,5,6-trideoxy-1,2-O-isopropylidene-3-C-methyl-β-L-lyxo-hexofuranose, and this was transformed into (3S, 5S, 6S)-6-ethyl-3,5-dimethyltetrahydro-2H-pyran-2-one, a key intermediate in the synthesis of serricornin.[46]

Radical cyclisation reactions have been employed to effect stereospecific carbon-branching at C-2 of some pyranoside derivatives. Thus, treatment of iodides (83) and (84) with tributyltin hydride afforded bicyclic acetals (85) and (86) respectively. Similarly iodides (87) and (89) gave rise to branched-chain derivatives (88) and (90) respectively (Scheme 5).[47] An analogous cyclisation of the unsaturated glycoside (91)

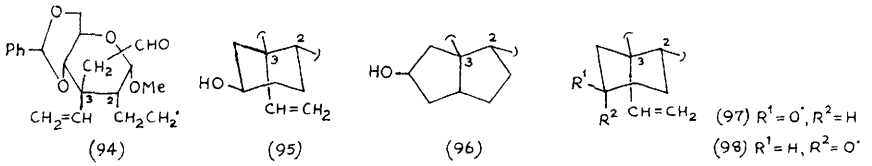


Scheme 5

afforded acetal (92) and conditions were developed ($CoCl_2$, AcCl) to effect the hydrolysis of the latter to the branched-chain derivative (93) via the corresponding glycosyl chloride.[48] The



cyclisation of radical (94) to give alcohols (95) and (96) (see SPR Vol.20, p.149) has been investigated in order to determine



whether the intermediate alkoxy radical (97) can equilibrate with the starting radical (94) and its epimeric alkoxy radical (98).

It was concluded that no such equilibration took place.[49]

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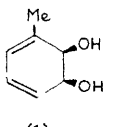
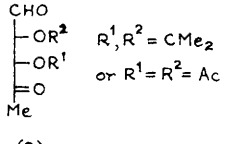
15
Aldosuloses, Dialdoses, and Diuloses

1 Aldosuloses

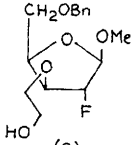
Oxidation of the dibutylstannylene derivative of methyl 3′,4′-O-isopropylidene-α-lactoside with bromine in acetonitrile in the presence of tributyltin methoxide led specifically to the 2-ketone isolated as its O-methyl or O-benzyl oxime, whereas the corresponding β-lactoside derivative gave the 3-ketone selectively.[1] Microbial oxidation of toluene (using Pseudomonas putida 39D) gave the cis-diol (1), which after O-protection and ozonolysis afforded the chiral pentosuloses (2).[2] Photochemical oxidation [Ph-I(OAc)$_2$, I_2, hν] of some carbohydrate 2-hydroxyethyl ethers has afforded some selectively oxidised products, e.g. compound (3) gave the aldulose acetal (4).[3] Solvolysis of the



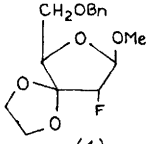
(1)



(2)



(3)



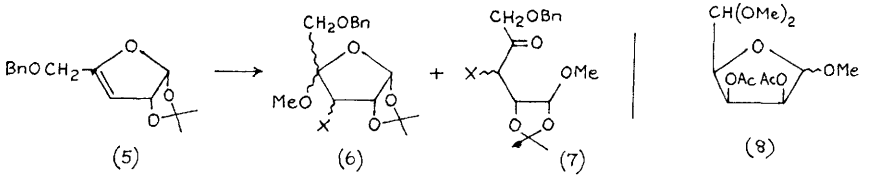
(4)

pent-3-enofuranose (5) in methanol in the presence of bromine or iodine and silver carbonate led to mixtures of adducts (6) and (7).[4] The preparation of an L-hexenulose from D-glucal via furan intermediates is covered in chapter 13, and the synthesis of an aldulose-containing degradation product of hygromycin A is mentioned in chapter 19. A case of alleged plagiarism in the report of some work on regioselective reduction of sugar enolones has been noted (Vol 20, p 152, reference 7).[5]

2 Dialdoses

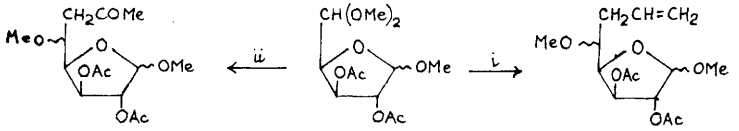
A general C-5 - C-6 bond cleavage of hexoses previously applied to D-glucose and D-galactose (see SPR Vol 17, p 143) has been extended such that photolysis of D-mannose in methanol in the presence of titanium tetrachloride afforded, after acetylation,

the dialdose derivative (8) in 50% yield. The product (9) of the



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

same reaction applied to D-glucose was treated with a number of nucleophiles in the presence of Lewis acids to give chain extended products, e.g. (10) and (11) (Scheme 1).[6] 1,2:3,4-Di-O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose has served as a



(11) (9) (10)

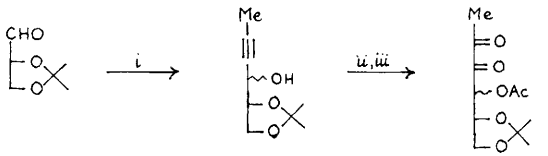
Reagents: i, $CH_2=CH\cdot CH_2TMS$; $TiCl_4$; ii, $MeC(OTMS)=CH_2$, TMSOTf

Scheme 1

precursor of several D-galactose derivatives modified at C-6, including unsaturated derivatives, epoxides and a difluoride.[7-9] The treatment of a dialdose derivative with lithiated methyl phenyl sulphone is discussed in chapter 11, and the preparation of a synthon of deazatunicamycin is covered in chapter 19. An improved synthesis of (6-^{13}C) aldohexoses from 1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose is included in chapter 2. The racemic synthesis of an aminosugar dialdose is mentioned in chapter 9.

3 Diuloses

The epimeric diketones (12) have been synthesized in good yield



Reagents: i, $MeC\equiv CMgBr$; ii, Ac_2O-Py; iii, $Ru(PPh_3)Cl_2$-PhIO

(12)

Scheme 2

from 2,3-O-isopropylidene-D-glyceraldehyde (Scheme 2).[10]

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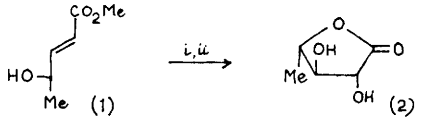
16
Sugar Acids and Lactones

1 Aldonic Acids

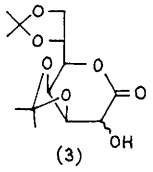
The potassium and calcium salts of D-[U-^{14}C]-gluconic acid have been prepared by oxidation of labelled glucose with potassium hypoiodite and with bromine in the presence of calcium carbonate, respectively.[1]

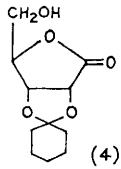
Hydroxylation of the E-alkene (1) by use of catalytic osmium tetroxide led to the L-arabino-product (2) in an 8:1 preponderance over the L-xylo isomer (Scheme 1), in accordance with the 'Kishi rule'.[2] Other workers have carried out similar reactions with other γ-alkoxy-α,β-unsaturated esters of E-configuration using stoichiometric osmium tetroxide in the presence of chiral amines to give double asymmetric induction; Z-isomers gave very low diastereoselectivity.[3]

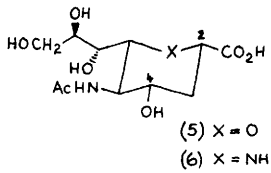


Reagents: i, OsO_4(cat), Me_3NO, H_2O; ii, H_3O^+

Scheme 1



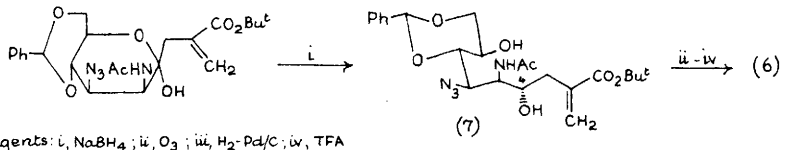




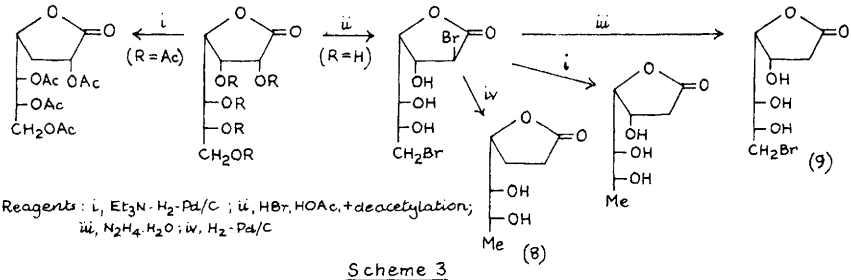
When 2,3:5,6-di-O-isopropylidene-D-mannofuranose was treated with potassium cyanide and ammonium carbonate in aqueous ethanol (conditions of the Bucherer reaction), the anomalous products (3) were obtained as the major component.[4] The D-ribonolactone acetal (4) can be converted into its enantiomer by interconversion of the oxidation levels at C-1 and C-5 followed by an acetal migration step.[5]

2-Deoxy-N-acetylneuraminic acid (5) was prepared by hydrogenation of a 2-ene,[6] whilst the epimer at C-2 was the major product formed by hydrogenolysis of the corresponding β-D-glycosyl chloride.[6,7] Neither (5) nor its epimer was an inhibitor of CMP-sialate synthetase, in contrast to the

behaviour of the analogous deoxy-derivatives of KDO.[6] The iminoanalogue (6) was synthesized as outlined in Scheme 2, with earlier stages not shown being similar to those used in previous work (Vol. 20, pp.110 and 160); the borohydride reduction also gave the C-4 epimer of alcohol (7), which by similar chemistry could be converted into the C-4 epimer of product (6), and the compound epimeric at both C-2 and C-4. Both compound (6) and its C-4 epimer were inhibitors of sialidases.[8] A paper dealing with labelled forms of 2-deoxy-KDO and it 8-amino-8-deoxyanalogues is mentioned in Chapter 9.



Scheme 2



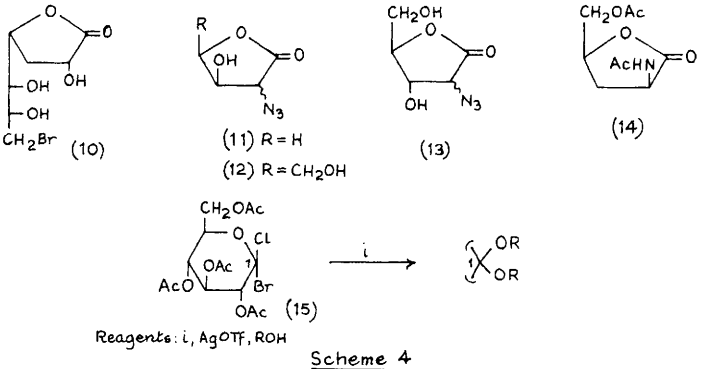
Scheme 3

D-Glycero-D-gulo-heptono-1,4-lactone and its penta-O-acetyl derivative have been converted into deoxy- and bromodeoxy derivatives as indicated in Scheme 3.[9] A study has been made of the complex reactions undergone by (8),(9) and (10) with aqueous base; initally an epoxide is formed from each substrate, and subsequent reactions depend on the base strength.[10] The α-azidolactones (11)-(13) are formed as isomeric mixtures by azide displacements applied to α–bromolactones, and in the case of compound (11) the same mixture of epimers is produced from either of the epimeric bromo-precursors. Isomers (12) and (13) both gave the D-threo- product (14) on hydrogenation and acetylation;[11] the use of products (12) and (13) for aminopentose synthesis is discussed in Chapter 9.

The gem -dihalo compound (15), reported last year, can be used as a precursor of orthoesters (Scheme 4), including spiro -bicyclic systems similar to those found in the orthosomycin antibiotics.[12]

Oxidation of D-gluconic acid with molecular oxygen and a platinum catalyst in aqueous medium occurs preferentially at the primary hydroxyl group, but addition of a lead(II) salt changes the site of oxidation to C-2,

presumably by formation of a chelate between carboxyl and α–hydroxy groups.[13]



Scheme 4

A study has been made by electron microscopy of the aggregation behaviour of a series of N-octylaldonamides,[14] and a number of bis(2-chloroethyl)amides of aldonic acids have been prepared from the per-O-acetyl acyl chlorides.[15]

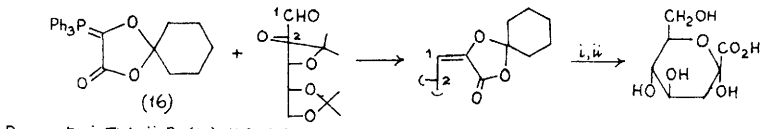
Some references to δ–lactams of 5-amino-5-deoxyaldonic acids are given in Chapter 9.

2 Saccharinic Acids

The degradation of D-glucoisosaccharinic acid, an alkaline degradation product of cellulose, has been studied under conditions of high-temperature pressure- heating in aqueous alkali, with or without a reducing atmosphere. A range of products, particularly mono- and dicarboxylic acids, was identified.[16]

3 Ulosonic and Ulosaric Acids

The synthesis of 2-ketoaldonic acids continues to attract considerable attention. The Wittig reagent (16) can be used for the synthesis of 3-deoxy-D-arabino-2-heptulosonic acid as indicated in Scheme 5; reagent (16) could also be used in conjunction with a D-mannose derivative to make KDO, but since



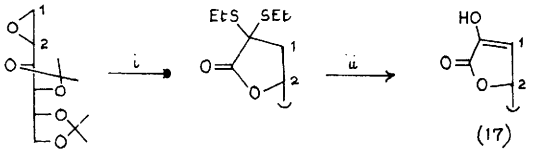
Scheme 5

di-isopropylidene D-mannofuranose did not react, it was necessary to use an aldehydo-mannose derivative.[17] Other workers have used similar Wadsworth-Emmons reactions of α–alkoxy- and α–silyloxy-phosphonate anions to convert

D-mannose derivatives into KDO by two-carbon chain extension.[18,19] An alternative type of two-carbon extension has been used to prepare the KDO derivative (17) (Scheme 6).[20] A free radical process involving chain extension at C-6 of a D-mannose derivative has also led to the ammonium salt of KDO (Scheme 7).[21]

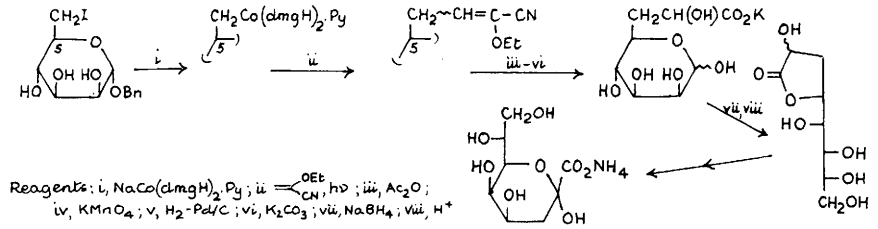
A multigram enzymic synthesis of KDO-8-phosphate has been devised; D-arabinose-5-phosphate is prepared by hexokinase action on the sugar, and is then condensed with phosphoenolpyruvate using KDO-8-phosphate synthetase. The ATP required for the hexokinase reaction is regenerated from phosphoenolpyruvate using pyruvate kinase.[22]

The derivative (18) of 3-deoxy-L-gulo-2-octulosonic acid has been prepared by NBS-catalysed hydrolysis of a dithioacetal, in a similar manner to the method illustrated in Scheme 6,[23] and the octulosonic acid itself has been made via oxidative decarboxylation of lactone (19).[24]



Reagents: i, $(EtS)_2CHCO_2H$, BuLi ; ii, NBS-H_2O-Me_2CO

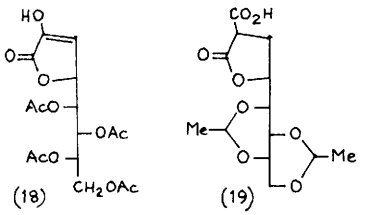
Scheme 6



Reagents: i, $NaCo(dmgH)_2Py$; ii, $=\!\!<^{OEt}_{CN}$, hν ; iii, Ac_2O ; iv, $KMnO_4$; v, H_2-Pd/C ; vi, K_2CO_3 ; vii, $NaBH_4$; viii, H^+

dmg = dimethylglyoximato

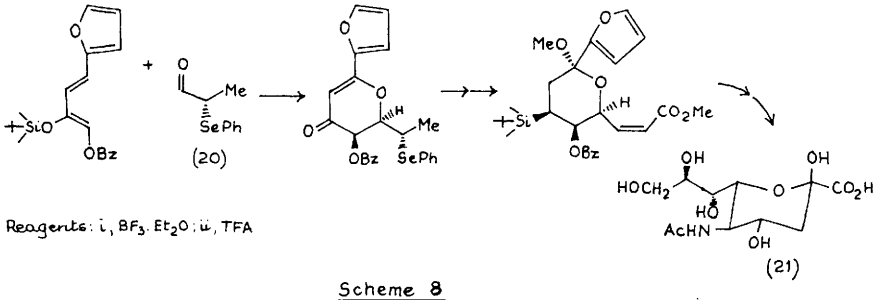
Scheme 7



(18) (19)

Danishefsky's route to racemic KDO (Vol. 19, p.153) has been used to prepare the optically-active material, starting from (R)-α–phenylselenopropionaldehyde, and use of the (S)-isomer (20) led to the

enantiospecific total synthesis of N-acetyl neuraminic acid (21) outlined in Scheme 8, where the attack of the activated diene on the chiral aldehyde (20) via a Felkin-type transition state was the key to the stereocontrol.[25] Vasella's

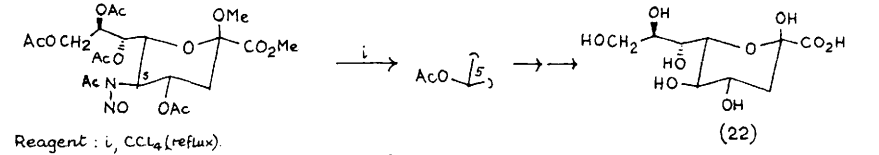


Scheme 8

group have also reported another route to N-acetyl neuraminic acid (NeuNAc, 21) with similarities in the later stages to their earlier method (Vol.20, p.160).[26]

Again, enzymic routes for large-scale synthesis of (21) have been developed by two groups[7,27] who treated N-acetylmannosamine with pyruvate in the presence of NeuNAc aldolase. It was observed that various other carbohydrates could also function as substrates, but only pyruvate as the nucleophile,[7] and one group extended their work to a synthesis of CMP-NeuNAc by allowing the NeuNAc formed to react with CTP (itself generated from CMP using adenylate kinase) in the presence of CMP-NeuNAc synthetase.[27]

The related nine-carbon compound 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN, 22) has been synthesized conventionally from



Scheme 9

D-mannose and oxaloacetate under basic conditions (40% yield),[28] and also in rather low yield (Scheme 9) from the indicated N-nitroso-derivative of NeuNAc.[29]

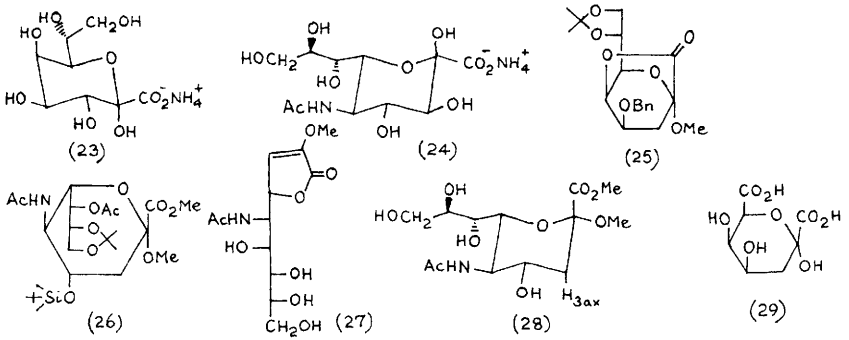
Hydroxylations of 2-enes led to the synthesis of the derivatives (23) and (24) of KDO and NeuNAc respectively, each with an additional equatorial hydroxyl group at C-3.[30]

The 4-O-phosphate of KDO has been prepared from the 5-O-benzyl ether (Vol.14, p.131) via a 7,8-O-isopropylidene derivative, and its chemical stability was investigated in connection with structural studies on endotoxins.[31]

The lactone (25) of KDO was produced when benzylation of the 4,5-diol was carried out via the dibutylstannylene derivative; a similar reaction on the 4,5-O-isopropylidene - methyl ester -α–methyl glycoside gave the 8-O-benzyl derivative with no 1,7-lactone formation.[23]

When the methyl ester -α–methyl glycoside of NeuNAc was sequentially acetonated, silylated, and acetylated the fully substituted (26) was produced, which could be deprotected by aqueous acetic acid to give a derivative of the starting material with an O-acetyl group on the least reactive 7-hydroxy group.[33] Similar chemistry was employed to give the 7-epimer of NeuNAc methyl ester methyl glycoside by a redox process, and the analogous 7,8-bis-epimer via the 7,8-epoxide.[34]

The minor product formed in the reaction of NeuNAc with Ac_2O-pyridine has been shown to be the peracetylated 1,7-lactone.[35] Benzoylation of NeuNAc can give 1,7- or 1,4-lactones depending on the conditions, and such bicyclic lactones are also formed during pivaloylation and ethoxycarbonylation.



Treatment of NeuNAc with diazomethane in acidic ethanol gives firstly the methyl ester, then the methyl ester - α–methyl glycoside, and then the lactone-enol ether (27); conclusions as to the equilibria present in acidic and basic solutions of NeuNAc were drawn.[36] The structure of spirocyclic bislactone formed from the α–NeuNAc-(2→3)-β–Galp units in the GD1a ganglioside by the action of DCC has been determined as involving interaction of O-2 of the galactose units and the carboxyl of the neuraminates.[37]

A potentially useful method for determining the anomeric configuration of sialic acid derivatives by ^{13}C-n.m.r. methods has emerged: the axial carboxyl group carbon atom of an α–D-derivative shows a large three-bond coupling (~6Hz) to the axial hydrogen at C-3 (see compound 28), whilst analogous equatorial-axial and diequatorial couplings are much smaller.[3]

The 2,3:4,6-diacetonide of 2-keto-4-gulonic acid has been used as a

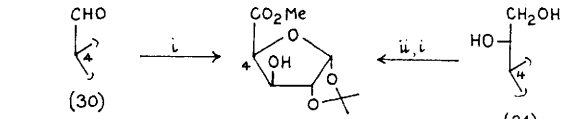
chiral resolving agent for imidazolidinones which are of use in amino-acid synthesis.[39]

The novel sugar 3-deoxy-D-lyxo-2-heptulosaric acid (29) has been found as a component of the pectic rhamnogalacturonan II of plant cell walls.[40]

4 Uronic Acids

D-[U^{14}C]-Glucuronic acid can be prepared by oxidation and hydrolysis of labelled glucan or methyl α–D-glucopyranoside.[41]

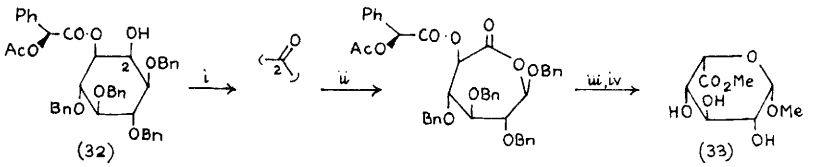
Bromine in an alcohol solvent can be used for the direct conversion of an aldehyde to an ester, as exemplified by the oxidation of compound (30) (Scheme 10), presumably via an intermediate hemiacetal;[42] the aldehyde can



Scheme 10

be generated in situ by Swern oxidation of an alcohol, or, as in the case of the diol (31), by periodate cleavage.[43] 1,2-O-Cyanoethylidene derivatives of alkyl glycopyranuronates can be prepared by oxidation of the 3,4-di-O-acetyl-1,2-O-cyanoethylidene-6-O-tritylhexose with excess of Jones reagent.[44] Similar oxidation has been used to prepare 2-acylamido-2-deoxy-D-glucopyranuronic acids.[45]

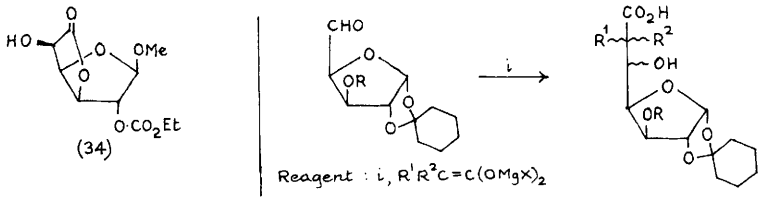
Racemic 1,4,5,6-tetra-O-benzyl-myo-inositol can be converted into separable diastereomeric esters with (S)-O-acetylmandelic acid; one of these isomers (32) gives the L-idopyranosiduronic acid derivative (33), as indicated



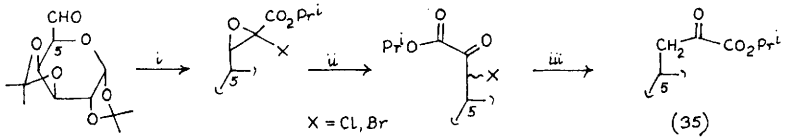
Scheme 11

in Scheme 11, via a regiospecific Baeyer-Villiger reaction, and the enantiomer of (33) was prepared from the other inositol diastereomer.[46] The L-iduronic acid derivative (34) has been prepared from the D-gluco-compound by displacement of a 5-O-triflyl group, and in the same way the equivalent L-guluronolactone was made from the D-manno-analogue.[47]

Ivanov-type reactions have been used to produce uronic acids with two-carbon chain extension (Scheme 12),[48,49] and a Darzens reaction was



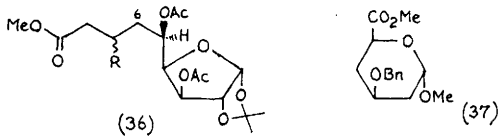
Scheme 12



Scheme 13

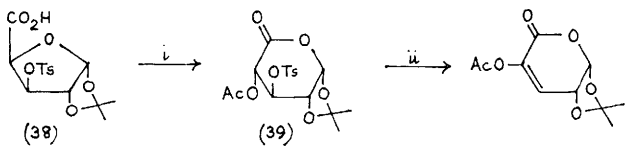
employed as in Scheme 13 to prepare the α–ketoester (35).[50] Addition of the free radical produced from a 6-deoxy-6-iodoglucose derivative to methyl acrylate and dimethyl maleate gave products (36, R=H, CO_2Me), and similar 3-carbon extensions were carried out on a 5-deoxy-5-iodo-D-ribofuranose.[51] A paper dealing with the chemistry of radicals derived by formal decarboxylation of uronic acid derivatives is mentioned in Chapter 13.

During the synthesis of a building block for forskolin, a study was made



of the methylation at C-5 of dideoxy systems such as (37); this compound gave a diastereomeric mixture of C-5 methyl derivatives on treatment with LDA and methyl iodide, although several related compounds could not be methylated.[52]

The reactions of tosylate (38) with BF_3 have been investigated; in addition to the high-yielding reactions shown in Scheme 14, use of BF_3 in dichloromethane gave a 1,1':2,2'-dianhydro derivative of the furanose form, whilst the amide of the acid (38) rearranged to a δ–lactam similar to the acetal lactone (39).[53]



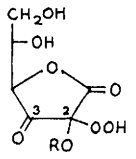
Scheme 14

A series of papers on the O-methylation of methyl (methyl D-glycopyranosid)uronates is covered in Chapter 5, and the synthesis of siastatin, an aza-analogue of a uronic acid, is referred to in Chapter 24.

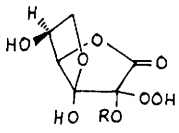
5 Ascorbic Acids

When L-ascorbic acid was subjected to rose bengal-sensitized photooxygenation at low temperatures in perdeuteriomethanol the hydroperoxide (40) was produced together with the analogous 2-oxo-3-hydroperoxy-compound. Adduct (40) gradually isomerized to the hemiacetal (41) the reactions being monitored by ^{13}C-n.m.r. spectroscopy. 2-O-Methyl-L-ascorbic acid similarly gave products (42) and (43).[54]

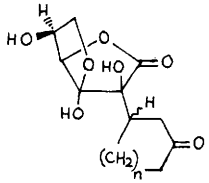
The effect of acetonitrile on the kinetics of oxidation of ascorbic acid by Cu(II) and the ferrocenium ion in aqueous acetonitrile has been studied,[55] as has the similar oxidation using the Cu(II)-tyrosine complex, for which a mechanism has been proposed.[56] A reinvestigation of the oxidation of ascorbic acid by Fe(III) has shown catalysis by even small amounts of added chloride,[57] and the kinetics and mechanism of the oxidation of ascorbate by manganese pyrophosphate have been studied.[58] The heat stability of aqueous solutions of ascorbic acid is increased with reduced oxygen concentrations, with Cu(II) and Fe(II) accelerating decomposition.[59]



(40) R = H
(42) R = Me



(41) R = H
(43) R = Me



(44)

The interaction between ascorbic acid and bile pigments, of relevance to the biochemical role of such bilins was determined by a silica gel t.l.c. interacting barrier technique.[60]
U.v., i.r., and ^{1}H-n.m.r. data for ascorbic acid and its 5,6-O-isopropylidene derivative have been reported.[61]

The Michael reaction of L-ascorbic acid with enones (see Vol.20, p.163) has been extended to cyclohexenone and cyclopentenone from which adducts (44, n=1,2) were produced in an acid-catalysed process.[62] The application of similar chemistry to natural product synthesis is mentioned in Chapter 24 of both this Volume and Vol.21.

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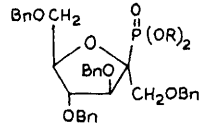
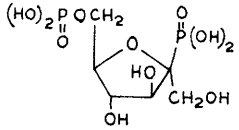
17
Inorganic Derivatives

1 Carbon-bonded Phosphorus Derivatives

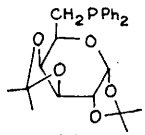
The synthesis of 2,4-dideoxy-4-[(S)-methyl- and (R)-cyclohexylphosphinyl]-α,β-D-erythro-pentofuranoses was described as the first phosphorus-in-the-ring sugar analogues of 2-deoxy-D-ribofuranose.[1] Treatment of 2-O-acetyl-1,3,4,6-tetra-O-benzyl-β-D-fructofuranose with trialkyl- or triaryl-phosphites in the presence of trimethylsilyl triflate gave largely compound (1) which was converted into the analogue (2) of β-D-fructose 2,6-bisphosphate.[2] An asymmetric grignard cross coupling reaction has been effected in the presence of the chiral phosphine ligand (3).[3]



(1)

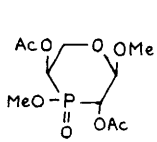


(2)



(3)

A racemic synthesis of 3,4-dideoxy-2-C-methyl-4-phenylphosphinyl-D,L-glycero-tetrafuranose has been reported[4] as has the preparation of the four epimers of 5-deoxy-3-O-methyl-5-C-[(R)- and (S)-phenylphosphinothioyl]-α- and β-D-xylopyranoses[5] (see SPR Vol 21, p 167). The preparation of 5-deoxy-5-[(RS)-ethylphosphinyl]-α,β-L-idopyranoses has been described,[6] and 1,2,4,6-tetra-O-acetyl-5-deoxy-3-O-methyl-5-[(RS)-phenylphosphinyl and methyl phosphinoyl] α,β-L-idopyranoses have been prepared.[7] The novel phosphorus-containing glycoside analogue (4) has been reported.[8] A stereoselective phase-transfer catalysed



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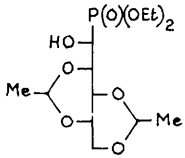

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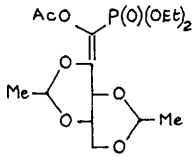


(6)

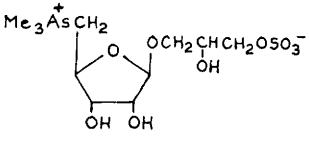
phosphorylation of 2,4:3,5-di-O-ethylidene-aldehydo-L-xylose

[$(EtO)_2PH$, $BnEt_3NCl$] gave largely the phosphonate (5) as well as some of its C-1 epimer,[9] and on oxidation (DMSO-Ac_2O) these afforded a mixture of the E,Z enol acetates (6).[10]

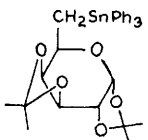
2 Other Carbon-bonded Derivatives

A novel trimethylated arseno-glycoside (7) has been isolated from brown kelp,[11] and another report on the isolation and identification of arsenic-containing ribofuranosides from edible brown seaweed includes some new compounds.[12]

6-Deoxy-1,2-O-isopropylidene-6-(trimethylstannyl)-α-D-glucofuranose was prepared from the corresponding 5,6-anhydro-compound and was readily transformed into 5,6-dideoxy-1,2-O-isopropylidene-α-D-*xylo*-hex-5-enofuranose.[13] Treatment of 1,2:3,4-di-O-isopropylidene-6-O-*p*-toluenesulphonyl-α-D-galactopyranose with Ph_3SnLi afforded the corresponding 6-deoxy-6-triphenylstannyl derivative (8), but attempts to apply Ph_3SiLi or Ph_3PbLi to the reaction did not give metallated products. However, separate treatment of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside with each of these reagents afforded the derivatives (9).[14] Hydrosilylation of 6-deoxy-1,2:3,4-di-O-isopropylidene-α-L-*arabino*-hex-5-enopyranose and subsequent



(7)



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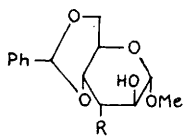
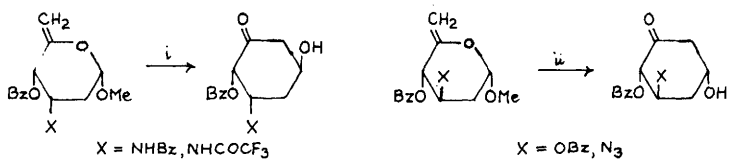


(9)

protodesilylation gave 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L-altrofuranose.[15]

The carbocyclisation of a number of 2,6-dideoxy-hex-5-enopyranosides has been studied (Scheme 1). In each case the



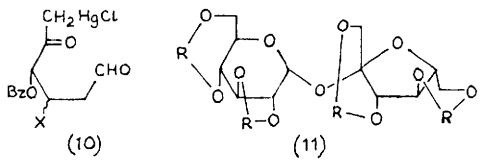
Scheme 1

orientation of the hydroxyl group at the new chiral centre was *trans*- to that of the 3-substituent. It was postulated that there

is complexation in the organomercurial intermediate (10) between the 3-substituent and the mercury so that the C-6 carbanionic methylene is delivered to the aldehyde from the same face as the C-3 substituent.[16] Some glycosyl cobalt compounds have been prepared and their photolysis in the presence of suitable acceptors to give C-glycosides has been studied.[17] An alkoxypalladation reaction of some glucals is mentioned in chapter 13.

3 Oxygen-bonded Derivatives

Pharmaceutical grade lactose has been shown to contain impurities in the form of the 6- and 6′-O-phosphates as well as the 3′- and 4′-O-phosphates.[18] Synthesis of L-ascorbate-6-phosphate from 6-bromo-6-deoxy-L-ascorbic acid has been described,[19] and the preparation of p-trifluoroacetamidophenyl β-D-glucopyranoside 4-(D-ribit-5-yl phosphate), a glycoside of the repeating unit of the Haemophilus influenzae type a capsular antigen was reported.[20] Inositol phosphates have been prepared by a phosphitylation reaction followed by peroxide oxidation to the phosphates.[21] Transesterification of xylitol with trialkylphosphites led to cyclic phosphite derivatives,[22] and the nature of the products obtained on extending the reaction to other pentitols has been examined.[23] Diphenylphosphinite derivatives of monosaccharides in combination with Rh(I) complexes have been used in the hydrogenation of Z-α-acetylaminocinnamic acid to give selectively (R)- or (S)-α-acetylaminophenylalanine.[24] Similarly, a study of the utility of 4,6-O-(R)-benzylidene-2,3-O-bis(diphenylphosphino)-D-hexopyranoside - rhodium(I) chelates for the enantioselective hydrogenation of dehydroamino acid derivatives has been made.[25] The O-(diethylamino)thiophosphate derivatives (11) and (12) of sucrose[26] and D-mannitol[27] have been prepared.

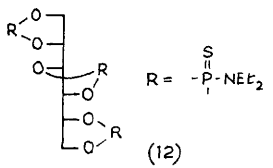


(10) (11)

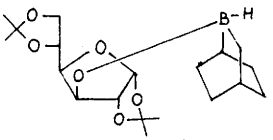
D-Glucuronic and D-gluconic acids interact with the anticancer agents cisplatin and transplatin $[PtCl_2(NH_3)_2]$ to give $[PtL_2(NH_3)_2].H_2O$ and $[PtL(NH_3)_2]L.H_2O$ where L is the carboxylic acid anion.[28] A variety of Pt(II) complexes of (1R,2R)-

cyclohexanediamine and 2-(aminomethyl)cyclohexylamine isomers containing D-glucuronate, D-gluconate and their tetra-O-acetyl derivatives have been synthesized and shown to have antitumour activity.[29]

The use of carbohydrate-borate eluants for separation of inorganic anions by single column low-capacity anion-exchange resin chromatography has been further investigated, with the mannonic acid-borate eluant being as efficient as the originally reported gluconate-borate eluant.[30] It has been shown using ^{11}B- and ^{13}C-NMR and potentiometric studies that contrary to earlier reports, the four pentoses, like the hexoses form 1:1 and 1:2 complexes in aqueous solution with borate and at vicinal-diol centres in the sugars. All sugars complexed in the furanose form.[31] In other work polarimetric, ^{11}B- and ^{13}C-NMR methods were used to study the reaction of 31 polyols and carbohydrates with borate ion in aqueous solution.[32] The stability constants of a



(12)

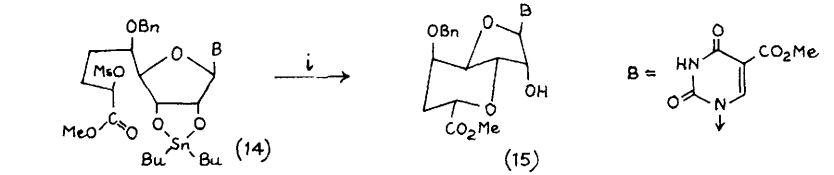


(13)

series of carbohydrate-borate and tungstate complexes have been compared in order to define a structure-reactivity relationship.[33] The stable chiral borohydride (13) has given high optical yields when used to reduce prochiral ketones.[34] The synthesis and structural characterisation of some cobalt-pentammine and cobalt-tetrammine sugar complexes containing D-gluconate and D-glucuronate anions has been reported,[35] and the interactions of vanadate ions with cyclic diols and monosaccharides have been investigated.[36] A series of O-glycosyl carboranes have been synthesized from the appropriate hydroxyalkyl carborane and an esterified carbohydrate in the presence of a Lewis acid.[37]

The use of tin compounds in carbohydrate and nucleoside chemistry has been reviewed.[38] The natures of the products formed from R_2SnO (R = Me, Bn, Octyl) and a number of sugars in methanol solution have been examined by IR and Mössbauer spectroscopy.[39] The 2,4-O-dibutylstannylene acetal of 1,6-anhydro-β-D-glucopyranose has been used to effect selective esterification and alkylation to give the 4-O-benzoate (55%) and 4-O-benzyl ether (40%) preferentially, but separation from the O-2 substituted isomer was

difficult.[40] A number of 1,4,5,6-tetra-O-substituted myo-inositols have been preferentially benzylated at the equatorial position via the 2,3-O-dibutylstannylidene derivatives.[41] A novel cyclisation of the dibutylstannylidene (14) afforded (15) (Scheme 2) during the synthesis of octosyl acid A.[42] The formation of



Reagents: i, CsF, DMF

Scheme 2

selenocarbonates from carbohydrate diols has been effected by treating the diol with Viehe's salt followed by NaHSe.[43]

The interaction of D-glucose with hydrated alkaline-earth metal halides has been studied in solution, and complexes of the type $Mg(D\text{-glucose})X_2.4H_2O$, $Ca(D\text{-glucose})X_2.4H_2O$, and $Ca(D\text{-glucose})_2X_2.4H_2O$, where $X=Cl^-$ and Br^-, have been isolated, and characterised by means of F.T.-I.R. and ^1H-NMR spectroscopy, X-ray powder diffraction, and molar conductivity measurements.[44] A study of sucrose interactions with the same magnesium and calcium ions showed that both form mono- and di- sucrose adducts,[45] and the isolation of several complexes formed between these metal ions and D-glucurono-1,4-lactone in ethanolic and aqueous solutions has been reported.[46] The interaction in aqueous solution of β-D-fructose with hydrated salts of Zn(II), Cd(II), and Hg(II) has given rise to solid adducts of the type $M(D\text{-fructose})X_2.nH_2O$, $X = Br^-$, Cl^- which were characterised by F.T.-I.R. spectroscopy, X-ray powder diffraction and molar conductivity measurements.[47] Potentiometric pH titration was used to measure the stability constants of the 1:1 complexes formed between a number of cations and tubercidin 5′-monophosphate.[48] The complexation of copper(II) ions with sucrose has been studied and a number of complexes were identified.[49] A molecular model has been used to describe the formation of iron(III)-glucosamine complexes in aqueous KOH at various mole ratios.[50]

4 Nitrogen-bonded Derivatives

$[Ni(R,R\text{- or }S,S\text{-1,2-Cyclohexanediamine})_2]Br_2.3H_2O$ reacts with certain aldoses to yield octahedral Ni(II) paramagnetic complexes

containing two N-glycosides. It was found that the R,R-compound reacts preferentially with aldoses having the S-configuration at C-2 and vice versa. Since the sugar can readily be recovered by acid treatment, the complexation can be used for molecular recognition and separation. Thus the R,R-isomer acted on a mixture of D-glucose and D-mannose to give only a mannose-containing complex.[51]

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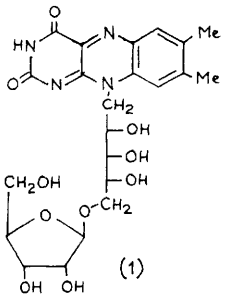
18
Alditols and Cyclitols

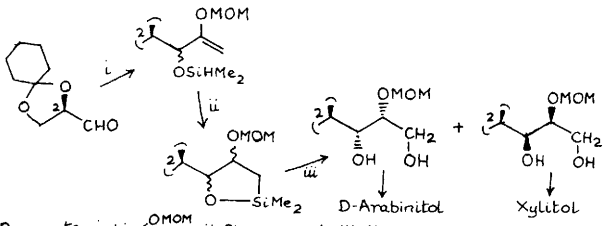
1 Alditols

1.1 Acyclic Alditols. - Lampteroflavin (1) has been isolated from a luminous mushroom.[1]

A review has been published on the relationship of the conformation of alditols to properties such as chromatographic affinity, complexation, and deuterium exchange.[2]



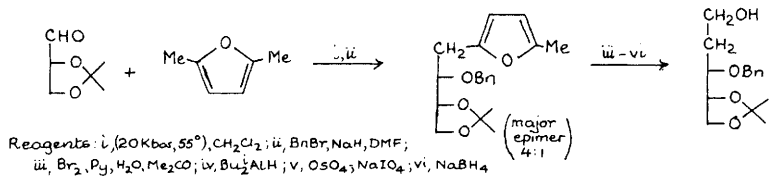
(1)



Scheme 1

A new route to 2,3-threo-1,2,3-triols involves the stereospecific intramolecular addition of a silyl ether to an α-enol ether as outlined for D-arabinitol and xylitol in Scheme 1.[3]

High-pressure addition of 2,5-dimethylfuran to 2,3-O-isopropylidene-D-glyceraldehyde furnishes a route to 2-deoxy-D-erythro-pentitol derivatives as shown in Scheme 2.[4]



Scheme 2

A full paper on the asymmetric synthesis of polyols using chiral allylic β-hydroxy sulphoxides has been published [5] (see Vol.21, p. 172).

Aldoses are smoothly decarbonylated by chlorotris(triphenylphosphine)rhodium in N-methylpyrrolidin-2-one giving the next lower

alditols; thus, D-glucose yielded D-arabinitol, and 2-deoxy-D-erythro-pentose gave 1-deoxy-D-erythritol. Ketoses yielded more complex dehydration-decarbonylation products, e.g., fructose gave furfuryl alcohol.[6]

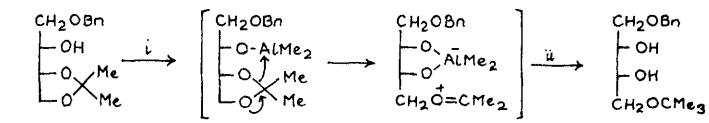
2,3-Unsaturated aldopyranosides can be converted to the corresponding unsaturated alditols with retained stereochemistry by conversion to the aldosyl hydroperoxide using hydrogen peroxide with molybdenum trioxide followed by borohydride reduction.[7] A combination of sodium dicyanoborohydride with trifluoroacetic acid similarly converts glycosides to alditols via free sugar intermediates, although varying amounts of 1,5-anhydro-alditols are also formed. Borane with 4-methylmorpholine could also be used with acid-sensitive glycosides.[8]

Ascorbic acid has been used as a source of 1,2-O-isopropylidene-L-threitol, and hence L-glyceraldehyde derivatives, by sequential ozonolysis and LAH reduction of 5,6-O-isopropylidene-2,3-di-O-methyl-L-ascorbic acid.[9] Similarly, 5,6-O-isopropylidene-D-isoascorbic acid has been used to prepare chiral erythritol derivatives from a 1,2-O-isopropylidene-L-erythritol intermediate.[10]

A synthesis of a dimeric ribitol fragment of a capsular polysaccharide is mentioned in Chapters 3 and 7, and a one-carbon chain elongation procedure converting hexoses to hept-1-ynitols is referred to in Chapter 13.

The polymorphism of hydrated D-glucitol has been studied by calorimetric and spectroscopic techniques; a new hydrate was obtained by crystallization of ultrapure D-glucitol.[11] 1,2:3,4-Di-O-ethylidene or benzylidene derivatives of D-glucitol have been incorporated into 18-crown-6-ethers having C_2 symmetry.[12] D-Glucono-1,5-lactone has been used to prepare 3,4:5,6-di-O-isopropylidene-D-glucitol.[13]

Treatment of erythritol and (±)-threitol with dimethoxymethane - toluene-p-sulphonic acid - lithium bromide permits the selective acetalation of these polyols to give 1,3-O-methylene derivatives in methanol or 1,3:2,4-di-O-methylene acetals in dichloromethane.[14] Trimethylaluminium has been found to rearrange tetraol vic-acetals to give alkyl ethers as illustrated in Scheme 3.[15]



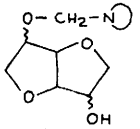
Reagents: i, Me_3Al; ii, H_2O

Scheme 3

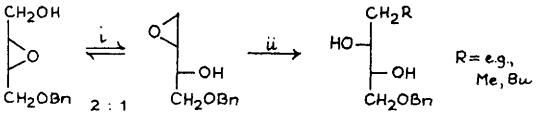
The poorer enantioselectivities observed in the Sharpless epoxidation of allylic alcohols following the use of 1:1 complexes of various sugar diols compared with diisopropyl tartrate has been ascribed to the observed formation of tricyclic dimers between the former and titanium tetraisopropoxide, whereas the latter gives a monocyclic 2:1 complex.[16]

1,2 Anhydro-Alditols. - 2-And/or 3-methyl or ethyl ethers of methyl α-D-glucopyranoside have been used to prepare a series of 2- and/or 3- and/or 6-methyl and/or ethyl ethers of 1,5-anhydro-D-glucitol, which can also be reductive cleavage products of partially methylated or ethylated celluloses.[17]

Nucleoside analogues (2) have been prepared by coupling 1,4:3,6-dianhydrohexitols to nucleoside bases via 2- or 5-O-chloromethyl ethers prepared from the dianhydrohexitol using methanal - hydrogen chloride.[18]



(2)



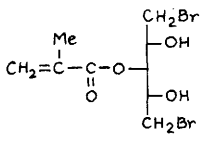
Reagents: i, BuLi, LiCl; ii, e.g., MeCu or BuCuCNLi

Scheme 4

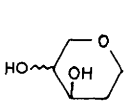
1,2- and 2,3-Anhydroalditols can be equilibrated using butyllithium - lithium chloride in THF; the 1,2-epoxide can be trapped in situ using certain "not-too-reactive" nucleophiles as illustrated in Scheme 4.[19]

Sodium methoxide treatment of 1,4-anhydro-5-chloro-5-deoxy-D-arabinitol or -xylitol yields 1,4:2,5-dianhydro-arabinitol and 1,4:3,5-dianhydro-xylitol respectively.[20]

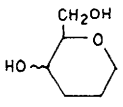
Unsaturated esters of 1,2:4,5-dianhydro-xylitol have been prepared; the methacrylic ester reacted with lithium bromide to yield the 1,5-dibromo-1,5-dideoxy analogue (3).[21]



(3)



(4)

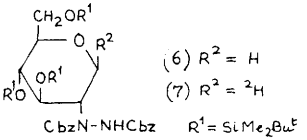


(both epimers) (5)

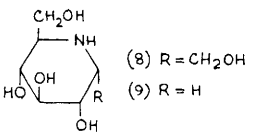
The chiroptical properties of carbohydrate-derived bidentate ligands (4) and (5) have been studied, as well as their complexes with $Mo_2(OAc)_4$. Their use as chiral ligands for some asymmetric reduction reactions resulted in only poor enantioselectivity.[22]

1.3 Amino-Alditols. - Aldose oximes, e.g., of mannose and arabinose, can be reduced electrochemically to 1-aminoalditols; glucose oxime reacted differently, because, it is proposed, of its strong tendency to cyclize to an N-glucosyl hydroxylamine derivative.[23] 1-Amino-2-acetamido-1,2-dideoxy-D-alditols have been prepared by sodium cyanoborohydride reduction of 2-acetamido-2-deoxy-glycosylamines (D-Glc, D-Man, and D-Glc-D-Glc).[24] 6-(5-deoxy-D-ribit-5-yl)amino-uracil has been condensed with 2-chloro-4-hydroxybenzaldehyde to give a flavin derivative which was further elaborated to Redox Coenzyme Factor 420.[25]

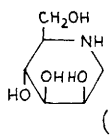
2,5-Anhydro-D-mannitol has been converted to the corresponding 1,6-diazido derivative (^{1}H n.m.r. data for which are claimed to correct previously reported data; see Vol.16, p.177, ref.29), and hence to 1,6-diamino-1,6-dideoxy-2,5-anhydro-D-mannitol and derivatives, which were incorporated into some chiral macrocyclic polyether ligands.[26] Cycloadducts formed between glycals and azodicarboxylate (see Chapter 9) on reduction with sodium cyanoborohydride - zinc iodide gave the corresponding 1,5-anhydroalditols, e.g., the glucitol derivative (6); the 1-deuterio analogue (7) was similarly prepared using cyanoborodeuteride.[27]



(6) R^2 = H
(7) R^2 = ^{2}H
R^1 = $SiMe_2Bu^t$



(8) R = CH_2OH
(9) R = H

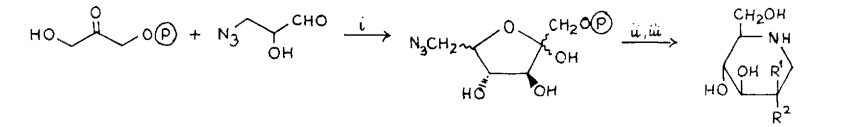


(10)

An aminomethyl C-glycoside derivative is mentioned in Chapter 3.

The burgeoning interest in cyclic imino-alditol derivatives is reflected in many papers in this field. α-Homonojirimycin (2,6-dideoxy-2,6-imino-D-glycero-L-gulo-heptitol)(8) has been isolated from the neotropical liana Omphalea diandra L; it is an inhibitor of several glucosidases.[28]

Conventional reactions have been used to prepare 1-deoxy-nojirimycin (9) from D-glucose via a protected 5-azido-glucofuranose intermediate, together with minor amounts of the manno epimer (10).[29] The manno-isomer was also synthesized, more satisfactorily, from D-mannose by an analogous sequence; in this case, a concomitant elimination occurred along with the required displacement of a 5-O-triflate ester when either azide or benzylamine was used.[30] Compounds (9) and (10) have also been synthesized by an enzyme-catalysed process as indicated in Scheme 5; 1,4-dideoxy-1,4-imino-D-arabinitol was also made from the same azido-hydroxypropanal using

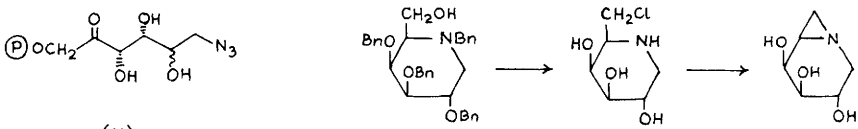


Reagents : i, Aldolase ; ii, Phosphatase ; iii, H_2, Pd/C

(9) R^1=H, R^2=OH
(10) R =OH, R^2=H

Scheme 5

a transketolase reaction with hydroxy-pyruvate; in this case, only the R-epimer reacted.[31] Another group has used this same propanal reagent with dihydroxyacetone phosphate in the presence of D-fructose 1,6-diphosphate aldolase to obtain, via the acyclic intermediates (11), 1-deoxy-mannojirimycin (10) as the major product with minor amounts of the gluco-epimer (9).[32]

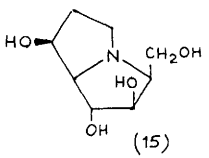


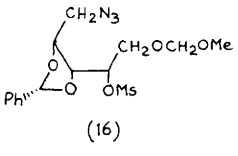
(11) (12) (14) (13)

The piperidine (12) has been converted to the aziridine (13) by conventional steps via the chloro-derivative (14); the aziridine was a potent irreversible inhibitor of green coffee bean α-galactosidase.[33]

Piperidine analogues of neuraminic acid are mentioned in Chapter 16, and a detailed n.m.r. study of N-methyl-1-deoxynojirimycin is referred to in chapter 21. 1-Deoxy-mannojirimycin is also mentioned in Chapter 19.

Several papers have dealt with pyrrolidine analogues. D-Xylose has been converted routinely to 4-amino-4-deoxy-L-arabinose, which on hydrogenation in weakly acid solution yielded 1,4-dideoxy-1,4-imino-L-arabinitol.[34] Full details of a synthesis of 2,5-dideoxy-2,5-imino-L-iditol have appeared.[35] (see Vol. 21,p.177) Fleet's group have published papers on the synthesis of 1,4-dideoxy-1,4-imino-D-glucitol and -D-allitol from D-galactono-1,4-lactone and D-gulono-1,4-lactone respectively,[36] and of 1,4-dideoxy-1,4-imino-D-talitol from 2,3:5,6-di-O-isopropylidene-D-mannose, and hence, by periodate cleavage, 1,4-dideoxy-1,4-imino-D-ribitol.[37] They have also reported the isolation of 3,8-diepialexine (15) from seeds of Castanospermum australe.[38] Other bridgehead-nitrogen bicyclic derivatives related to swainsonine are mentioned in Chapter 24.


(15)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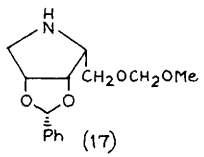
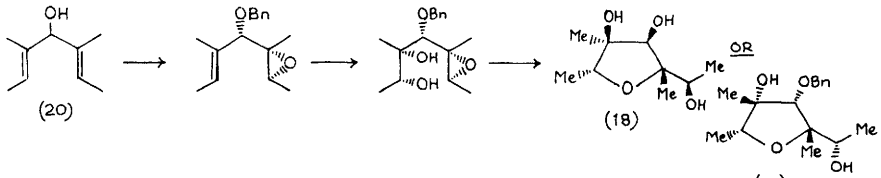
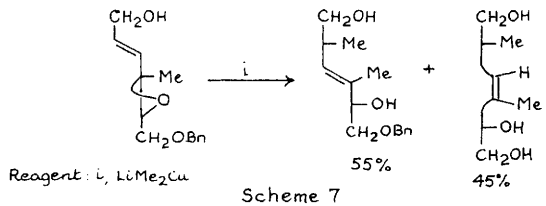

(17)

An improved synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol derivatives, required for preparing swainsonine, starts from 3,4-O-benzylidene-D-ribono-1,5-lactone, going via the azido-ribitol (16) to the pyrrolidine (17).[39]

1.4 Miscellaneous Alditols. - 2-C-Methyl-D-erythritol has been isolated from the autumn leaves of Liriodendron tulipifera.[40] Asymmetric synthesis of poly-substituted tetrahydrofuran derivatives (18) and (19) have been achieved using Sharpless oxidation of the divinylcarbinol (20) as indicated in Scheme 6; compound (19) was incorporated into verrucosidin.[41] S_N2'-Additions to acyclic vinyloxiranes can yield unsaturated alditol derivatives as illustrated in Scheme 7.[42]


(20) (18) (19)

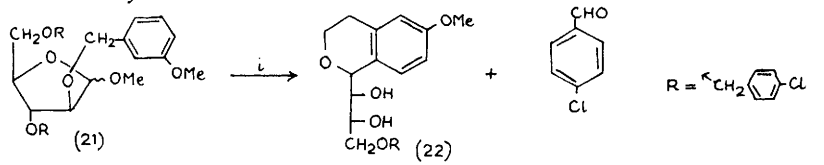
Scheme 6


Reagent: i, $LiMe_2Cu$

Scheme 7

Reaction of 1,6-dichloro-1,6-dideoxy-D-mannitol with hexaethyl phosphorous amide leads to 2,3:4,5- and 2,4;3,5-bis-cyclicphosphoramide derivatives.[43]

D-Glucose has been converted to 1-thio-D-glucitol derivatives, including mono- and di-sulphide dimers.[44] Stannic chloride reduction of the arabinoside benzyl ether (21) yielded the glyceryl-heterocycle (22)(Scheme 8); the paper discusses the mechanism of the reaction involved in detail.[45] Nitroheptenitol derivatives undergo



Reagents: i, $SnCl_4$-CH_2Cl_2

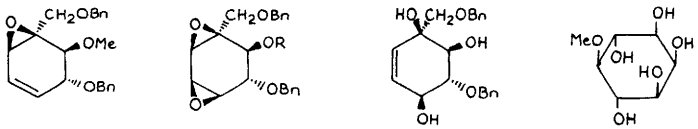
Scheme 8

Michael addition with β-dicarbonyl compounds to yield adducts which readily cyclize to polyhydroxyalkylated heterocyclic derivatives (difuranylhydroxylamines).[46] N.m.r. data on peracetylated 1-deoxy-1-nitroheptitols have been used to deduce preponderant conformations in solution; these were compared with data from other alditols having the same configurations.[47]

The cyclopropyl chemistry of a D-arabino-tetritol-1-yl-nitrocyclopropane leading to branched-chain compounds is mentioned in Chapter 14. A thiolane derived from D-mannitol is referred to in Chapter 11.

2 Cyclitols

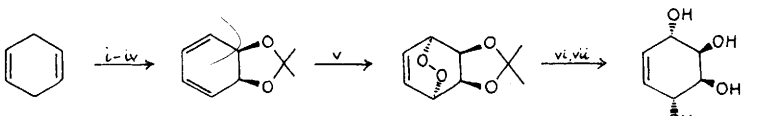
A new digalactosyl cyclitol from the seed balls of sugar beet has been characterized as O-α-D-Gal p(1→6)-O-α-D-Gal p(1→2)-1-D-chiro-inositol.[48] A series of cyclitol derivatives (23)-(25) have been



isolated from the stem bark of Monanthotaxis buchananii.[49] The configuration of sequoyitol (26) has been established by ^1H n.m.r.[50]

Racemic cyclohexane-1,2,3,4-tetrols have been prepared via endoperoxides of cyclohexa-1,3-diene.[51] Cyclohexa-1,4-diene has served as a starting material for synthesizing conduritol-A (27), as outlined in Scheme 9.[52]

Diastereoisomeric myo-inositol mannosides have been prepared



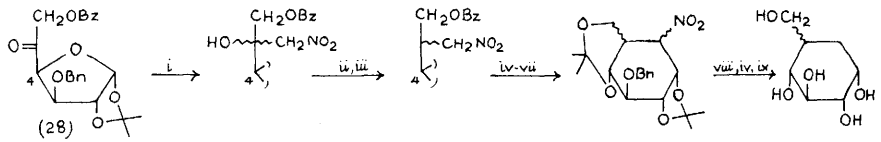
Reagents: i, Br_2; ii, $KMnO_4$; iii, $Me_2C(OMe)_2$-H^+; iv, DBU; v, O_2-hν-tetraphenylporphyrin; vi, $CS(NH_2)_2$-MeOH; vii, HCl-MeOH

Scheme 9

using an ortho-ester procedure with racemic acetates of myo-inositol.[53] Glycosidation reactions and syntheses of enantiomeric myo-inositol derivatives have been reviewed.[54]

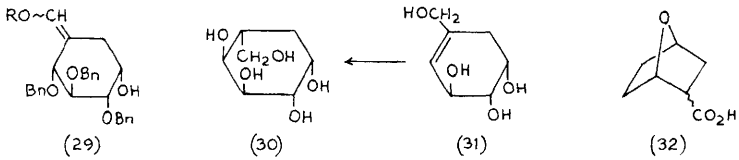
Mono-pseudo-trehaloses with all four possible α- or β-linkages have been prepared, together with the diastereoisomers containing the L-pseudo sugar. Standard methods using the racemic α- or β-ψ-glucose together with 1-O-acetyl-D-glucose derivatives were employed.[55] Pseudo-trehalosamine has been synthesized from racemic α-ψ-glucose using a 2-deoxy-2-dinitrophenylamino-D-glucosyl bromide derivative.[56]

The synthesis of pseudo-sugars has been reviewed.[57] ψ-α-D-Glucopyranose and ψ-β-L-idopyranose have been made from D-glucose via nitromethane addition to the 5-keto intermediate (28) as outlined in Scheme 10.[58] Similarly ψ-α- and β-D-arabinofuranose and ψ-β-L-xylofuranose were made from D-glucose, using lead tetra-acetate to cleave the C(1)-C(2) bond before cyclization of the deoxy-nitromethyl sugar.[59] Barton's group have used a Wittig



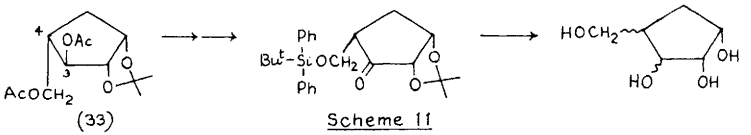
Reagents: i, $MeNO_2$, NaH, 15-Crown-5; ii, Ac_2O-H^+; iii, $NaBH_4$; EtOH; iv, HOAc, H_2O; v, KF, 18-Crown-6, DMF; vi, NaOMe, MeOH; vii, $Me_2C(OMe)_2$, H^+; viii, Bu_3SnH; ix, Na-NH_3(l).

Scheme 10

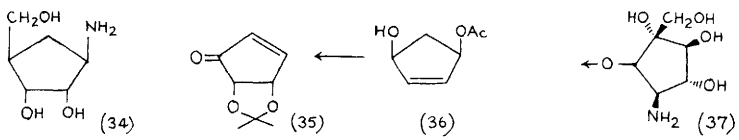


reaction on a cyclohexanone obtained by Ferrier rearrangement of a glucose derivative leading to intermediate (29) in an alternative synthesis of ψ-α-D-glucopyranose and ψ-β-L-idopyranose, and they also obtained ψ-β-L-altropyranose (30), together with the α-gluco isomer, by Brown's borane - hydration procedure on the cyclohexene (31), which could be obtained from the Ferrier rearrangement reaction.[60] The furan - acrylic acid Diels-Alder adducts (32) have been used to prepare a range of ψ-D,L-hexopyranoses using standard hydroxylation and anhydride ring opening procedures, including allo-, manno-, and galacto-isomers.[61]

The previously-reported procedure for synthesizing ψ-furanoses for carbocyclic C-nucleosides by acetoxymethylene-malonate addition to cyclopentadiene (see Vol. 20, p. 214) has been modified to give chiral products by asymmetric synthesis using (-)-menthyl malonate reagent.[62] ψ-Pentofuranoses have also been prepared from D-erythrose via the initially-obtained ψ-β-L-arabinofuranose derivative (33)(known procedure) which could be isomerized at C(3) and C(4) using a 3-keto intermediate (Scheme 11); ψ-β-D-ribosylamine (34), a key intermediate for ψ-nucleosides, was also prepared.[63]



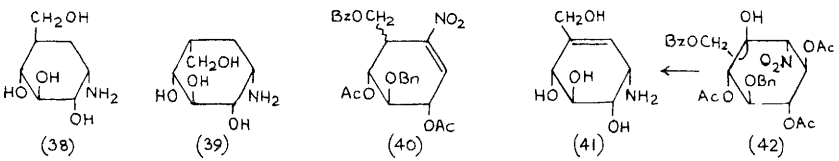
(33) Scheme 11



(34) (35) (36) (37)

The cyclopentenone (35), a chiral precursor for neplanocin, has been prepared from the intermediate (36) obtained by chiral, enzymatic hydrolysis of cis-3,5-diacetoxycyclopentene.[64] Biosynthetic studies have been made on the carbocyclic ψ-pentofuranose (37) which occurs ether-linked to bacteriohopanetetrol in Methylobacterium organophilum.[65]

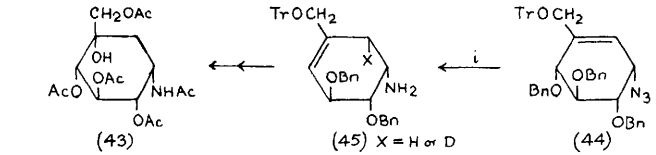
The 5-C-nitromethyl sugars mentioned above, obtained from D-glucose, have also been used to prepare validamine (38) and 5-epi-validamine (39), by use of a Michael addition of ammonia to the nitrocyclohexene intermediates (40); a related sequence yielded



(38) (39) (40) (41) (42)

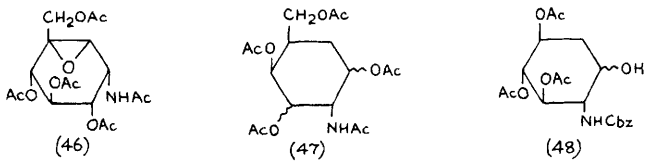
valienamine (41) following C(1)-acetoxy displacement by ammonia in the nitro-cyclitol precursor (42).[66] Penta-N,O-acetylvaliolamine (43) has been prepared from a known cyclohexene precursor (44) derived from glucose; unexpected allylic reduction accompanied azide reduction giving (45), which was stereospecifically cis-hydroxylated leading to (43)(Scheme 12).[67] Two stereoisomers of valienamine

epoxide have been synthesized to confirm the configuration of an α-amylase inhibitor obtained from S.flavochromogenus, which proved to have the stereochemistry of (46).[68]



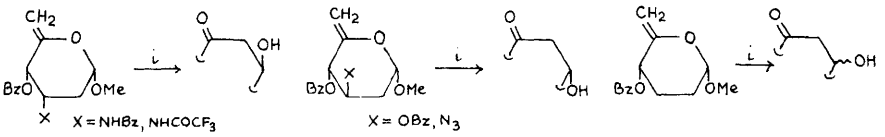
Reagents: i, $LiAlH_4$ or $LiAlD_4$, Et_2O

Scheme 12



Periodate oxidation of 4,6-O-isopropylidene-ψ-α-D-galactopyranose followed by basic nitromethane yielded 2-nitro-analogues which were converted to amino analogues (47).[69] The furan-acrylic acid Diels-Alder adduct has served as a source for racemic penta-acetyl valid-amine and its uronate analogue, together with the regioisomeric penta-acetyl 2-amino-2-deoxy-ψ-α-D,L-mannopyranose (stereoisomer of (47)).[70] The Ferrier ring synthesis has been used to convert a 2-amino-2-deoxy-hex-5-enoside derivative to an amino-inosose and hence the amino-cyclitols (48), which were coupled to aromatic compounds to give analogues of podophyllotoxin.[71]

The carbocyclization of 3-substituted- and 3-deoxy-hex-5-eno-pyranosides has been studied, and is summarized in Scheme 13; in each case the new hydroxy group was trans to the 3-substituent,



Reagents: i, $HgCl_2$, Me_2CO-H_2O

Scheme 13

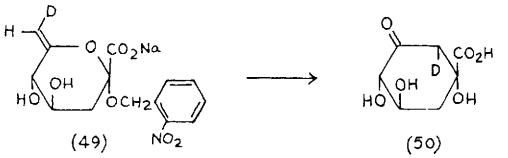
which was explained by putative complexation of the mercury reagent and the substituent, resulting in delivery of the methylene carbon to the same face; in the absence of a 3-substituent, both hydroxy-centre stereoisomers were obtained.[72]

As an alternative to the Ferrier procedure using mercury compounds, a palladium (II)-catalysed reaction has been reported, and

was applied to the conversion of 2-acetamido-2-deoxy-D-glucose to a 4-amino-inosose derivative.[73]

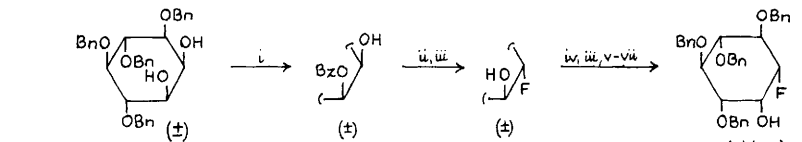
The oligosaccharides acarbose and adiposin-2 have been synthesized by coupling protected valienamine to a trisaccharide 3",4"-epoxide derived from 1",6"-anhydro-maltotriose; the anticipated 3"-linked regioisomers were obtained along with the required 4"-linked compounds.[74]

Photolytic deprotection of the ulosonic acid p-nitrobenzyl glycoside (49) did not yield the expected enolpyranose but the rearranged 3-dehydroquinic acid (50); the stereospecific label rearrangement implies a chair transition state, and suggests the biosynthetic pathway by this route is not enzyme-catalysed.[75]



Various reactions of 2,3-anhydro-1,5,6-tri-O-mesyl-epi-inositol have been used to prepare 3-substituted-muco-inositol derivatives (azido-, bromo-, and chloro-deoxy), including its 1,3,5,6-tetra-O-mesylate.[76]

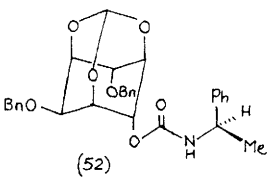
1 L-1-Deoxy-1-fluoro-myo-inositol (51) has been prepared from myo-inositol by the procedure outlined in Scheme 14, including a camphonate resolution.[77]



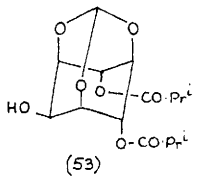
Scheme 14

Inositol Phosphates. - 1D and 1L-Myo-inositol 1,3,4,5-tetraphosphate have been prepared by a procedure similar to that used for the racemate reported last year (see Vol. 21, p. 183); the enantiomers of the starting 2,4-di-O-benzyl-myo-inositol were obtained following resolution of the diastereoisomeric carbamates (52) or enantioselective enzymic deacylation of meso-4,6-di-O-butanoyl 1,3,5-orthoformate (53).[78] Another synthesis of chiral myo-inositol 1,3,4-triphosphate resolved a 4,5-dibenzyl ether derivative using a chiral

column or using diastereoisomeric menthoxyacetate derivatives.[79] Other papers describe the "total" synthesis of optically active myo-inositol 1,4,5-triphosphate and 1,3,4,5-tetraphosphate,[80] the synthesis of D-myo-inositol 1,2-cyclic-4,5-, 1,4,5-, and 2,4,5-triphosphate,[81] the synthesis of D,L-myo-inositol 1,4,5-triphosphate



(52)



(53)

from cis-cyclohexa-1,3-diene-1,2-diol obtained by microbial oxidation of benzene,[82] and syntheses of myo-inositol 1,3,4- and 1,4,5-triphosphate and 1,3,4,5-tetraphosphate.[83]

Sulphur analogues have also been prepared. A report on the synthesis of D,L-myo-inositol 1-phosphate includes the synthesis of its thiophosphate analogue (using $PSCl_3$),[84] and D,L-myo-inositol 1,2-cyclic thiophosphate has been made, which gives rise to separable endo- and exo-sulphur diastereoisomers.[85] Myo-inositol 1,4-diphosphate 5-thiophosphate has been prepared and tested biochemically.[86] The C(1)-tritiated isomer of myo-inositol 1,3,4-triphosphate has been prepared, as well as 2-deoxy-2-fluoro analogues (using DAST); both epimers and the 2,2-difluoro compound were obtained.[87]

D,L-Myo-inositol 1,4,5-1-H-phosphonate has been synthesized.[88]

An analogue of phosphatidyl inositol 4,5-diphosphate has been prepared from chiral 1,4-di-O-benzyl-5,6-di-O-allyl-myo-inositol,[89] and D-myo-inositol 1-phosphate, obtained from a resolved 1,2:4,5-di-O-isopropylidene-myo-inositol 3-silyl ether derivative, has been coupled with 1,2-dipalmitoyl-sn-glycerol.[90]

The separation of all eight inositol stereoisomers, and a method for determining myo-inositol using immobilized enzymes are mentioned in Chapter 23.

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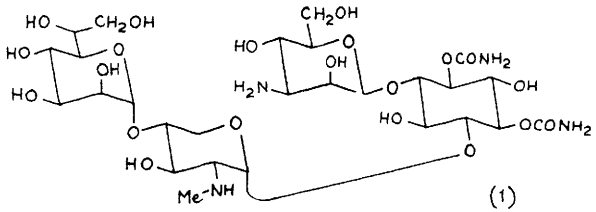
19
Antibiotics

A review on some recent trends in the chemistry of carbohydrate-containing antibiotics has been published (in Russian).[1]

1 Amino-Glycoside Antibiotics

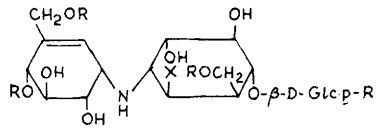
A new amino-glycoside antibiotic, boholmycin (1), has been isolated from a strain of S. hygroscopicus; the pseudo-tetrasaccharide contains a heptose, two amino-sugars, and dicarbamoyl-scyllo-inositol.[2] A complex of antibiotics produced by a strain of S. fradiae, "dekamycin", has been shown by m.s. and n.m.r. techniques to be mainly a mixture of neomycins.[3]



(1)

1-N-(D-Threo- and racemic erythro-3-amino-2-hydroxy-butanoyl)-2',3'-dideoxykanamycin A has been prepared using a standard esterification procedure with the corresponding azido-hydroxy-butanoic acid.[4] Glucuronide saponins have been used to furnish paromamine and ribostamycin by means of lead tetraacetate or anodic oxidative decarboxylation procedures.[5] Phase-sensitive 2D ^{1}H-^{1}H COSY spectra have been used to identify amikacin and its N-hemisuccinyl derivatives.[6]

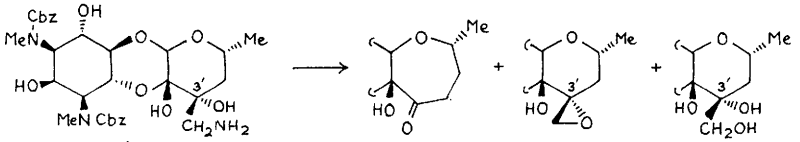
An intermediate used in the synthesis of (+)-validamycin B mentioned in last year's report (see Vol. 21, p. 188) has now been used to prepare (+)-validoxylamine A, giving a formal total synthesis of validamycin A.[7] A full paper on the synthesis of (+)-validamycin B and validoxylamine B has been published.[8] New n.m.r. methods have been used to reinvestigate the position of glycosidic linkage in minor components of the validamycin complex, encompassed by the general formula (2); α-D-glucopyranoside units may be found at any of the positions indicated (one unit per component).[9] Several pseudo-sugar analogues of trehalosamine have been prepared



(2) R = H or α-D-Glc.p, X = H
Validamycin A X = H, R = H
Validamycin B X = OH, R = H

from appropriate ψ-DL-glucopyranose and ψ-DL-mannopyranose derivatives and glycosyl halides.[10]

Highly active 3'-aminomethyl-dihydrospectinomycins have been prepared by an efficient procedure via spectinomycin 3'-cyanohydrin intermediates.[11] Spectinomycin analogues have also been prepared incorporating ring-expanded septanose sugars made via the Tiffeneau-Demjanov diazonium ion rearrangement of 3'-(R)-N,N'-dibenzyloxycarbonyl-3'-aminomethyl-dihydrospectinomycin (3)(Scheme 1); the 3'-(S)-isomer of (3) only gave epoxide.[12]



(3)

Scheme 1

The active principle of blastolysin has been characterized as incorporating oligomers of muramic acid with peptide residues or teichoic acid; some related di- and tetra-saccharide compounds were prepared.[13]

2 Macrolide Antibiotics

Structural studies on the desertomycin complex have confirmed and extended previous evidence to show that its major component is a 42-membered non-polyene macrolide ring carrying a residue of α-D-mannopyranose.[14,15] (See Vol. 17, p.175.)

The structure and biological activity of lipiarmycin B have been investigated. It contains the same sugars (rhamnose and 5-C-methyl-rhamnose) and 18-macrolide ring as does lipiarmycin A, but carries an isobutyryl residue at O-2 rather than O-4 in the 5-C-methyl-rhamnose unit.[16] Nystatin A_3 is an L-digitoxose glycoside of nystatin A_1.[17]

The synthesis of 12- and 14-macrolides from sugars has been reviewed (in Russian).[18] A seven-step sequence for removing desosamine and oleandrose from oleandomycin has been described, the amino-sugar being selectively hydrolysed following Cope elimination

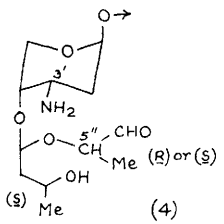
of the amino group.[19]

The ^{13}C n.m.r. spectrum of erythromycin A has been completely assigned (correcting previous errors),[20] and ^{1}H and ^{13}C n.m.r. data have been reported for neoisomidecamycin.[21] N.m.r. spectra and molecular modelling have been used to study the conformation of 9-(S)-9-hydroxy-9-deoxo-erythromycin A and some related derivatives.[22]

3 Anthracycline and Related Polycyclic Antibiotics.

A review of the synthesis of antitumour antibiotics includes references to anthracycline derivatives,[23] and the synthesis of anthracycline compounds using regiospecific cycloadditions of homophthalic anhydrides has also been reviewed (in Japanese).[24]

New potent anthracyclines, barminomycin I and II, have been isolated from a strain of Actinomadura which also produces carminomycin. They are 4'-O-acetalated derivatives (4, part structure) of the carminomycins; aminol and Schiff base derivatives can form by condensation between the 5''-formyl and 3'-amino groups.[25] Antibiotic SN-07 is identical to barminomycin I.[26]



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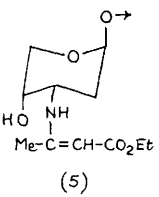
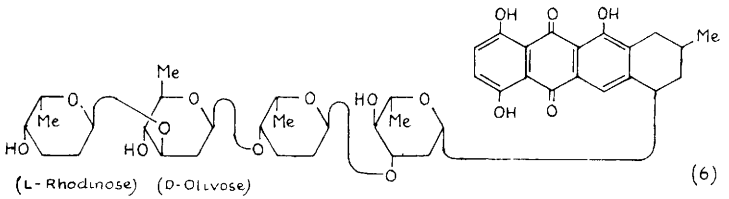


(5)

A method for preparing 4'-acyl derivatives of anthracyclines via a 3',4'-oxazoline intermediate prepared from the antibiotic (adriamycin exemplified) using trimethyl ortho-acetate has been described.[27] N-Enamine derivatives have been prepared from daunorubicin, the most potent anti-leukemic compound being the 3-substituted ethyl but-2-enoate derivative (5, part structure).[28] Amino-glycal precursors to daunosamine derivatives are mentioned in Chapter 9, and the glycosidation of daunomycinone derivatives is referred to in Chapter 3.

Galtamycin (6), a new anthracycline antibiotic, has been identified as a C-glycoside in which a tetrasaccharide is linked to galtamycinone.[29] New aureolic analogues, demethylchromomycin A_2 and A_3 and demethylolivomycins A and B, produced by S. aburaviensis, have been identified as 4-O-demethyl analogues of the parent compounds, i.e., they contain 4-O-demethyl-chromose A (oliose).[30]

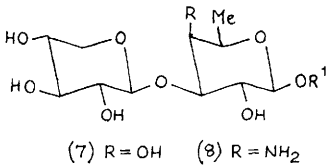


(6)

N.m.r. studies on chromomycins and olivomycins which contain di- or tri-saccharide units have been made, correcting some previous ^{13}C and ^{1}H assignments; the data support the assigned $\alpha 1 \rightarrow 3$ disaccharide linkage, and information generally useful for structural saccharide studies was reported.[31]

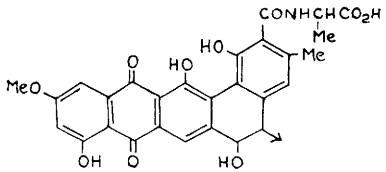
Full details of the synthesis of nogalamycin cogeners have been published (see Vol. 19, p.257;[32] Vol. 20, p.192 [33]), and the results of some structure-activity studies given.[34] An alternative synthesis of the fused glycosidic unit in nogalamycin using non-carbohydrate precursors and leading to a racemic product has been described.[35]

New antifungal antibiotics, benanomicins A (7) and B (8), have been isolated from an Actinomycete; evidence was presented to indicate that they possess a benzo[a]naphthalene quinone skeleton



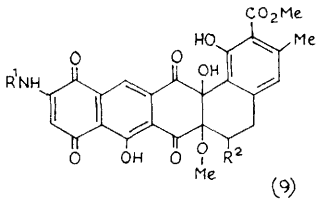
(7) R = OH (8) R = NH_2

R^1 =



carrying a disaccharide unit composed of D-xylose and D-fucose or thomosamine (4-amino-4,6-dideoxy-D-galactose).[36,37] Very closely related compounds, pradimicin A and B, have been obtained from Actinomadura hibisca (pradimicin A is (8), R = NHMe).[38] A related aglycone is present in some new antibiotics SF 2446 A1-A3 and B1-B3, generalized in structure (9); in these compounds 2,4-di-O-methyl-L-rhamnopyranose is present as part of an α- or β-linked glycosylamine.[39]

Sibanomycin (10) is a new pyrrolo[1,4]benzodiazepine antitumour antibiotic produced by a Micromonospora strain; it contains 4,6-dideoxy-3-C-methyl-4-methylamino-α-L-mannopyranose linked to a tricyclic aglycone;[40] a very closely related compound DC 102 (11) has



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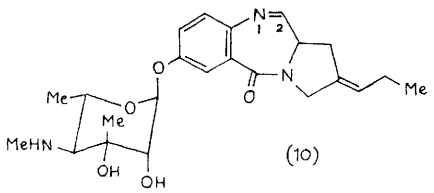

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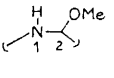


(11)

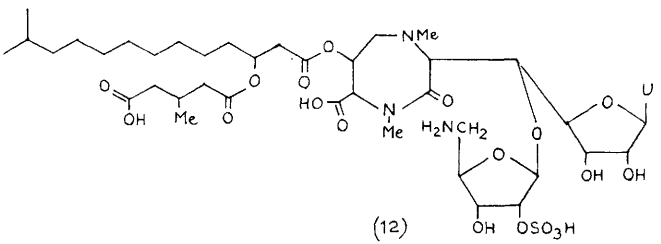
been isolated from a Streptomyces strain.[41]

The structures of urdamycins C and D have been reported; they possess the same sugars as does urdamycin A, but have a more elaborate pentacyclic aglycone (see Vol. 20, p. 191-2).[42]

4 Nucleoside Antibiotics

Reviews have been published on the structure, biological activity, and biosynthesis of nucleoside antibiotics [43] and on synthetic approaches to them.[44]

Liposidomycin B, a powerful inhibitor of bacterial peptidoglycan synthesis, has been assigned structure (12).[45] The structure of

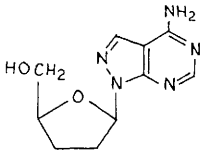


(12)

capuramycin has been confirmed by n.m.r. and X-ray crystal data (see Vol. 20, p. 193; the uronamide has an L-talo rather than the D-allo configuration given there).[46]

Improved syntheses of tubercidin and related pyrrolo[2,3-d]pyrimidine nucleosides using the stereospecific sodium salt procedure have been reported.[47] An enzymic synthesis of ribavirin has been described which uses 1,2,4-triazole-3-carboxamide with purine nucleoside reagents.[48]

5'-α-D-Glucopyranoside derivatives of tubercidin and toyocamycin, besides the parent compounds, are responsible for the cytotoxic, fungicidal activity of some blue green algae.[49] The dideoxy nucleoside analogue (13) has been prepared from the 2'-deoxy-ribose analogue by a radical 3'-deoxygenation procedure; it was inactive againtst HIV.[50] Amino-acyl analogues (14) of ascamycin (15) have been prepared and tested,[51] and base analogues (U, T, C, 5-Me-C) of ascamycin have likewise been converted to N-acyl sulphamido analogues.[52] Phosphono- and methylphosphino- analogues of amino-acyl-5'-adenylic acid (16) have been prepared which show interesting



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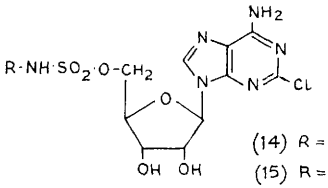
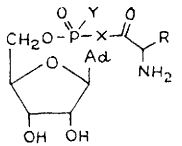
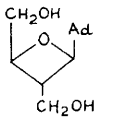


(14) R = L-Phe, L-Pro, D-Ala
(15) R = L-Ala



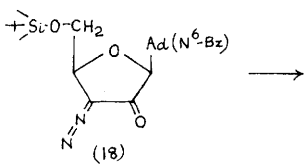
(16) X = O → X = CH_2
Y = OH → Y = Me



(17)

antibiotic activity.[53] Some 5'-O-phosphatidyl derivatives of antibiotic nucleosides showed enhanced antileukemic activity compared with the parents.[54]

Further syntheses of oxetanocin have been described. A branched-chain tetroside whose synthesis is covered in Chapter 14 was converted in standard steps to oxetanocin (17) together with its α-anomer.[55] Another sequence started from adenosine, and proceeded via a 3'-deoxy analogue to the diazoketone (18), which underwent the necessary ring contraction to give (19) on photolysis.[56] An oxetanocin analogue derived from 3,5-anhydro-D-xylofuranose is mentioned in Chapters 20 and 22.



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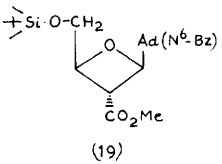

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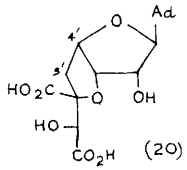
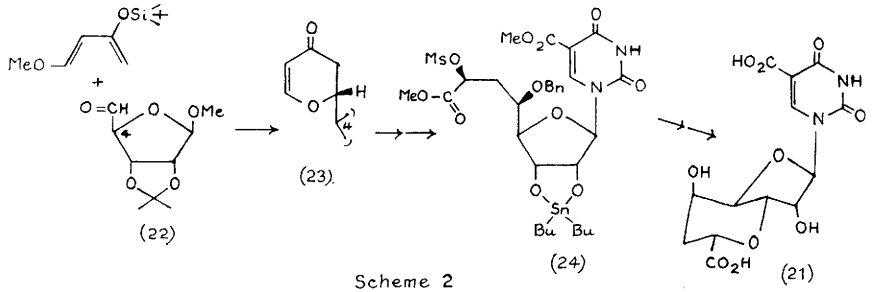


(20)

The C(4')-C(5')-dihydro cis-analogue (20) of griseolic acid has been prepared, and found to be a much weaker inhibitor of phosphodiesterase activity than the parent acid or the C(4') trans-fused

epimer of (20).[57]

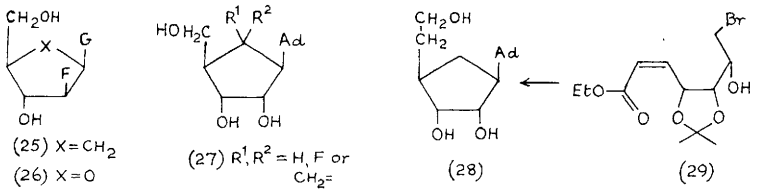
Two syntheses of octosyl acid A (21) have been reported. In one case the ribodialdose derivative (22) underwent a hetero Diels-Alder reaction to give the pyrone derivative (23) which was then



Scheme 2

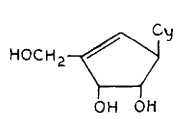
converted to (21) via the octosyl intermediate (24)(Scheme 2)(see also Chapter 17).[58] In the other case the octosyl side-chain was built by condensation of a 5-deoxy-5-nitro-ribofuranose derivative with 2,3-O-isopropylidene-D-glyceraldehyde.[59]

Carbocyclic Analogues - Carbocyclic 2'-fluoro-ara-guanosine (25) has been synthesized by two routes from cyclopentane precursors, with enzymic resolution; the (+)-isomer showed extremely high levels of activity against herpes simplex viruses without affecting uninfected cells, whereas normal 2'-fluoro-ara-guanosine (26) was ~1000 times less active.[60]



Aristeromycin (carbocyclic adenosine) has been converted to its 2'-deoxy-2'-fluoro-ara-analogue using DAST together with a 3,5-dibenzoate, the product being a potent antiviral agent.[61] Epimeric 6'-fluoro-analogues of aristeromycin as well as its 6'-methylene derivative (27) have also been prepared and found to be potent inhibitors of a hydrolase, but are not antiviral.[62] Racemic 6'-β-hydroxyaristeromycin has also been made by standard steps from 5-t-butoxynorbornadiene.[63] L-Ribono-γ-lactone served as a starting material for synthesizing 5'-homoaristeromycin (28) via the ω-bromo-unsaturated ester (29).[64] The neplanocin analogue cyclopentenyl-cytosine (30) has been synthesized from the corresponding cyclo-

pentenylamine, and found to have antitumour and antiviral properties.[65]



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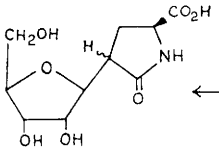

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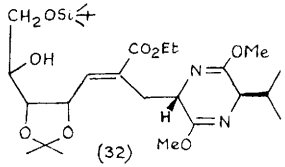
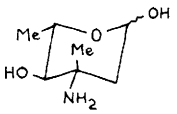


(32)

C-Nucleosides - A synthesis of showdomycin from D-ribose has been described which involves condensation of a bromo-acetate Wittig reagent with an aldehydo-ribose derivative (for a similar synthesis using a chloro-acetate analogue, see Vol. 18, p. 183).[66] Possible intermediates (31) in C-nucleoside biosynthesis have been prepared by Michael addition of a pyrazine anion to a 2-acrylyl C-glycoside derived from D-ribose giving initially the acyclic product (32), which was then cyclized and degraded to the stereoisomers (31).[67] The synthesis of 6-(β-D-ribofuranosyl)picolinamide, an isostere of tiazofurin, is mentioned in Chapter 20.

5 Miscellaneous Antibiotics

The vancomycin relatives orienticins A - D, obtained from Nocardia orientalis, have been characterized; they contain one or two units of L-4-epi-vancosamine (33) together with D-glucose, and in the case of orienticin B, L-olivose. The amino-sugar is present either as a monosaccharide or linked with glucose as a disaccharide.[68] Chloro-orienticins obtained from related Nocardia orientalis strains contain a chlorinated aglycone linked to the same sugars present in the corresponding orienticins.[69] Selective cleavage of vancosamine and glucose from vancomycin and related antibiotics can be achieved using trifluoroacetic acid, leaving deglycosylated products which are still potent antibiotics.[70]



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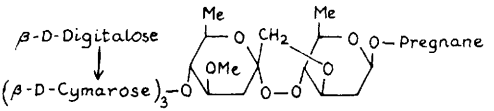
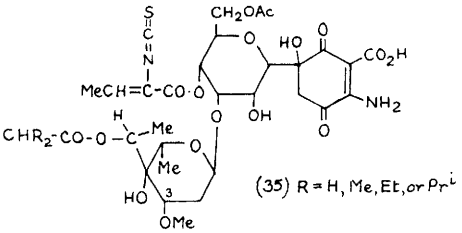


(34)

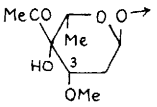
The antitumour pregnane oligosaccharide (34) periplocoside C contains a very unusual peroxy bridge linking the D-arabino-heptulose and canarose units.[71]

A new ansamycin antibiotic, kanglemycin A, obtained from a Nocardia strain, contains 3,4-O-methylene-β-digitoxose linked to the ansa chain.[72]

New paulomycin variants (35) have been isolated from S. paulus as minor components of the antibiotic complex; they contain the same nucleus and sugars as do the major components A and B, but with differing acids esterifying the branched-chain sugar; this sugar is unesterified in paulomycin F, and paulomycin E contains the corresponding acetyl branched-chain sugar (36).[73] The same workers have



(35) R = H, Me, Et, or Pr^i



(36)

related paulomycins E and F to senfolomycins A and B respectively; the compounds are apparently epimeric at C-3 of the branched-chain sugar.[74]

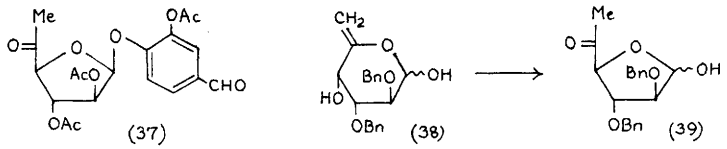
Phenelfamycins, a novel complex of elfamycin antibiotics produced by a strain of S. violaceoniger, have been characterized as a set of seven closely related components phenelfamycins A-F, and unphenelfamycin; all are glycosides of a complex acyclic polyene aglycone, which contain a mono-, di-, or tri-saccharide chain of 2,6-dideoxy-3-O-methyl-hexopyranoses.[75] Closely related compounds LL-E19020 α and β, from a S. lydicus strain, have been found to be growth-promoting agents in animals.[76]

A 'practical' synthesis of nojirimycin from D-glucose has been described, giving an overall yield of 50% from 1,2-O-isopropylidene-D-glucofuranose; oxidation of this compound with tributyltin oxide/bromine selectively gave the 5-keto sugar, which was then converted to the 5-amino-sugar and hence to nojirimycin.[77] The isolation of 1,5-dideoxy-1,5-imino-D-mannitol from S. lavendulae has been noted.[78] Other references to 1,5-dideoxy-1,5-imino-D-hexitols, including 1-deoxy-nojirimycin, are given in Chapter 18.

Quaternary ellipticine glycosides have been prepared from per-acylated glycosyl bromides with the corresponding base, many showing useful antitumour activity, some more active than doxorubicin.[79]

A full paper on the synthesis of destomycin C has appeared.[80] (See Vol. 19, p. 177.)

The degradation product (37), representing half the structure of hygromycin A, has been synthesized from D-glucose, utilizing the rearrangement (38) → (39) to form the hexosulose moiety.[81]



Structural studies on bicyclomycin have been reported which involve complete assignments of ^{1}H and ^{13}C n.m.r. spectra, and X-ray crystal structures.[82]

Chitahexaose and hexa-N-acetylchitohexaose have been reported to have *in vivo* antitumour activity.[83] Platinum (II) complexes involving cyclohexane-1,2-diamine or 2-aminomethyl-cyclohexylamine together with D-glucuronate, D-gluconate and their tetra-O-acetyl derivatives have been prepared, which also show good to excellent antitumour activity.[84]

A set of eight 4-alkylcatechol glycosides of D-glucopyranosiduronic acid have been prepared, some of which show melanoma-inhibiting properties.[85] 2-Amino-2-deoxy-sugars and 1-methylamino-1-deoxyalditols have been N-acylated with phenylalkanoic acids and aminoacids, and tested for antitumour activity; the derivative obtained from 1-methylamino-1-deoxy-D-glucitol with p-[bis(2-chloroethyl)amino]phenylacetic acid showed high activity.[86]

References to the synthesis of a part-structure of papulacandin and of disaccharide analogues of a moenomycin degradation product are given in Chapter 3, and a synthesis of prumycin from D-arabinose is referred to in Chapter 9.

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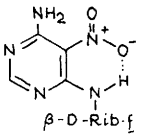
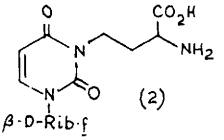
20
Nucleosides

Clitocine (1), an insecticidal nucleoside from a mushroom species, has been synthesized by two groups; in one route, the key step involved condensation of a ribofuranosylamine derivative with a 4-chloropyrimidine,[1] whilst in the other a silyl-Hilbert-Johnson approach was used.[2]



(1)

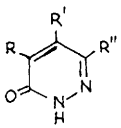


(2)

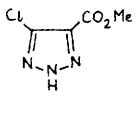
3-(3-Amino-3-carboxypropyl)uridine (2) has been isolated and characterised from human urine; it is present in smaller amounts in the urine of cancer patients.[3]

1 Synthesis

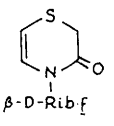
Conventional heterocycle-sugar condensation methods have been used to prepare β–D-ribofuranosyl derivatives of various mono- and bicyclic imides,[4] 3-substituted pyrroles,[5] 5-alkylcytosines,[6] N[4]-acylcytosines,[7] pyridazinones of type (3),[8] and 5-benzyl- and 5-(m-benzyloxy)benzyl uracil, acyclonucleoside derivatives of which are inhibitors of uridine phosphorylase; in this case β–D-arabinofuranosyl and 2'-deoxy systems were also prepared via the 2,2'-anhydronucleoside.[9]



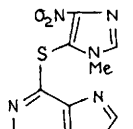
(3)



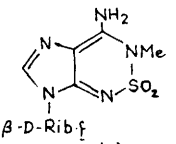
(4)



(5)



(6)



(7)

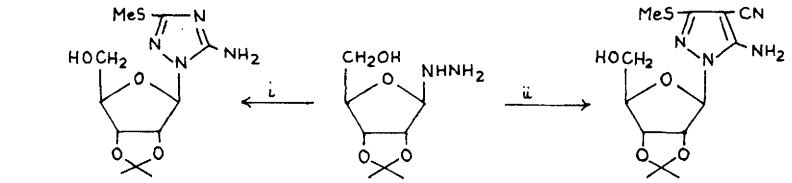
β–D-Ribofuranosyl derivatives of various 1,2,4-triazoles have been reported, along with β–D-arabinofuranosyl and 2'- and 5'-deoxy- analogues.[10,11] Ribofuranosylation of 1,2,3-triazole (4) gave the 2- substituted nucleoside,[12] while the 1,4-thiazin-3-one nucleoside (5), and its S-oxide, a potential tetrahedral intermediate analogue for enzymes in pyrimidine nucleoside metabolism, have been prepared by silyl-Hilbert-Johnson methods.[13] Also available by standard methods are β–D-ribofuranosyl derivatives of N[2]-

phenylguanine (and its 2'-deoxy analogue),[14] some halogenated 5-amino-benzimidazoles,[15] 2-methylthionaphthimidazole,[16] azathioprine (6),[17] and various pyrazolo[3,4-d]pyrimidines;[19] the sulphonyl analogue (7) of doridosine has also been reported.[19]

Reaction of pentaacylglucopyranoses or tetraacylribofuranoses with the tris-TMS derivative of $\underline{N}^2$-acetylguanine gives the $\underline{N}^7$-glycosylated products regioselectively under conditions of kinetic control ($SnCl_4$,CH_3CN,RT), whilst $\underline{N}^9$-glycosylation occurs predominantly under conditions of thermodynamic control (TMSOTf, $(CH_2Cl)_2$, reflux); this chemistry offers the first effective way of controlling the regiochemistry of formation of guanine nucleosides.[20]

The technique of solid-liquid phase-transfer glycosylation has been used for the preparation of α– and β–D-ribofuranosyl derivatives of pyrrolo-[2,3- d]pyrimidines (7-deazapurines).[21,22]

A route to pyrazole and 1,2,4-triazole nucleosides is exemplified by the cases outlined in Scheme 1.[23]



Scheme 1

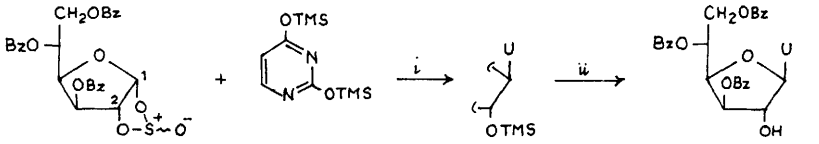
Ribofuranosyl nucleosides tritiated at the 5'-position have been prepared by borotritiide reduction of 5'-aldehydes, and also by using [5'-^{3}H]- uridine as ribosyl donor in an enzymic transribosylation using immobilised nucleoside phosphorylase.[24] Routes have been developed for the synthesis of adenosine labelled with ^{18}O at either O-2' or O-3', and for the corresponding isotopomers of ara-A; in each case label was introduced from [^{18}O]-cesium propionate by reaction with an epoxide or a triflate.[25]

Convenient routes to β–D-arabinofuranosyl derivatives of guanine, 6-thioguanine, and related purines proceed via the stereospecific sodium salt glycosylation method.[26] 4,6-Disubstituted-1-α–D-arabinofuranosyl-pyrazolo[3,4-d]pyrimidines have been prepared by standard methods,[27] as have various glycopyranosyl derivatives of 4-cyano-5,6-dimethyl-3-pyridazinone.[28]

A new route to 1', 2'-trans-nucleosides has been developed which involves the reaction of a carbohydrate 1,2-cyclic sulphite with a silylated heterocycle. The example in Scheme 2 is typical, and glycopyranosyl nucleosides were similarly prepared.[29,30]

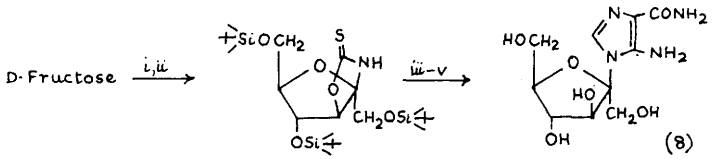
The fructofuranosyl nucleoside (8) has been synthesized from D-fructose in five steps as indicated in Scheme 3.[31] An improved route to derivatives of

D-psicofuranose and its 1-deoxy analogue, suitable for nucleoside synthesis, is discussed in Chapter 2.



Reagents: i, Δ ; ii, MeOH, HCl

Scheme 2



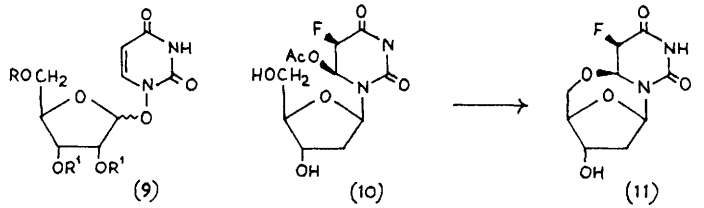
Reagents: i, KSCN, H_3O^+; ii, TBDMSCl, DMF; iii, Raney Ni; iv, NC·CN(NH$_2$)CONH$_2$; v, HCl, MeOH

Scheme 3

Mitsunobu reactions between appropriate ribose derivatives and N-hydroxyheterocycles gave novel 'C-O-N' nucleoside analogues of type (9) in moderate yield.[32] The triester (9, R=R'=Bz) is also available by interaction of the ribofuranosyl chloride with 1-hydroxyuracil and triethylamine under pressure.[33]

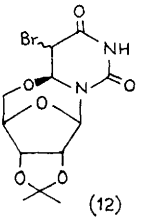
2 Anhydro- and Cyclo-nucleosides

A full account has been given of the synthesis of 3', 5'-epithio- 3', 5'-dideoxy-1-β-D-xylofuranosylpyrimidines (see Vol. 20, p.204 and Vol. 21, p. 204).[34] Earlier work on the synthesis of 6,3'-methanouridine (Vol. 20, p.207) and its 2'-deoxyanalogue (Vol. 21, p.205) has been more fully reported and extended to cytidine[35] and thymidine cases.[36]

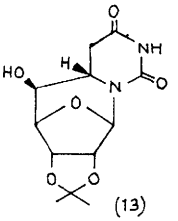


When 2'-deoxyuridine was allowed to react with acetyl hypofluorite, adduct (10) was formed together with the alternative cis-diastereomer. Treatment of (10) with ferric chloride in dry acetonitrile gave the O^6, 5'-cyclonucleoside (11), and the other diastereomer behaved similarly. Similar reactions occur with uridine and ara-U, but in the latter case some O^6, 2'-cyclonucleoside formation is also found.[37]

Treatment of isopropylidene uridine with NBS in chloroform and acetic acid gives a mixture (1:1) of the diastereomers (12), both of which with base gave 5-bromo-2', 3'-O-isopropylideneuridine.[38] The 6,5'-cyclonucleoside (13)



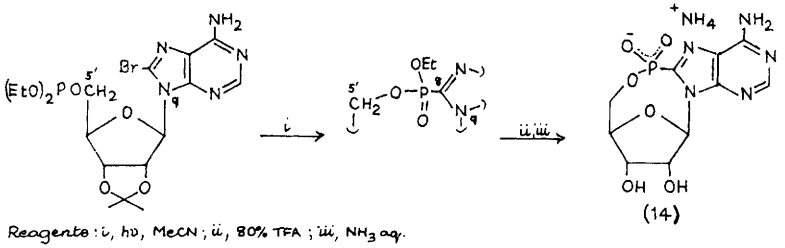
(12)



(13)

was prepared by treatment of 2',3'-O-isopropylideneuridine-5'-aldehyde with tributyltin hydride and AIBN; a similar reaction with N^6-benzoyl-2',3'-O-isopropylideneadenosine 5'-aldehyde gave an analogous 8,5'-cycloadenosine.[39] Treatment of 2',3'-O-isopropylidene purine nucleosides with N-halogenosuccinimides in acetic acid gives 5'-O, 8-cyclonucleosides.[40]

A photochemical cyclisation was used as a key step in the synthesis of a novel type of cyclonucleoside, P, 5'-anhydroadenosine-8-phosphoric acid (14) (Scheme 4).[41]



(14)

Reagents: i, hν, MeCN; ii, 80% TFA; iii, NH_3 aq.

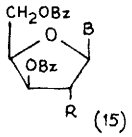
Scheme 4

3 Deoxynucleosides

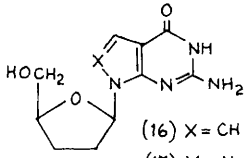
A number of 2'-deoxy-β-D-threo-pentofuranosyl nucleosides (15, R=H) have been prepared from alcohols (15, R=OH) by Barton deoxygenation; the alcohols were prepared by selective hydrazinolysis of 2'-O-acetyl systems.[42] 3'-Deoxy-β-D-threo-pentofuranosyl nucleosides can be prepared efficiently from 2',3'-anhydro-β-D-lyxofuranosyl analogues by reductive opening of the epoxide with lithium triethylaluminium hydride.[43] An improved preparation of 5'-deoxyadenosine uses a standard coupling procedure, as opposed to manipulation of adenosine itself.[44]

2',3'-Dideoxyinosine has been prepared by Barton deoxygenation of the 5'-O-benzoyl-2'-deoxy compound.[45] Liquid-liquid and solid-liquid phase transfer methods have been used to prepare 2'-deoxyribofuranosides of pyrrolo[2,3-d]pyrimidines (7-deazapurines),[46,47] which have been converted to 2',3'-dideoxycompounds by Barton-type procedures;[47,48] amongst the

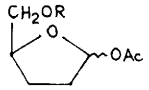
analogues so produced is the 7-deaza-analogues of dideoxyguanosine (16).[48] The sodium salt glycosylation procedure has also been used for making 2'-deoxynucleosides of 7-deazapurines, and 2',3'-dideoxy analogues were again accessible by deoxygenation.[49] Solid-liquid phase transfer was also employed to produce 2-deoxy-β–D-ribofuranosides of pyrazolo[3,4-d]pyrimidines (8-aza-7-deazapurines);[50,51] the guanosine analogue was deoxygenated to give (17).[50] Very similar methods were used to prepare 3,7-dideaza-2'-deoxyadenosine and related pyrrolo[3,2-c]pyridine 2'-deoxy- and 2',3'-dideoxynucleosides.[52]



(15)



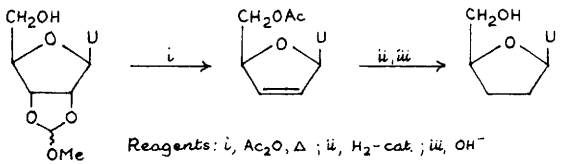
(16) X = CH
(17) X = N



(18)

An alternative approach to the synthesis of 2',3'-dideoxynucleosides which has been developed by two groups[53,54] involves the intermediacy of compounds (18; R=Bz or TBDMS) which are accessible from deaminative lactonisation of L-glutamic acid. Using this route ddC[53,54] and ddA[54] have been prepared.

A direct conversion of ribonucleosides into 2',3'-dideoxy systems has been applied to the synthesis of ddU (Scheme 5); dideoxy-adenosine and --inosine could be subsequently prepared by microbiological base exchange.[55]



Reagents: i, Ac_2O, Δ ; ii, H_2-cat ; iii, OH^-

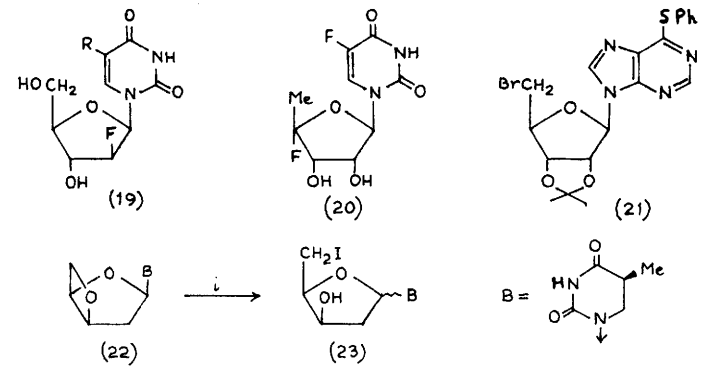
Scheme 5

4 Halogenonucleosides

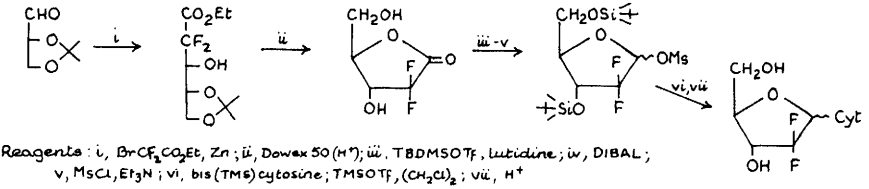
An efficient stereospecific route to 2'-deoxy-2'-fluoro-β–D-arabinofurano-syluracils (19) involves reaction of the di-O-benzoyl-α–glycosyl bromide with silylated uracils,[56,57] and this approach was also used to make [2-^{14}C]-2'-deoxy-5,2'-difluoro-β–D-arabinofuranosyluracil.[58] A number of 2'-deoxy-2,2'-dihalo-β–D-arabinofuranosyladenines have been reported, relying on displacement of a 2'-O-triflyl group to introduce the sugar-bound halogen.[59]

5'-Deoxy-5,4'-difluorouridine (20) has been prepared from 5-fluorouridine by addition of HF (as the pyridine complex) to a 4'-ene.[60] When isopropylideneinosine is treated with triphenylphosphine dibromide, followed by thiophenol, the product is (21), a useful precursor for 1,5'-dimodified adenosines.[61]

When treated with iodide ion in the presence of acid, the dihydrothyminyl cyclonucleoside (22) gave a mixture of both anomers of the product (23), with the α–isomer predominating (Scheme 6). This α–anomer was recyclized to the α–anomer of (22). It also gave the same mixture (23) when treated with iodide and acid.[62]



Scheme 6



Scheme 7

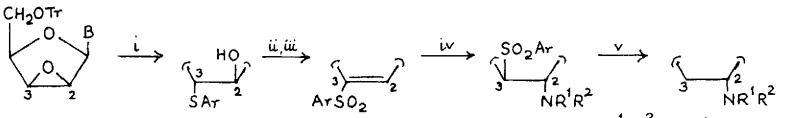
A route to 2'-deoxy-2',2'-difluororibofuranosylpyrimidines is outlined in Scheme 7; the indicated product of the Reformatsky reaction predominated over its diastereomer by a factor of 3:1, but the nucleoside formation favoured the α–anomer.[63]

A new synthesis of 2'-deoxy-2'-fluoroarabinofuranosylguanine is mentioned in Section 10.

5 Nucleosides with Nitrogen-substituted Sugars

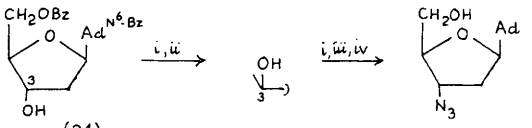
Some 2',3'-dideoxy-2'-amino- and -alkylamino nucleosides have been prepared by the chemistry outlined in Scheme 8.[64] Chemistry reported last year (Vol.21, p.208, Scheme 10) has been applied to the synthesis of 2'-azido-2'-3'-dideoxycytosine.[65] 2'-Azido-2'-deoxy-2-halo-derivatives of ara-A have been prepared by displacement of a 2'-O-triflyl group.[59]

When the deoxyadenosine derivative (24) (Scheme 9) was treated with triflic anhydride, the configurational inversion shown took place in good yield, presumably by intramolecular participation of the 5'-ester. This chemistry then led to a synthesis of 3'-azido-2',3'-dideoxyadenosine.[66] The synthon



Reagents: i, ArSNa; ii, MCPBA; iii, MsCl, Py, then H_2O, Δ; iv, R^1R^2NH; v, Na-Hg, MeOH

Scheme 8



(24)

Reagents: i, Tf_2O, Py; ii, H_2O; iii, LiN_3, DMF; iv, OH^-

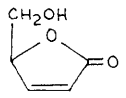
Scheme 9

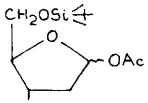
(25) (Vol.21, p.258), derived from D-mannitol, has been converted, via (26), into AZT and 3'-azido -2',3'-dideoxyuridine,[67] and a full report has appeared on the synthesis of the highly crystalline (27) from D-xylose, and its use for preparing 3'-azido -2',3'-dideoxynucleosides (see Vol 21, p 104).[68] An alternative approach to a synthon closely related to (26) is mentioned in Chapter 10. A number of other base-modified 3'-azido -2',3'-dideoxynucleosides have also been reported and evaluated for anti-HIV activity,[69] and AZT has been prepared labelled with tritium at C-5' by a redox procedure.[70]

N-Alkylhydroxylamino-systems of type (28) have been prepared by reduction of the corresponding nitrones.[71] and the aziridinyl phosphonamide (29) has been synthesized as a potential antitumour agent from the 3'-amino-3'-deoxynucleoside; the analogous 5'-amino-5'-deoxy system was also prepared.[72]

Various N-acyl and N-sulphonyl derivatives of 5'-amino-5'-deoxythymidine and 5'-amino-2',5'-dideoxy-5-iodouridine have been prepared as viral thymidine kinase inhibitors.[73] The N-acyl derivative (30), and the corresponding compound with the enantiomeric N-acyl group, have been synthesized as lipophilic analogues of ATP; each compound has a geometrical similarity to one of the preferred conformations for a metal-chelated triphosphate chain.[74] A number of stable nitrogen analogues of S-adenosylmethionine, such as (31), have been reported.[75]

Various 2' and 4'-aminohexopyranosyl nucleosides of thymine and theophylline have been prepared from corresponding ketonucleosides by reduction of their oximes.[76]


(25)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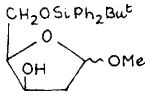
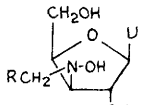
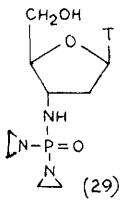
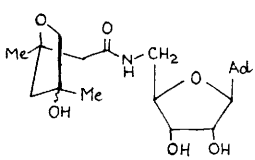

(27)


(28)


(29)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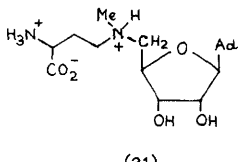
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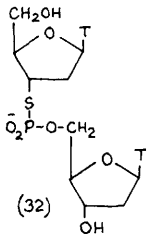
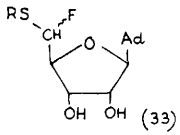

(32)

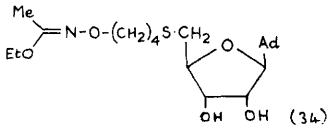
6 Thionucleosides

3'-Thiothymidine has been prepared and incorporated into the dinucleotide analogue (32): mild oxidative hydrolysis by iodine in aqueous acetone caused P-S cleavage, thus indicating the potential of such units for selective cleavage once incorporated into DNA.[77]

The synthesis of some 2',3'-unsaturated -3'-arylsulphononucleosides was referred to earlier (Scheme 8).[64]

When 2',3'-di-O-acetyl-5'-deoxy-5'-aryl(alkyl)sulphinyladenosines were treated with DAST and catalytic $SbCl_3$, followed by deacylation, novel fluorothionucleosides of type (33) were produced. These compounds, rather unstable for the case R=Me, were designed as potential inhibitors of S-adenosylhomocysteine and methylthioadenosine metabolism.[78] The adenosine derivative (34) has been prepared in connection with studies of enzyme inhibition.[79]

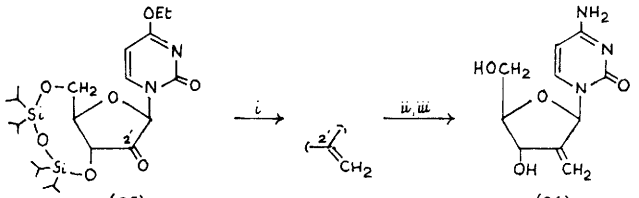

(33)


(34)

7 Branched-chain Nucleosides

A brief review of the synthesis and properties of C'-methyl nucleosides has been published,[80] as has a further account of the synthesis of 2'-C-methyl nucleosides via 2-hydroxymethyl 2,3-O-isopropylidene-5-O-trityl-D-

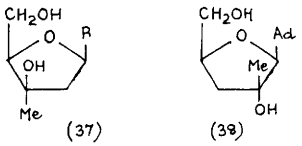
ribofuranose (see Vol. 21, p.209).[81] Full details have been given of the formation of C-methyl nucleosides by addition of organometallics to (35) (see Vol. 21, p.210),[82] and the same group have also reported on synthesis and antineoplastic activity of 2'-deoxy-2'-methylidenecytosine (36), prepared from (35) as indicated in Scheme 10.[83] The use of stabilised carbanions in the Michael addition shown in Scheme 8 has given rise to C-2'-branched nucleosides.[64]



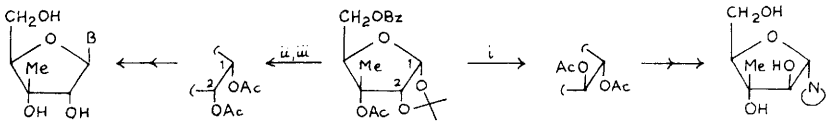
Reagents: i, $Ph_3P{=}CH_2$; ii, Bu_4NF; iii, NH_3,MeOH

Scheme 10

The 3'-C-methylnucleoside (37, R=Ad) has been prepared by two groups using deoxygenative rearrangement of a 2'-O-tosyl derivative with MeMgI;[84,85] it is necessary to reverse the previously assigned configuration at C-3' for the uridine analogue (37, R=U) (see Vol. 19, p.208).[84] This conclusion was also arrived at by another worker, who prepared the thymidine analogue (37, R=T) by treatment of a 3'-keto compound with $Me_4AlMgCl$, a near-neutral reagent which does not cause β–elimination; the configuration of (37, R=T) was proved by cyclization to a 3',6'-anhydro derivative.[86] One group of workers also prepared 3'-deoxy-2'-C-methyl adenosine(38) in the same way, from a 3'-O-tosyl derivative.[85]



When (39) was subjected to acetolysis (Scheme 11), the major product (40) had undergone epimerization at C-2; from (40), 3'-C-methyl-α–D-



Reagents: i, AcOH, Ac_2O, H_2SO_4; ii, H^+; iii, Ac_2O, Py

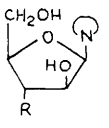
Scheme 11

arabinofuranosyl nucleosides (41) could be prepared. Acid hydrolysis and acetylation gave a ribo-intermediate from which 3'-C-methyl-β–D-ribofuranosyl purines were obtained.[87]

A number of 1-(3-alkyl-2,3-dideoxy-α– and β–D-erythro-pentofuranosyl) thymines have been prepared, a key step being the Michael addition of an organoocuprate to the diphenyl-t-butyl silyl derivative of (25).[88] 3'-Deoxy-3'-methyl-β–D-arabinofuranosylpyrimidines (42, R=Me) have been prepared by opening lyxo-epoxides with MeMgCl-CuCl,[43] whilst similar reactions using Et_2AlCN or LiCN gave the nitriles (42, R=CN)[89,90]

Reports in the patent literature (and popular press) in mid-1987 that 3'-cyano-3'-deoxythymidine(CNT, 43) showed good anti-HIV activity has led to a flurry of activity in its synthesis. Synthetic routes have involved opening of an epoxide and subsequent 2'-deoxygenation,[90] formation of the cyanohydrin of a 3'-ketonucleoside followed by deoxygenation and base equilibration of the cyano substituent,[91,92] free-radical cyanation of a 3'-iodo compound [$(Me_3Sn)_2$, t-BuNC, AIBN],[93] displacement of a 3'-β–triflate,[68,94] and Michael addition of cyanide to the TBDMS-derivative of (25) followed by glycosidation.[53] Several of these papers also report related hydroxylated compounds and stereoisomers. Several[53,90,93,94] also report that genuine CNT is devoid of significant anti-HIV activity!

A Cannizzaro reaction of a protected guanosine-5'-aldehyde was the key step in a synthesis of 4'-(hydroxymethyl)guanosine (44), which was devoid of antiviral activity.[95]



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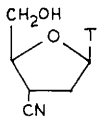
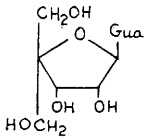
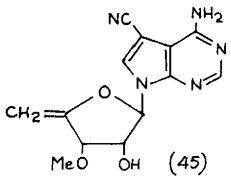


(43)



(44)



(45)

8 Nucleosides of Unsaturated Sugars, Keto-sugars, and Uronic Acids

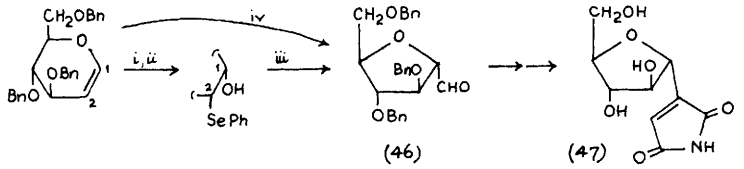
The natural product mycalisine A (45) has been prepared from its corresponding ribonucleoside toyocamycin; the 4',5'-unsaturation was introduced via a selenoxide elimination, but the 3'-O-methyl group was introduced nonselectively by reaction with CH_2N_2-$SnCl_2$.[96] Condensation of acetylated glycals with purine or pyrimidine derivatives, using trityl perchlorate as catalyst, gave 2',3'-unsaturated nucleosides as anomeric mixtures.[97]

A compilation of ^{13}C- and ^{1}H- n.m.r. data on ketohexose nucleosides has been assembled.[98]

Conventional glycosylation was used to prepare $N^{5'}$-ethylguanosine 5'-carboxamide.[99]

9 C-Nucleosides

Various analogues of the C-nucleoside antibiotic showdomycin have been made by the route illustrated in Scheme 12; tribenzylglucal could be induced to undergo ring contraction in two ways to give (46), convertible, using earlier precedent, into the α–D-arabinofuranosyl analogue (47) of showdomycin.

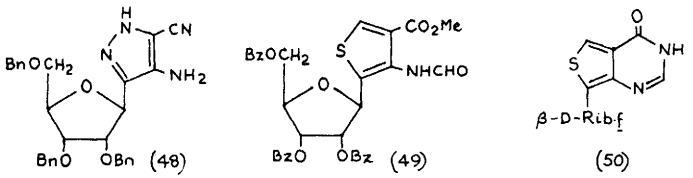


Reagents: i, PhSeCl ; ii, Et_3N, H_2O ; iii, MCPBA ; iv, $Tl(NO_3)_3.3H_2O$, MeCN.

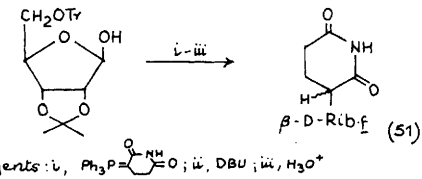
Scheme 12

The 2'-deoxy-derivative of (47), and the α–D-lyxofuranosyl analogue were prepared similarly.[100,101] A new large-scale synthesis has been reported for (48), an intermediate in the synthesis of formycin and analogues.[102]

A C-glycosylation under Friedel-Crafts conditions was used to prepare the thiophene C-nucleoside (49), which was converted in one further step (NH_3, MeOH) to the thieno [3,4-d]-pyrimidine analogue (50) of inosine.[103]



The glutarimide C-nucleoside (51) was prepared as indicated in Scheme 13, and a Wittig reaction was also involved in making the isomeric 3-(β–D-ribofuranosyl)glutarimide.[104]

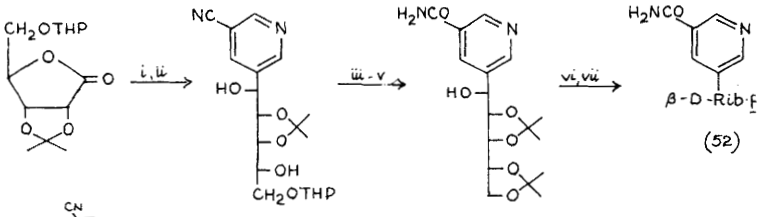


Reagents: i, Ph_3P=(cyclic imide); ii, DBU ; iii, H_3O^+

Scheme 13

C-Nucleoside analogues of nicotinamide continue to attract attention. 2-Carboxamido-6-(β–D-ribofuranosyl)pyridine has been prepared in a way similar to that noted in Vol. 21 (p.211) for the isomer (52),[104] but an alternative approach was also used.[105,106] This new method was also applied to make (52), as outlined in Scheme 14. During the borohydride reduction two

separable isomers were produced in 1:1 ratio, and the allo-isomer was used to produce the α–isomer of (52).[106,107] 2-Deoxyribose has been converted into 3-(2-deoxy-D-ribofuranosyl)pyridine.[108]

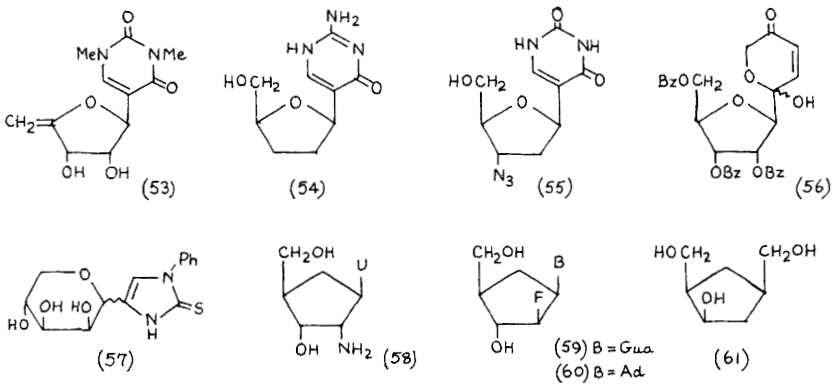


Reagents: i,  Li ; ii, $NaBH_4$; iii, TsOH,MeOH ; iv, Me_2CO,TsOH ; v, IRA-400(OH^-); vi, MsCl-Py ; vii, TFA

Scheme 14

The known 1,3-dimethyl pseudouridine has been converted conventionally into the 4',5'-ene (53)[109] and also into the pseudoisocytidine analogue (54) and its 2' -ene, and the AZT analogue (55) was prepared from 2'-deoxypseudouridine via 2'-deoxyxylopseudouridine derivatives.[110]

Oxidation of a protected ribofuranosyl furfuryl alcohol gave (56) which was used as a precursor of 2-(C-glycosyl)pyrroles and -pyrrolo [1,2-a] pyrazines.[111] The D-lyxopyranosyl imidazole (57) was prepared by cyclization of a polyol precursor.[112]



10 Carbocyclic Nucleoside Analogues

An improved synthesis of chiral carbocyclic 2'-deoxyadenosine proceeds along similar lines to the carbocyclic thymidine synthesis described by the same group in Vol 21 (p.212).[113]

Carbocyclic analogues of 2'-azido- and 2'-amino-2'-deoxyuridine (58) have been made from the known carbocyclic uridine via the 2,2'-cyclonucleoside.[114] The carbocyclic analogue of 2'-deoxy-2'-fluoro-ara-G (59)

has been prepared by two routes, one of which was similar to that used earlier for the synthesis of the corresponding thymidine analogue (Vol 21, p.212-3); it was resolved by enantioselective enzymic hydrolysis of the 5'-phosphate, and the (+)-isomer proved to have potent antiherpetic activity. The corresponding furanosyl nucleoside was also synthesised by an improved route and found to be ca. 1000 times less active.[115] The 2'-deoxy-2'-fluoro-arabino- analogue (60) of aristeromycin was prepared from the natural antibiotic, and also found to be an effective antiviral agent.[116]

There has been a further report on the use of optically-pure (61), prepared enzymically, to make carbanucleosides, (-)-carbocyclic-ddT and (-)-carbocyclic-2',3'-dideoxy-3'-fluorothymidine being the targets thus prepared.[117] A synthon for carbocyclic C-nucleosides, previously available as a racemate (Vol.20, p.214, Scheme 16), has now been made in chiral form by use of a di-l-menthyl ester as a chiral auxiliary.[118]

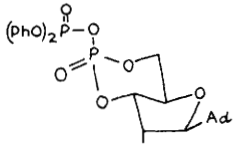
Some references to aristeromycin and neplanocin analogues are mentioned in Chapter 19.

11 Nucleoside Phosphates and Phosphonates

A method has been reported for the synthesis of 5'-triphosphates of acid-sensitive nucleosides which involves treating the nucleoside in trimethyl phosphate containing proton sponge with phosphoryl chloride, and then treatment of the phosphoryl dichloride with bis-tributylammonium pyrophosphate.[119] An enzymic method has been used to convert CMP and phosphoenolpyruvate to CTP and pyruvate; a membrane-enclosed enzymic reactor allows conversions on the gram scale.[120] 5'-O-Phosphatidyl nucleosides have been prepared by interaction of the nucleoside with phosphatidyl choline in the presence of phospholipase D,[121] and the same enzyme has been used to transfer a simpler monoalkylphosphate group from choline to a nucleoside.[122] Two groups have reported the enzymic synthesis of CMP-N-acetylneuraminic acid,[123,124] in one case[124] with the sialic acid being produced enzymically from N-acetylmannosamine.

Reaction of a nucleoside with thiophosphoryl chloride, followed by base-promoted cyclization, provides a direct synthesis of nucleoside-3',5'-cyclic phosphorothioates (both epimers at phosphorus).[125] Treatment of cyclic AMP with diphenylphosphoryl chloride produces the mixed anhydride, predominantly of R_P configuration (62), due to the greater basicity of the axial oxygen in the cAMP. The anhydride reacted with dimethylamine with inversion to give the cyclic phosphoramidate.[126] Activation of cAMP with $POCl_3$ in $(MeO)_3PO$, followed by treatment with an amine, also gave predominantly the S_P-phosphoramidate (63),[127] and in the case of a protected cAMP, oxalyl chloride activation achieved a similar result.[128] The hydrolysis of

both diastereomers of adenosine cyclic 3',5'-phosphoramidates has been studied, and the results, in terms of which bond is cleaved, were rationalised on stereoelectronic grounds.[129] Adenosine 2',3'-cyclic phosphate is cleaved specifically to the 2'-phosphate at pH 11.1 and 20°C, using β– and γ–cyclodextrins as catalysts, α–cyclodextrin giving a 2:1 predominance of 3'-phosphate.[130]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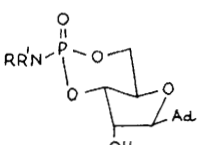
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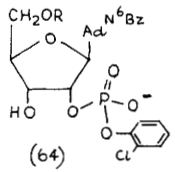
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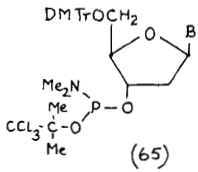
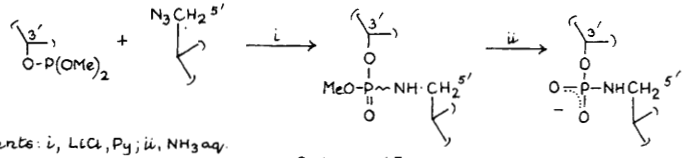

(65)

The dinucleotides araU-p-dA, dA-p-araU, xyloT-p-dA, and dA-p-xyloT have been prepared, and their stacking studied.[131]

Two intermediates (64:R=MMTr or pixyl) have been synthesised and used to make 'branched' ribonucleic acids, since they permit extension in all three directions.[132] Phosphoramidites of type (65) have been prepared, where the base is also protected by a group removable by reductive cleavage.[133]

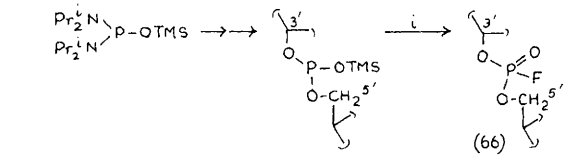
There have been two reports of the synthesis of di- and oligonucleotides with P-NH-5'-phosphoramidate internucleotide links;[134,135] in one approach[135] a Staudinger-type reaction is used to form the link (Scheme 15). Another paper has reported the synthesis of building blocks for 5'-amino- and 5'-mercapto-oligodeoxy nucleotides.[136]


Reagents: i, LiCl, Py; ii, NH_3 aq.

Scheme 15

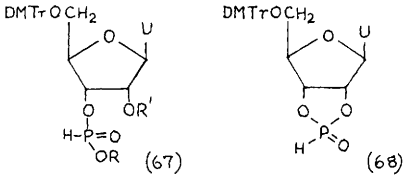
Deoxynucleoside 5'-O-monothiophosphates and 5'-O-(1-thio)triphosphates have been prepared in very high yields using thiophosphorylation with $PSCl_3$ in trialkylphosphate-pyridine.[137] Dinucleoside phosphorodithioates have been prepared by chemistry analogous to the phosphite triester method,[138] and other workers have described model studies along very similar lines.[139] A further report has been given (see Vol 21, p.215) of work by Pfleiderer's group on the synthesis of P-thio-analogues of 2'-5'-adenylate dimers, trimers and tetramers, four of the eight possible isomers of the tetramer being described.[140]

Deoxynucleoside phosphorofluoridates, and similar dinucleoside analogues (66), have been prepared as outlined in Scheme 16.[141]

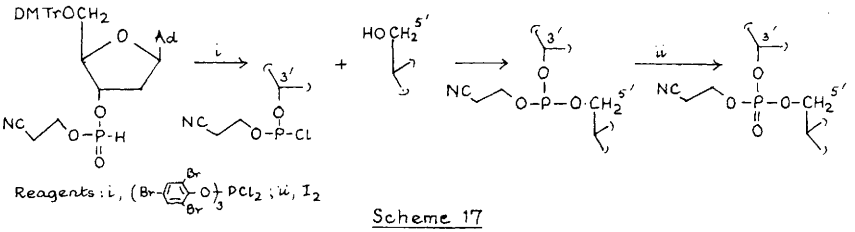


Scheme 16

Two procedures have been described for the synthesis of deoxynucleoside-3'-hydrogenphosphonates.[142,143] Various nucleoside -3'-hydrogenphosphonates of the ribo- and deoxyribo- series were prepared and condensed with a second nucleoside to give the H-phosphonate dimers in high yields.[144] Possible side reactions during the formation of such dinucleoside H-phosphonate diesters in the presence of various condensing agents have been investigated by ^{31}P-n.m.r.[145] It has been shown that H-phosphonate diesters of type (67, R'=H), with a vicinal hydroxy group, cannot be prepared, the cyclic phosphonate (68) or products derived from it, being obtained instead. Compounds (67, R'=TBDMS) therefore could not be



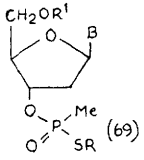
desilylated without cyclization occurring.[146] However, if a dinucleoside H-phosphonate of type (67, R'=TBDMS) was firstly oxidised to the phosphate, then desilylation occurred without problems.[147] 2-Cyanoethyl nucleoside 3'-hydrogenphosphonates have been used in oligodeoxynucleoside synthesis as outlined in Scheme 17.[148]

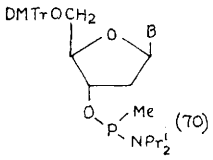


Scheme 17

2'-Deoxynucleoside-3'-O-(S-alkyl)methylphosphonothioates of type (69, R=Et, iPr, substituted benzyl) can be prepared by successive displacements on methylphosphonic bis(oxybenzotriazolide) by a nucleoside derivative with 3'-OH free, followed by a thiol; the diastereomers of (69) can be resolved by flash chromatography.[149] Methyl phosphonamidites (70) have been prepared and used in oligodeoxynucleotide synthesis.[150]

Compounds (71, R=Me, Ph, OH) have been prepared as analogues of


(69)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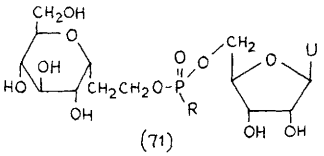
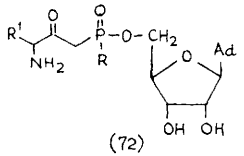

(71)

UDPG in which the chain length between sugar and nucleoside is the same length as in the natural material, and the compounds were indeed inhibitors of glycolipid biosynthesis.[151] Phosphono- and methylphosphinoanalogues of aminoacyl adenylates (72, R=Me, OH) have been synthesized, and shown to have interesting antibiotic activity.[152] Isosteric phosphonate analogues of 5'-nucleotides have been prepared from D-glucose via (73); Arbusov reaction was followed by acetolysis and coupling with a silylated base.[153] The same group has also reported similar products made via 5-deoxy-1,2-O-isopropylidene-α-D-xylo hexofuranose.[154]

Some further references to related nucleoside derivatives are mentioned in the next section.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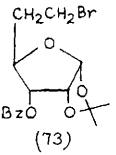
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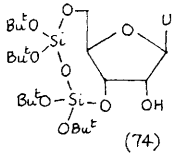
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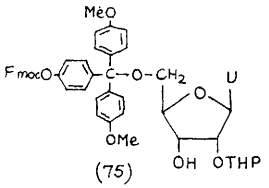

(75)

12 Ethers, Esters and Acetals of Nucleosides

The use of the 3',5'-tetra(t-butoxy)disiloxane-1,3-diyl protecting group, as in (74), has been investigated as an alternative to the TIPDS unit; it is more stable than TIPDS to acid and alkali, but easily cleaved by fluoride ion, and its use is advocated in cases where mgration of a TIPDS group can be problematic.[155] The use of di-t-butoxy-dichlorosilane for protection of O-3' and O-5' as a monosilaheterocycle has also been studied, but the acid- and base-lability of this group is high.[156]

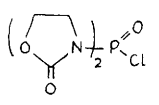
A new trityl-based protecting group, shown in (75), has been developed, with a mild two-step removal procedure. Treatment with base gives an extremely acid-labile group, whilst with the Fmoc unit in place, acid-stability is increased; a dimethoxytrityl group could not be removed cleanly without affecting the 2'-O-THP unit.[157]

Crown-ether catalysis has been used to prepare 5'-O-alkyl-derivatives of 2',3'-O-isopropylidene uridine.[158]

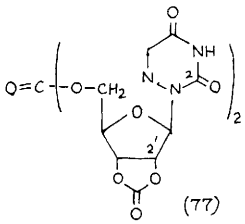
Tri-O-benzoyl- and O-acetyl-thymidine and uridine can be deacylated by KCN in MeOH.[159]

Routes have been developed for the synthesis of the 2',5'- and 3',5'-di-O-benzoyl derivatives of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA-Riboside),[160] and 5'-acyl-deoxyribonucleosides have been obtained in high yields by activation of the carboxylic acid with the reagent (76).[161] 5'-O-Succinoyl-2',3'-cyclic adenosine monophosphate has been prepared for conjugation to protein and subsequent antibody production.[162] Phosphonoacetyl esters, at either the 3'-O- or 5'-O- positions, of 5-substituted 2'-deoxyuridines have been prepared, but none were more active than the parent compounds as antivirals.[163]

When 6-azauridine was treated with phosgene in HMPA, the dimeric carbonate (77) was obtained, which could be selectively deblocked at the cyclic carbonates with methoxide in methanol, or converted into the bis-2,2'-anhydro-compound by use of imidazole in DMF.[164]



(76)



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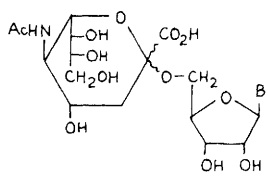

(78)

The usefulness of the p-nitrophenylethylsulphonyl (NPES) group for protection of the 2'-OH in oligonucleotide synthesis has been further investigated,[165] and other ethylsulphonyl esters with electron-withdrawing groups at the β–position have also been studied in nucleoside and nucleotide chemistry.[166]

There has been a further report on sulphamyl analogues of UDPG of the type mentioned in previous volumes (Vol.19, p.209; Vol.20, p.218).[167] Work discussed previously (Vol.21, p.217) on the selective formation of 3',5'-di-O-benzoyl nucleosides, and hence 2'-O-THP derivatives, has been extended to other cases, giving building blocks for oligonucleotide synthesis.[168] Similarly, treatment of 3',5'-di-O-acetyluridine with 4,4-dimethoxytetrahydropyran, or its 1-thio-analogue, in DMF in the presence of TMSCl gave, after deacetylation, the 2'-O-(4-methoxytetrahydropyranyl-4-yl)-derivative or its sulphur analogue. This procedure was not successful with the 3',5'-O-TIPDS derivative, due to migration of the silyl group to the 2',3'-position.[169]

Nucleoside derivatives of N-acetylneuraminic acid (78) have been synthesized as separable anomeric mixtures by Königs-Knorr methods.[170]

13 Reactions

It has been shown that, for N^7-methyl-guanine nucleotides, the intramolecular

interaction between the negatively-charged 5'-phosphate and the positive imidazole ring markedly retards the attack of hydroxide ion at C-8, but there is hardly any effect on the acidities of the interacting base and phosphate moieties.[171] Similarly, in a study of the hydrolysis of $\underline{N}^7$-methyl-GMP, the influence of intramolecular electrostatic interactions on the stability of the C-N bond was hardly detectable, lending support to the idea that the influence of such interactions should not be overestimated in explaining the chemical behaviour of cap-analogues.[172] The rates of hydrolysis of wyosine and its $\underline{O}$-acetylated derivatives were studied as part of a broader investigation of the properties of this nucleoside.[173]

It was found that, at various temperatures, 2-aminopurine-2'-deoxynucleoside is severalfold more prone to degradation than its isomer deoxyadenosine in neutral aqueous buffer. The major UV-active product from the 2-aminopurine nucleoside was 2,4-diamino-5-formamidopurine, whilst deoxyadenosine yields adenine.[174] The protective group present at the amino-group of deoxyguanosine can have a marked effect on the stability of the glycosidic link; electronegative groups give greater lability, which is associated with a change in site of protonation from the 6-membered to the 5-membered ring, as shown by ^{13}C-n.m.r.[175]

The products of γ-irradiation of thymidine in frozen aqueous solution were found to include 2-deoxy-D-ribonolactone suggesting the intermediacy of a C-1' radical, but other evidence suggested the formation of C-3' and C-4' radicals also.[176]

Various products have been derived from 2',3'-secouridine[177] and 2',3'-secopurine nucleosides[178] produced by periodate-borohydride treatment of the ribonucleosides.

14 Spectroscopic and Conformational Studies

The free energy of the sugar moieties of deoxyribonucleosides was calculated for a wide range of puckering parameters using different force fields. The resulting data were compared with 224 structures from DNA single crystal X-ray data. A modified Weiner's force field yielded excellent agreement.[179]

Sugar-ring conformations of guanine nucleosides have been studied by 250 MHz ^{1}H-n.m.r.,[180] and a conformational correlation of purine nucleosides has been carried out by high-field ^{13}C n.m.r. A key to the correlation is the $\Delta\delta$ between C-2' and C-3'.[181]

A ^{15}N-n.m.r. study of $\underline{O}^4$- and $\underline{N}^3$-substituted pyrimidine and $\underline{C}^6$-substituted purine ribonucleosides has shown that the position of the protecting group (substituent) has a strong influence on the electronic properties of the pyrimidine system. The basicity of $\underline{N}^3$ was studied by following ^{15}N chemical shifts of protonated species in DMSO and in $CHCl_3$.

Little difference was found in basicities of N^3 of pyrimidines and N^1 of purine nucleosides.[182]

An analysis of ^{13}C- ^{14}N residual dipolar coupling in the ^{13}C CP/MAS n.m.r. spectra of ribonucleosides has been carried out. Successful spectral simulation incorporated data from X-ray diffraction and NQR studies.[183]

Some further references to n.m.r. of nucleosides are in Chapter 21, and X-ray crystal structures are noted in Chapter 22.

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21
N.M.R. Spectroscopy and Conformational Features

1 Theoretical and General Considerations

Reviews have been published on the use of ^1H spin-lattice relaxation rates in the structural analysis of carbohydrate molecules in solution[1] and on the application of 2D n.m.r. spectroscopy to the structural analysis of oligosaccharides and other complex carbohydrates.[2]

The structure and energetic properties of 2-deoxy-*erythro*-pentose have been investigated by use of Newton potential energy methods; a geometry very close to that found in practice was predicted.[3] *Ab initio* Calculations have been performed to determine the minimum energy state of 6-*O*-methyl-β-D-tagatofuranose which served as a model for β-D-tagatofuranose 6-phosphate; the results indicated a minimum energy structure different from that previously produced by simpler, force-field calculations.[4] The assignment of all signals in the ^{13}C- n.m.r. spectra of 2-deoxy-L-*arabino*- and D-*lyxo*-hexose, 2-deoxy-L-*erythro*-pentose, calcium L-ribonate and calcium-2-deoxy-L-*erythro*-pentonate has been reported.[5]

The resonances of the benzyl methylene carbon atoms of eight per-*O*-benzylated methyl furanosides have been assigned by means of INADEQUATE and ^{13}C-^1H correlation n.m.r. methods. The chemical shifts of these carbons and the $^1J_{C,C}$ values between the ring carbon atoms were found to be related to the relative orientations of substituents on the furanosyl ring.[6] From a similar investigation involving the benzyl methylene carbon signals of per-*O*-benzylated methyl pyranosides it was concluded that these parameters may be used to determine the structure of oligosaccharides, once a library of shifts has been created.[7] For assigning the resonances of carbonyl carbons of carbohydrate acetates a method employing the INAPT n.m.r. technique has been proposed.[8]

A detailed (ϕ,ψ) map for cellobiose has been constructed with the assistance of the MM2 computer program,[9] and a near-

spherical shape of cellobiose has been deduced from a ^{13}C spin-lattice relaxation study, whereas n.O.e., 2D HECTOR and HOMCOR ^{1}H-n.m.r. evidence confirmed a folded structure.[10] In the course of a theoretical investigation of the conformational properties of mannobiose the low energy regions of the calculated (ϕ,ψ) maps of methyl β-mannobioside in five different solvents were subjected to optimisation by the PCILO method; an evaluation taking into consideration electrostatic, dispersion and cavity terms showed that the prevailing conformation in solution depends on the solvent and may differ from that found in the crystalline state.[11] A similar study of a 1,4-linked mannobiose included estimates of solvation energy.[12] ^{13}C Spin-lattice relaxation rates and n.O.e. measurements at varied temperature, concentration and magnetic field strength allowed the determination of the spherical density function for the ^{1}H-^{13}C dipole-dipole interactions at each of the three hydroxymethyl groups of sucrose.[13] ^{13}C Spin-lattice relaxation time values for auto- and cross-correlations of CH vectors were used to study the complex formation between carbohydrates (*inter alia*) and DMSO. Comparison of experimental with calculated data confirmed that this method is suitable for predicting probable solution conformations.[14] Parameters have been derived for calculations of carbohydrate systems involved in glycoconjugates,[15] and a microcomputer program (ANMROL) has been developed to facilitate the structural analysis of linear and branched oligosaccharides from ^{13}C- n.m.r. spectroscopic data.[16]

2 Acyclic Systems

Although significant differences were found, in a 620 MHz ^{1}H-n.m.r. study of ^{2}H-exchanged pentitols, between the vicinal coupling constants measured in aqueous (D_2O) and in non-aqueous (pyridine-d_5, acetone-d_6) solutions, application of the Karplus equation indicated that unique conformations in solution are unlikely; instead the measured ^{3}J are thought to reflect the presence of different populations of rapidly interconverting rotamers, all in near *gauche* or *trans* arrangements.[17] A ^{1}H-n.m.r. investigation of 1,5-dihalo- and 1,5-bis(diethylamino)-1,5-dideoxy-2,4-di-*O*-methylenexylitols and their esters confirmed their symmetrical structures, the 1,2-*gauche* arrangements of their chain carbon atoms, and the existence of an intramolecular hydrogen bond between the hydroxyl group at C-3 and a dioxane oxygen.[18]

3 Furanose Systems

On the basis of ^{1}H- and ^{13}C- n.m.r. data it can be shown that the dimeric anhydride formed by treatment of methyl D-ribosides with acetone in the presence of sulphuric acid and copper(II) sulphate has structure (1), in agreement with an earlier assignment (J. Am. Chem. Soc., 1957, 79, 1182). Using this evidence together with the ^{13}C- n.m.r. parameters for the four methyl D-ribosides, which were recorded at the same time, it could then be demonstrated that the polymerisation products of 1,5-anhydro-2,3-O-isopropylidene-β-D-ribofuranose are α- and β-D-ribofuranans, not as was previously claimed, an α-D-ribofuranan and a β-D-ribopyranan.[19] ^{1}H Spin-lattice relaxation times (T_1) of ribonucleosides (2) were measured in order to obtain generally applicable criteria for assigning nucleoside anomeric configurations. It was found that T_1 values for the anomeric protons in the α-D-series were significantly smaller than those in the β-D-series, while the opposite was true for T_1 of H-8. Details of the synthesis of nucleosides (2) are given in Chapter 20.[20] The anomerisation of furanoses has been investigated by ^{13}C saturation-transfer n.m.r. spectroscopy using 5-deoxy-L-pentoses, 5-O-methyl-D-pentoses, D-pentose 5-phosphates, and D-tetroses, substituted with ^{13}C at the anomeric centre. Unidirectional rate constants for ring-opening and ring-closing were obtained and several structure-reactivity correlations were revealed.[21]

^{1}H- N.m.r. spectroscopy (^{3}J values) was used in the conformational analysis of several 2-deoxy-α- and β-*erythro*-pentofuranosides in solution,[22] of two penturonofuranosyl rings in natural glycosides,[23] and of carbocyclic compounds such as (3) which were chosen as models for β-D-xylofuranosyladenine 3′,5′-cyclic phosphate.[24]

The eight diastereomeric 2-O-ethoxycarbonyl-hexofuranosidurono-6,3-lactones (4) (*i.e.*, the α- and β-D-*gluco*-, D-*manno*-, L-*ido*-, and L-*gulo*-derivatives) were the subject of a conformational study by both ^{1}H- and ^{13}C- n.m.r. spectroscopy. (Their synthesis is covered in Chapter 16).[25] The ^{1}H- and ^{13}C- n.m.r. spectra of the eight diastereomeric 1,6-anhydrohexofuranoses (5) were recorded in D_2O together with the ^{13}C- n.m.r. spectra of their triacetates in $CDCl_3$, and a first-order interpretation of the ^{1}H- n.m.r. data was given.[26] Assignment of the prochiral C-5′ protons in the 300 MHz ^{1}H- n.m.r.

spectra of ribonucleosides, facilitated by stereoselective deuteration, showed that the pro-(R) protons are more shielded than the pro-(S) protons. These findings allowed estimates to be made regarding the C-4′ - C-5′ rotamer populations.[27]

4 Pyranose Systems

A detailed n.m.r. study of the α-glucosidase inhibitor 1,5-dideoxy-1,5-methylimino-D-glucitol (N-methyl-1-deoxynojirimycin) has been undertaken. It was observed that in acidic D_2O the two isomers (6a) and (6b) with an equatorial or axial N-methyl group respectively, are present in 11:1 ratio, and that the predominant (>90%) rotamer state about the C-5 - C-6 bond, both in the cationic diastereomer (6a) and in the free base is gauche-gauche.[28] The ^1H- and ^{13}C- n.m.r. parameters of racemic α- and β-pseudo-gluco-, pseudo-galacto-, and pseudo-manno-pyranose have been reported,[29] and the fully assigned ^1H- and ^{13}C- n.m.r. spectra of novobiocin, an antibiotic containing the sugar moiety noviose (7), has been published.[30] ^{13}C- N.m.r. spectroscopy has been used to determine the anomeric configuration of sialic acid and its derivatives (see also Chapter 16). In the gated proton-decoupled spectrum of the α-anomer (8a), for example, C-1 gave rise to a doublet, coupling of 6.1 Hz being observed between C-1 and H-3_a. The value for $^3J_{C-1,H-3a}$ of (8a), on the other hand, was small, as were both $^3J_{C-1,He}$ and $^3J_{C-1,Ha}$ of the β-anomer (8b), so that the signal for C-1 of the β-anomer was effectively a singlet.[31]

The lanthanide induced shifts in the ^1H- n.m.r. spectra of seven methyl 2,3-anhydro-4,6-O-benzylidene-D-hexopyranosides have been measured to provide conformational data for oxiran carbohydrate systems (the X-ray crystal structure of the β-D-manno-isomer is referred to in Chapter 22).[32] Lanthanide shift reagents have also been used to acquire information on complex formation by glucuronate and galacturonate anions; it could be concluded that in the α-anomers the metal ions are coordinated to O-5 and one of the carboxylate oxygen atoms, whereas in the β-anomers O-5 is not involved in complexation.[33] The aminoanhydroheptitol (9), available by a short synthesis from tri-O-acetyl-D-glucal, exists in solution as an equilibrating mixture of the two possible chair conformers ($^5C_2$ and $^2C_5$) as evidenced by n.m.r. spectroscopy. The X-ray structures of amine (9) and an N-protected analogue are referred to in Chapter 22.[34]

The rotamer distribution about the C-5 - C-6 bond of D-glucopyranose derivatives has been established from the ^{1}H- n.m.r. spectra of compounds with chiral deuteration at C-6 (see Vol. 20, p. 59 for their synthesis). Irrespective of solvent and protecting groups the predominant conformers were those with gauche-gauche (gg) and gauche-trans (gt) arrangements in 60:40 ratio, with negligible tg populations.[35] The long range ^{13}C-^{1}H coupling constants of six methyl tetra-O-acetylhexopyranosides have been determined by heteronuclear 2D-J n.m.r. spectroscopy and the results were discussed in terms of conformational effects.[36] ^{13}C-^{1}H Coupling constants have also been used, in combination with molecular mechanics calculations, in a conformational analysis of dioxolane rings 1,2-fused to pyranose derivatives.[37]

5 Disaccharides, Oligosaccharides and Related Systems

All signals in the ^{1}H- and ^{13}C- n.m.r. spectra of 3-O-α-D-galactopyranosyl-L-arabinose have been assigned by means of high resolution 1D methods and 2D correlation experiments (COSY, HECTOR).[38] Complete assignment of the ^{1}H and ^{13}C resonances of maltitol has been achieved by application of 2D n.m.r. methods and observation of H/D isotope effects on nuclear shielding (SIMPLE and DIS techniques) in three different solvents (H_2O, D_2O, DMSO-d_6). This represents a powerful new technique for analysis of molecules with many exchangeable hydrogen atoms such as carbohydrates.[39]

^{1}H- And ^{13}C- n.m.r. methods assisted by computation and theoretical calculation (e.g. by the HESA program) have been used in extensive investigations of di- and some tri-saccharides with a view to assigning and rationalising chemical shifts and to determining preferred conformations in solution. The compounds examined included 1,6-anhydro-β-maltose hexaacetate,[40] ten (1→3)-linked methyl 6-deoxyhexosyl hexosides in which the deoxysugar was L- or D-rhamnose or fucose (referred to in Chapter 3),[41] eight (1→4)-linked disaccharides in which the glycosidic linkage was in different stereochemical environments,[42] di- and tri-saccharides containing L-idopyranose units (referred to in Chapter 3),[43] galactobiose, its methyl and ethyl glycosides as well as the 3-deoxy, 3-O-methyl, 3-deoxy-3-C-methyl, and 6-deoxy analogues,[44] (1→2)-, (1→3)-, and (1→4)-linked methyl glycosylrhamnosides,[45,46] (1→3)- and (1→4)-linked methyl glycosylgalactosides,[47] and other glycosides of (1→2)-, (1→3)-, and (1→4)-linked disaccharides.[48,49]

It was concluded that the preferred solution conformation of a disaccharide depends on the absolute configurations of the constituent monosaccharides, the position and configuration of the glycosidic linkage, and on the orientation of the proton at the aglycon carbon associated with the glycosidic linkage and the adjacent carbon atoms.

$^{3}J_{C,H}$ Values have been obtained for COCH fragments in various carbohydrates by means of 2D heteronuclear J-resolved n.m.r. spectroscopy. Measurements on rigid model substrates (g_1g_1, $^{3}J_{C-5,H-1}$ of 1,6-anhydroglucose) were used to establish a Karplus-type relationship between $^{3}J_{COCH}$ and dihedral angles. $^{3}J_{C,H}$ Values for sucrose (10), melezitose (11), and stachyose (12) in D_2O and in DMSO-d_6 were found to be similar to each other but different from those predicted from conformations adopted in crystals. Based on this new technique, some assignments in the published ^{13}C- n.m.r. spectrum of melezitose (11) were corrected.[50] A similar investigation involving the inter-unit linkages of several disaccharides, for example methyl β-cellobioside, has been published, as is also mentioned in Chapter 3.[51]

A number of papers have appeared aimed at elucidating the conformational aspects of the inter-glycosidic linkages of di- and trisaccharides by ^{1}H- n.m.r. methods. Stereospecific ^{2}H-labelling at C-6 allowed the identification of the signals due to H-6(R) and H-6(S) in the ^{1}H- n.m.r. spectra of methyl β-maltose and methyl β-isomaltose, and determination of the $J_{5,6(R)}$ and $J_{5,6(S)}$ values from which the predominant rotamer states could be inferred (58% gg for the maltose, 65% gg for the isomaltose derivative). Synthetic details are given in Chapter 3.[52] Related studies, some using unlabelled substrates and/or n.O.e. and relaxation rate measurements, have been performed with β-(1→6)-linked galactodisaccharides,[53] α- and β-(1→6)-linked mannodisaccharides,[54] the mono-, di-, and tri-saccharides (13)-(15) (synthetic details in Chapter 9),[55] and the four stereoisomeric methyl 4,6-di-O-(α or β)-D-glucopyranosyl-β-D-glucopyranosides (synthetic details in Chapter 4).[56,57]

The peracetylated 4-O-α-D-glucopyranosyl-3-O-α-(D or L)-rhamnopyranosyl-D-glucopyranoses, the respective β-glycosyl fluorides, α-glycosyl bromides, and 1,6-anhydrides, which are also referred to in Chapter 4, have been subjected to conformational analysis by ^{1}H- and ^{13}C- n.m.r. spectroscopy to show that, in consequence of the operation of the exo-anomeric effect, the

conformation of the central glucopyranosyl ring depends not only on the nature and orientation of the substituent at C-1 but also on the absolute configuration of the rhamnose unit.[58]

The ^{1}H- n.m.r. spectra of the blood group tetra- and hexasaccharide alditols (16) and (17), respectively, have been fully assigned by use of COSY and HOHAHA techniques,[59] and the ^{1}H- and ^{13}C- n.m.r. spectra of milk oligosaccharides containing the blood group determinants Le^{a}, Le^{d}, or Le^{b} have been recorded and assigned by application of 2D ^{13}C-^{1}H shift-correlation spectroscopy and by comparison with literature data. Results from additional, 2D rotating-frame n.O.e. experiments indicated a large number of dipolar interactions consistent with the preferred conformations reported for these compounds.[60] The main features of the primary structure of the octasaccharide (18) have been determined in the ab initio manner by ^{1}H n.m.r. spectroscopy without resorting to biochemical methods.[61] N.m.r. studies with Lewis b and Y blood group determinants and with D-glucose residues in hydrolysable tannins are referred to in Chapters 4 and 7, respectively.

6 Nuclei other than ^{1}H and ^{13}C

Crystalline 2′-deoxythymidines specifically deuterated in a number of positions have been analysed by solid-state ^{2}H- n.m.r. spectroscopy in order to determine internal motion in the crystalline state.[62] ^{15}N- N.m.r. spectroscopy has been used in an investigation of wyosine tri-O-acetate (19) and its 7′-methyl analogue; ^{15}N- Chemical shifts and ^{15}N- ^{1}H coupling constants have been recorded.[63]

The ^{13}C- and ^{31}P- n.m.r. spectra of a single crystal of dipotassium α-D-glucose-1-phosphate dihydrate for different orientations in the external magnetic field have been recorded in the course of an application of a ^{13}C-{^{1}H, ^{31}P} triple resonance technique to the determination of ^{13}C and ^{31}P shielding tensors.[64]

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22
Other Physical Methods

1 I.r. Spectroscopy

I.r. spectra of the 2- and 3-nitrates of methyl β-D-glucopyranoside, the 6-nitrate of its α-anomer, and the 2,3-di-, 3,6-di- and 2,3,6-tri-nitrates of methyl 4-O-methyl-β-D-glucopyranoside have been reported.[1] As a contribution to assessing the value of the C-H stretching force constants in carbohydrate compounds, the i.r. and Raman spectra of epi-, muco- and myo-inositol, and of methyl α-D-gluco- and manno-pyranoside and their 2,3,4,6,6′-d_5 substituted analogues have been recorded. A linear equation relating such force constants to the dihedral angles formed by the C-H bonds with the lone pair electrons on the closest oxygen atoms was derived, and its usefulness in conformational analysis was considered.[2]

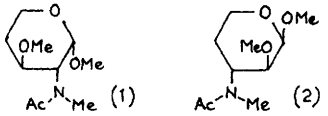
2 Mass Spectroscopy

The Fast atom bombardment (FAB)-m.s. of carbohydrates has been reviewed.[3] FAB-m.s. has been used to characterise individual oligogalacturonic acids (in both the +ve and -ve ion modes).[4] FAB-m.s. and mass-analyzed ion kinetic energy (MIKES) spectra were used to characterise components of peptide-nucleoside antibiotics including blasticidin S and mildomycin analogues.[5] From a FAB-m.s. and collision activated dissociation study of three linkage isomeric trisaccharides it was concluded that this technique showed promise for distinguishing linkage isomers.[6] MIKES CID sequential mass spectra with FAB ionization was used to elucidate the m.s. fragmentation pathways of peracetylated glucose and galactose.[7]

Laser-desorption time-of-flight m.s. using a 300 ps u.v. laser gave a cationized parent ion and structurally significant fragments from sucrose, amongst other compounds.[8] Negative-ion laser desorption ionization Fourier transform ion cyclotron resonance m.s. provided information on sequence and anomeric

configuration of individual units in an underivatized linear pentasaccharide.[9]

E.i.-m.s. data for acetylated 2-ketopyranoses and their glycosides,[10] and for per-O-acetylated N-(4-substituted phenyl)-D-xylo- and D-gluco-pyranosylamines have been reported,[11] as have both e.i.- and c.i.-m.s. data for the amino-sugar derivatives (1) and (2).[12] The g.c.-m.s. (e.i. and c.i.) of the per-O-methylated



and per-O-acetylated derivatives of methyl 7-deoxy-D- and L-*glycero*-β-D-*galacto*-heptopyranoside, and of a range of partially methylated alditol acetates derived from these novel heptoside residues, have been investigated and fragmentation patterns proposed.[13] Partially methylated sugars present in mycobacterial glycolipids were determined using methanolysis - trimethylsilylation followed by g.c.-m.s. (e.i.) analysis; seven partially methylated methyl rhamnopyranosides were synthesized as a mixture and isolated by h.p.l.c. as standards. Characteristic fragmentations permitted the positions and numbers of methoxy-groups to be determined.[14]

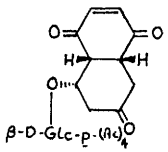
The c.i.(CH_4 and i-C_4H_9)-m.s. of acetylated glyco-furanosyl and -pyranosyl fluorides has been investigated and the influence of configuration reported.[15,16] Other reported c.i.-m.s. studies have been on nitro-sugars (in which negative ion analysis gave $[M+NO_2]^-$ peaks),[17] methyl hexopyranoside nitrates,[18] and the xanthate and S-methylthiocarbonate derivatives of 1,2:5,6-di-O-isopropylidene-3-C-methyl-α-D-allofuranose.[19]

Deoxynucleoside pentafluorobenzyl, cinnamoyl and mixed derivatives have been examined by e.i.-, positive ion c.i.(CH_4)-, and ECNI (electron capture negative ion) m.s., the latter technique being found suitable for high sensitivity detection.[20]

Further applications of coupled h.p.l.c.-m.s. systems have appeared. The efficacy of adding ammonium acetate to the mobile phase to enhance MH^+ and $[M+NH_4]^+$ ion intensities was tested with a variety of underivatized, per-O-acetylated, and per-O-alkylated carbohydrates.[21] Qualitative analysis of crude saponins containing oligoglycoside and oligoglycosyl ester moieties was performed on a system with a new FRIT-FAB interface.[22]

3 X-ray Crystallography

Specific crystal structures have been reported as follows:
Free Sugars and Simple Derivatives Thereof.- 2-Deoxy-β-D-arabino-hexopyranose,[23] 1,2-O-isopropylidene-α-D-allofuranose,[24] 1,2:5,6-di-O-isopropylidene-α-D-gulofuranose,[25] 3,5-di-O-acetyl-1,2-O-[1-endo-cyanoethylidene]-β-L-arabinofuranose,[26] 3,4-di-O-acetyl-1,2-O-(S)- and (R)-(1-cyanoethylidene)-β-L-lyxopyranose,[27] and potassium β-D-glucopyranose 6-sulphate.[28]
Glycosides and Derivatives Thereof.- Octyl α-D-glucopyranoside anhydrous (and comparison with its hemi- and mono-hydrate),[29] 4-methylumbelliferyl β-D-glucopyranoside,[30] (25R)-3β,26-dihydroxy-5α-cholestane-6,22-dionyl 3-O-β-D-glucopyranoside,[31] methyl 6,7,8-tri-O-acetyl-2,3,4-tri-O-benzyl-β-L-threo-D-gluco- and β-L-threo-D-manno-octopyranosides,[32] the β-glucoside (3),[33] methyl (S)-2,3-O-benzylidene-α-D-mannopyranoside,[34] methyl 2,3:4,6-di-O-isopropylidene-α- and β-D-galactopyranosides,[35] the selenocarbonate (4),[36] methyl β-D-glucopyranoside 3,4,6-trinitrate,[37] and the C-glycosides 3,4,5-tri-O-acetyl-2,6-anhydro-D-mannonitrile (tri-O-acetyl-α-D-arabinopyranosyl cyanide),[38] 2,3,5,6-tetra-O-acetyl-β-D-galactopyranosyl cyanide, and α-D-ribo-, β-D-xylo-, and α-D-galacto-furanosyl nitromethanes,[39] the glycosyl aminomethanes (5) and (6),[40] the thione (7),[41] and the β,α-linked glycosyl dimer (8).[42]



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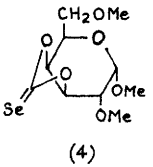

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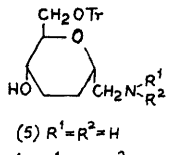
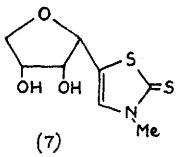
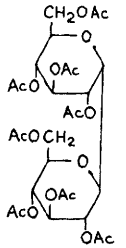


(5) $R^1=R^2=H$
(6) $R^1=Bn, R^2=CO_2Bu^t$



(7)

Oligosaccharides.- α-D-Glucopyranosyl-(1→6)-α-D-glucopyranosyl-(1→4)-α-D-glucopyranose (α-panose),[43] and the inclusion complex of m-iodophenol with permethylated β-cyclodextrin (in which one glucose unit has an unusual $^{O}S_{2}$ skew-boat conformation).[44]
Anhydro-sugars.- 1,6-Anhydrohexofuranoses with the β-D-gluco-, α-L-ido-, β-D-allo-, α-D-talo-, β-L-altro- and β-D-galacto-configuration,[45] methyl 2,3-anhydro-4,6-O-benzylidene-β-D-mannopyranoside,[46] the 2,3-anhydro-D-taloside (9),[47] 1,2-anhydro-3,4:5,6-di-O-isopropylidene-1-nitro-D-mannitol,[48] the 2,3-anhydro-α-L-lyxo-hexoside (10),[49] and di-β-D-fructofuranose 2′,1:2,3′-dianhydride.[50]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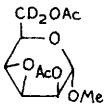
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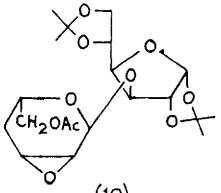
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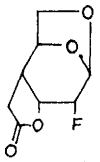
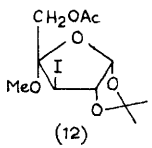

(11)

Halogen-, Nitrogen-, Sulphur- and Seleno-containing Compounds.- 1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro-β-D-galactopyranose,[51] the tricyclic fluoride (11),[52] 4,1',6'-trichloro-4,1',6'-trideoxy-galacto-sucrose,[53] the iodo-aldulose derivative (12),[54] 6-deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose,[55] allyl 1-deoxy-1-[(1-methyl-2-benzoylvinyl)amino]-α-D-fructofuranoside,[56] the 1,6-lactam (13),[57] the natural products alexine (14)[58] and 3,8-diepialexine (15),[59] the 2-amino-2-deoxy-D-mannose derivative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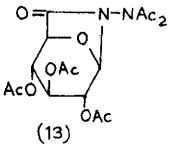
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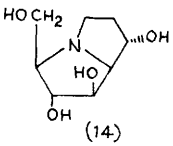
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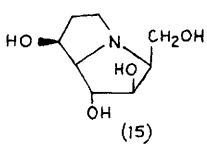
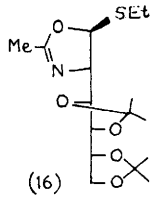

(15)

(16),[60] 3,5-di-O-acetyl-6-S-(2,3,4,6-tetra-O-acetyl-β-D-galacto- and gluco-pyranosyl)-6-deoxy-1,2-O-isopropylidene-6-thio-α-D-glucofuranoses,[61] and the phenylselenide (17).[62]

Unsaturated Compounds.- The acetylide (18),[63] C-glycoside (19),[64]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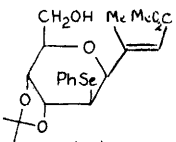
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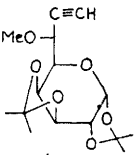
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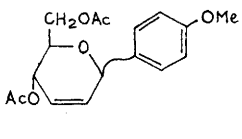
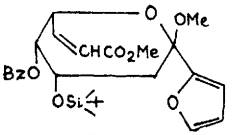

(19)

both E- and Z-isomers of compound (20), and the oct-6-enopyranoside (21).[65]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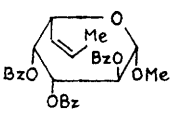
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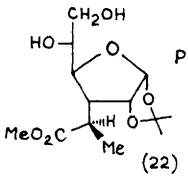
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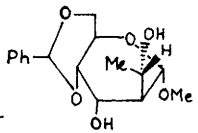
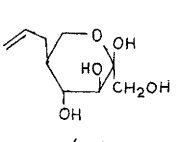
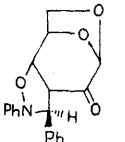

(23)

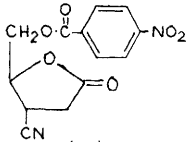
Branched-chain Sugars.- 1,2,3-Tri-O-acetyl-5-O-benzoyl-3-C-

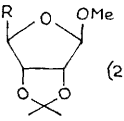
methyl-α-D-arabinofuranose,[66] the 3-branched 3-deoxyhexose (22),[67] the 2-branched 2-deoxyhexoside (23),[68] the C-allyl-ketose (24),[69] the cycloadduct (25) of levoglucosenone,[70] and the cyano-sugar lactone (26).[71]

Dialdoses, Aldduloses, Sugar Acids, and their Derivatives.- The dialdose glycoside acetal (27) and its cycloadduct (28),[72] the

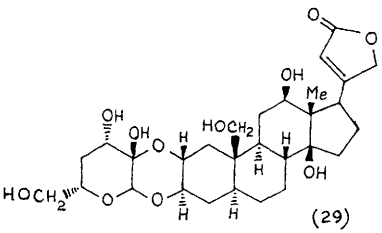

(24)

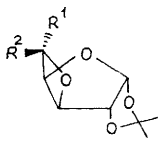

(25)


(26)


(27) R = CHO
(28) R =

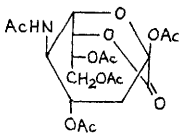
cardiac glycoside ghalakinoside (29) (which has a doubly linked 4-deoxyhexosulose unit),[73] the α-chloro-oxetane (30)[74] and its derived oxetane nucleoside (31),[75] N-(n-heptyl)- and N-(n-decyl)-D-gluconamides,[76] methyl 2-deoxy-α-D-neuraminate pentaacetate,[77] N-acetyl-2,3-dehydro-2-deoxy-neuraminic acid,[78] the 1,7-lactone (32)


(29)


(30) R^1 = Cl, R^2 = H
(31) R^1 = H, R^2 = Adenin-9-yl

from N-acetylneuraminic acid,[79] and the adducts (33) formed from L-ascorbic acid and cyclopentenone and cyclohexenone.[80]

Inorganic Derivatives.- The racemic phosphono-sugar derivative (34).[81]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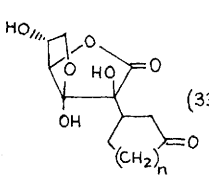
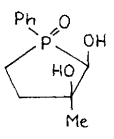
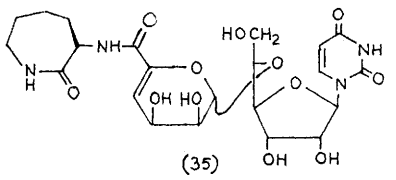

(33) n = 1 and 2


DL-(34)

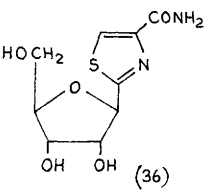
Alditols, Cyclitols and Derivatives Thereof.- 1,2,3,4,5-Penta-O-acetyl-1-C-[(5S,6S)-5-exo-nitro-bicyclo[2.2.1]hept-2-en-6-endo-yl]-D-manno-pentitol and its 5-endo-6-exo-isomer,[82] and the (RS)-P-diastereoisomers of 1,6-dichloro-1,6-dideoxy-D-mannitol 2,4:3,5-bis-O-(N-piperidylphosphate).[83]

Nucleosides and their Analogues and Derivatives.- Adenosine

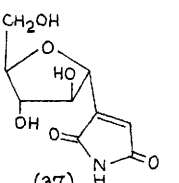
trihydrate at 105 and 295 K,[84] 3-N-β-D-ribofuranosyladenine (3-isoadenosine),[85] 1-N-β-D-ribofuranosylpyridin-4-one-3-carboxamide (in which a rare pucker of the ribose ring is reported),[86] 2′,3′-O-isopropylideneguanosine dimethylsulphoxide solvate,[87] 5-nitro-1-β-D-arabinofuranosyluracil,[88] 2′,3′,5′-tri-O-acetyl-8-bromoguanosine,[89] 4-amino-6-methylthio-1-β-D-ribofuranosylpyrazolo[3,4-d]pyrimidine 5′-monophosphate monohydrate,[90] 2-amino-6-[(4-nitrobenzyl)thio]-9-β-D-ribofuranosylpurine,[91] 3′-O-acetyl-[92] and 5′-O-acetyl-thymidine,[93] 5-methyl-2′-deoxycytidine,[94] 3′-O-acetyl-2′-deoxy-5-methoxymethyluridine,[95] 5′-(hydroxymethyl)-5′-deoxy-1-β-D-arabinofuranosyl-3H-cytosine(homo-AraC),[96] 5′-chloro-5′-deoxy-arabinofuranosylcytosine,[97] 6,5′-anhydro-6-hydroxy-2′,3′-O-isopropylideneuridine,[98] 3′-azido-3′-deoxythymidine (AZT),[99,100] 3′,5′-di-O-acetyl-2′-deoxyguanosine,[101] 2′,3′-dideoxyadenosine and 2′,3′-dideoxycytidine,[102] the nucleoside antibiotic capuramycin (35),[103] and the C-nucleosides tiazofurin (36) and its β-D-arabinofuranosyl, β-D-xylofuranosyl, and 2′-deoxy-α-D-erythro-pentofuranosyl analogues,[104] and the α-D-arabinofuranosyl (37), 2′-deoxy-α-D-erythro-pentofuranosyl,[105] and α-D-lyxofuranosyl analogues of showdomycin.[106]



(35)



(36)



(37)

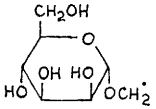
4 E.s.r. Spectroscopy

Radicals produced by γ-irradiation of various sugars in the solid state at different temperatures and in aqueous solution have been studied by a spin-trapping method which used h.p.l.c. to separate the nitroxides formed and hence gave simplified e.s.r. spectra.[107] Radiation induced free radicals derived from solid D-mannose, D-glucose, and sucrose have been shown by lyoluminescence and e.s.r. spectroscopy to persist in melts at the m.p. for comparatively long times without being dimerized.[108] The radical (38), trapped in single crystals of methyl α-D-mannopyranoside, has been characterised by ENDOR at 77 K. The geometry and electron

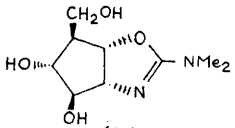
densities were deduced.[109]

5 Polarimetry, Circular Dichroism and Related Studies

Further applications of a semiempirical theory of optical activity have been reported. Calculated sodium-D line molar rotations for methyl pyranosides were consistently low, but the general dependence on structure was reproduced.[110] The dominant origin of sodium-D rotation has been correlated with a vacuum-u.v. band near 150 nm, observed in c.d. spectra of polysaccharide films.[111]



(38)



(39)

Circular dichroism of carbohydrates has been reviewed.[112] In connection with the exciton chirality method, Nakanishi and co-workers have reported the c.d. spectra of many galactopyranosides variously protected as *p*-bromobenzoate and/or *p*-methoxycinnamate esters. Spectra, recorded with nanomolar quantities, were diagnostic for the sugar, the substitution pattern, and the absolute configuration.[113] All 18 di-*O*-(*p*-phenylbenzyl)ethers of methyl α-D-galacto-, gluco- and manno-pyranosides were prepared to provide standard A values for the bichromophoric units. All the corresponding possible ether derivatives of tri- and tetra-saccharides were examined to further test the additivity relationship. Very good agreement was attained between calculated and observed A values, and the method was applied to a saponin.[114] The exciton chirality method was used to assign the absolute configuration of allosamizoline [(39), a constituent unit of the chitinase inhibitor allosamidin], by examination of its 3,4-bis-*O*-[(*p*-dimethylamino)benzoyl]-6-*O*-trityl derivative.[115] An analytical method for the determination of D-fructose using c.d. has been reported. It works for ketoses generally (*e.g.*, D-tagatose, L-sorbose, and turanose), and at concentrations up to 4.5 M (81% w/v). Other compounds such as aldoses, sucrose, and inulin, did not appear to affect the determination.[116]

Fourier-transform i.r. vibrational c.d. spectra (800 - 1650 cm^{-1}) of simple carbohydrates in DMSO-d_6 have been reported. Some

useful correlations with configuration and conformation were observed, and difficulties in deciphering spectra were pointed out.[117]

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23
Separatory and Analytical Methods

1 Chromatographic Methods

Gas-Liquid Chromatography.- Unless otherwise stated, all analyses were performed on capillary g.c. columns.

A systematic investigation has shown that the high-polarity phase SP-2330 permits the separation of virtually all possible partially methylated alditol acetate derivatives of deoxysugars, pentoses and hexoses.[1] Conditions for the quantitative analysis of 2-amino-2-deoxy-D-glucose residues in aminopolysaccharides by g.c. analysis of the aminoalditol acetate derivative have been investigated, and neutralization of the hydrolysate has been shown to be a step requiring care.[2] Analysis of alditol acetates and 1,2-O-ethylene-D-glucose acetates derived from hydroxyethyl-starch and -cellulose has been performed using a packed column.[3]

Seventeen alditols, including all possible C_4-C_6 alditols, have been separated as their per(trifluoroacetate) derivatives in 18 minutes under isothermal conditions, the method being useful for the analysis of aldoses after borohydride reduction.[4]

Partially methylated aldose units in mycobacterial glycolipids have been identified by methanolysis - trimethylsilylation followed by g.c.-m.s. (e.i.) analysis, seven partially methylated methyl rhamnopyranosides being synthesized as standards.[5] Phenolic glucosides in Saliaceae species[6] and naturally occurring hydroxybenzoic acid glucosides[7] were satisfactorily analyzed by g.c. of their per(trimethylsilyl) ethers. The g.c.-m.s. analysis of permethylated natural cytokinins using synthetic internal standards has also been reported.[8]

The anticonvulsant drug topiramate (2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulphamate) has been determined in plasma by selective absorption onto 'Cyano-Bond-Elut' cartridges and g.c.[9]

König and co-workers have reported the resolution of a variety of racemic carbohydrate derivatives, e.g. methyl

glycosides, 1,4- and 1,5-anhydroalditols, polyols and polyhydroxy acid methyl esters, as their per-O-trifluoroacetates on a remarkably enantioselective new chiral phase - fully pentylated α-cyclodextrin. Baseline resolution of enantiomers was attained in just a few minutes, and the phase was superior to previously reported polysiloxane-based phases being quite thermostable.[10,11]

High-Pressure Liquid Chromatography.- Post-column detection systems applicable to h.p.l.c. eluants have been investigated. Alditols and aldoses present in neutral eluants (H_2O or H_2O - organic solvents) from Pb^{2+}- or Na^+-form cation exchange columns have been detected by pulse amperometry with a 10-50 pmole limit, once the eluant had been converted to the requisite alkaline pH in a membrane reactor.[12] Optimization of a copper bicinchinonate reducing-sugar colourimetric analytical system for aqueous eluants from Ca^{2+}-form polystyrene-based resin or reversed-phase (Dextro-Pak) columns, and use of a post-column H^+-form resin reactor column to hydrolyse non-reducing oligosaccharides (sucrose, stachyose, raffinose), permitted detection down to 1 ng. The method was applied to determine the major soluble carbohydrates in very small pieces of wheat endosperm.[13] Sequential immobilized-enzyme reactors having β-glucosidase and glucose oxidase covalently attached to controlled pore glass beads were used to hydrolyse β-glucosides in eluant from reversed-phase h.p.l.c., and then oxidize released glucose to gluconic acid. The hydrogen peroxide so produced was then detected by chemiluminescence (reaction of H_2O_2 with luminol). Buffered eluant with up to 30% acetonitrile had little deleterious effect, and a detection limit for β-glucosides of 2 pmole was attained.[14]

Degradation of a variety of sugars has been demonstrated during aqueous chromatography on Pb^{2+}-form sulphonated polystyrene-based resins at 60°C. The extent of degradation was correlated with the portion of the open-chain form of the sugar in solution, implicating the involvement of 2,3-endiol intermediates as in alkaline degradation. Thus minor, serious, and prohibitive interference was observed in the analysis of 2-hexuloses, 2-pentuloses, and trioses, respectively. No such problems occurred with equivalent Ca^{2+}-form resins.[15]

The advantages, problems and practicalities of using a new 2% cross-linked polystyrene-based H^+-form cation-exchange resin for the separation of malto-, cello- and galacturono-oligosaccharides (DP 1-10) have been well detailed. High

molecular weight material elutes first as in size-exclusion chromatography and useful separations were achieved. The gel is soft, however, so that low flow rates were employed. A temperature of 85°C proved best, but the gel is acidic so that hydrolysis can occur.[16] Another group using the same column reported separations of cello- and malto-oligosaccharides up to DP 12, and concluded that separations occurred largely by size exclusion and were comparable to those obtained on Ag^+-form, 4-6% cross-linked resins.[17]

A recently developed C_{18}-bonded vinyl alcohol copolymer gel (Asahipak ODP-50) was used to separate homologous series of β-(1→2)-, (1→3)-, (1→4)-, (1→6)- and α-(1→3)- and (1→6)-D-gluco-oligosaccharides of DP 2-23, the aqueous alkaline eluant (pH 11) ensuring fast anomerization and hence a single peak per reducing moiety.[18] The behaviour of cyclodextrins bearing one or more malto-oligosaccharide (DP 2-5) branch, generated by enzymic reactions, has been investigated on eight different C_{18}-reversed-phase columns, with both silica gel and porous polymer gel based packings.[19] The isolation of ^{14}C-labelled sucrose from Chlorella vulgaris has been achieved on both an analytical and preparative scale on a Li^+-form cation-exchange column. Sucrose hydrolysis was observed on Pb^{2+}- and Ca^{2+}-form columns eluted with 80% aqueous ethanol at 80°C.[20]

Reversed-phase h.p.l.c. has been employed in the analysis of flavonol glycosides in the crude drug from plants of the genus Epimedium,[21] phenolic glucosides in Saliaceae species,[6] and naturally occurring hydroxybenzoic acid glucosides and hydroxybenzoyl glucoses.[7] In the last case, benzoylated derivatives were also analyzed by normal phase h.p.l.c. on silica.[7] Crude saponins containing oligoglycoside and oligoglycosyl ester moieties were qualitatively characterized using a new h.p.l.c.-m.s. system employing a FRIT-FAB interface, a semi-microbore column (1.5 mm i.d.) with a primary amine bonded silica packing, and gradient elution.[22]

Monosaccharides released by acid hydrolysis of glycoproteins were analyzed in the pmole range following N-acetylation and perbenzoylation, on a narrow bore (2.1 mm i.d.) reversed-phase column.[23] Sialic acids released from human lymphocytes by hydrolysis were determined in the nmole range by h.p.l.c. on either on anion-exchange resin or primary amine bonded silica packing. Lymphocytes of cancer patients showed increased sialic acid content and a change in distribution towards higher O-

acetylated sialic acid derivatives.[24]

A review on methods for analysis of urinary glycosaminoglycans (e.g., chondroitin sulphate, hyaluronic acid, and heparin) has covered h.p.l.c. analysis of enzymically produced di- and oligo-saccharides.[25] Oligosaccharide-alditols released from human meconium glycoproteins by alkaline borohydride treatment have been separated by employing anion-exchange, primary amine bonded silica, and reversed-phase columns, and many neutral and acidic oligosaccharides were isolated for further structural analysis.[26] The successful separation of 45 pyridylamino derivatives (produced by a reductive amination technique) of oligosaccharides released from brain glycoproteins by hydrazinolysis - N-acetylation has been achieved by h.p.l.c. on size exclusion and reversed-phase columns, the elution behaviour being analyzed on a 2D-map.[27] A series of dansylated ovalbumin-derived glycopeptides [(antennary manno-oligosaccharide)-(1→4)-β-D-GlcNAc-(1→4)-β-D-GlcNAc-Asn-DNS] have been examined by h.p.a.c., the h.p.l.c. version of affinity chromatography, on silica-immobilized concanavalin A or wheat germ agglutinin with a high content of lectins; the separations achieved were structure dependent.[28]

Natural cytokinins, including zeatin riboside, have been analyzed by reversed-phase h.p.l.c. using synthetic internal standards.[8]

An attractive appearing reversed-phase h.p.l.c. method, in which ionization of sugar acids is prevented by use of acidic eluant (e.g., pH 2), has been used for analysis with fluorometric detection of estriol 3- and 16-glucuronides in urine of non-pregnant women after initial concentration onto graphitized carbon black cartridges,[29] and of L-ascorbic acid in fruit juice.[30] Other analyses of L-ascorbic acid (Vitamin C) amongst other water soluble vitamins have been effected by reversed-phase h.p.l.c. with electrochemical or u.v. detection.[31,32]

The aminoglycoside antibiotic sisomycin has been assayed by reversed-phase h.p.l.c. following pre-column derivatization with o-phthalaldehyde and β-mercaptopropionic acid to yield intensely fluorescent 1,2-disubstituted isoindole derivatives. Normally such derivatives are formed post-column because of their instability, but in these studies satisfactory stability was attained.[33,34] The semisynthetic aminoglycoside netilmicin was determined in plasma by reversed-phase h.p.l.c. after pre-column derivatization with 1-fluoro-2,4-dinitrobenzene, optimal

conditions for derivatization of the primary functions being established.[35] Reversed-phase analyses have been described for monitoring the production of nucleoside antitumour agents in fermentation broths with minimal sample preparation,[36] and for structurally related peptide-nucleoside antibiotics including blasticidin S and mildiomycin analogues in fermentation matrices, with photodiode array u.v. detection.[37]

A number of papers on the reversed-phase h.p.l.c. analysis of nucleosides and related compounds have appeared. A procedure for the analysis of blood plasma pyrimidine nucleosides and bases has been applied to monitor the fate of radiolabelled material.[38] The solvophobic theory has been applied to explain the observed retention of natural and modified pyrimidine nucleosides and bases.[39] Other papers have reported analyses of 21 synthetic compounds potentially present after treatment of DNA with anti-cancer nitrosoureas, *e.g.*, dinucleosides (linked by $-CH_2CH_2-$ *via* base O- and N-atoms) and their degradation products,[40] a series of cycloalkylated nucleosides, bases and 5′-monophosphates,[41] common and modified deoxyribonucleosides from DNA hydrolyzates,[42] and the antiviral drugs (*E*)-5-(2-bromovinyl)-2′-deoxyuridine[43] and 3′-azido-3′-deoxythymidine (AZT)[44,45] and its 5′-*O*-glucuronide[45] in plasma and urine. 5′-Deoxy-5′-methylthioadenosine has been concentrated from biological fluids on a phenylboronate column prior to reversed-phase h.p.l.c. analysis,[46] while its β-D-xylofuranosyl analogue, present in the nudibranch mollusc *Doris verrucosa*, has been isolated and assayed by reversed-phase h.p.l.c.[47] An on-line pre-column bearing phenylboronate ligands for concentration of diols, especially ribonucleosides, from biological samples has been detailed. After elution of proteinaceous material, the eluant is changed from base to acid (pH 3) and the diols are passed to a reversed-phase column for analysis.[48]

2′,3′-Dideoxy-adenosine, -inosine, and -cytidine have been determined in biological samples by both reversed-phase and ion-pair reversed-phase methods.[49] An ion-pair ($Bu^n_4N^+$) reversed-phase analysis of purine nucleosides, bases, nucleotides, dinucleotides, and nucleoside derivatives (adenosyl-homocysteine, -succinate, and -methionine) from acid-extracted tissues was undertaken to investigate adenosine reservoirs in rats on treatment with a metabolic inhibitor which blocks adenosine transport.[50]

Column and Continuous Annular Chromatography.- The chromatographic separation of glucose and fructose has been reviewed, with the application of Ca^{2+}-form cation-exchange resins being discussed in detail.[51] Optimization of the separation of α-cyclodextrin and D-glucose, required for the purification of enzymically produced mixtures, on Na^{+}-form polystyrene-based cation-exchangers has shown a 6% cross-linked resin to be the most suitable.[52] α-, β- and γ-Cyclodextrins have been separated from linear malto-oligosaccharides and partly hydrolysed starch on an N-benzoylated polyacrylamide resin eluted with water. The resin was prepared by reacting Bio-Gel P6 with ethylenediamine then coupling of ca. 20% of the available amino-groups with benzoic acid using a carbodiimide reagent. Quantification with this system and by an h.p.l.c. method were compared.[53]

Sugar phosphates and other biologically important anions have been determined simultaneously by ion chromatography (Dionex system, with anion-exchange columns, anion membrane suppressor, and conductivity detection). Glucuronic acid 1-phosphate, fructose 6-phosphate, glucose 6-phosphate, and inositol phosphates were detected down to 20-100 pmole and in rat brain and liver samples.[54]

Oligo-galacturonic acids (DP 1-8) have been separated analytically on a partially quaternized hydroxyethyl methacrylate-based anion-exchange resin (QAE-Spheron 40).[55] Preparative isolation of oligo-galacturonic acids (up to gram quantities for DP 3-5, lesser amounts of DP 2, 6 and 7) derived by enzymic hydrolysis of α-D-polygalacturonic acid from citrus pectin, has been achieved utilising the improved performance of a formate-form macroporous strong base anion-exchange resin eluted stepwise with a sodium formate gradient (pH 4.7). A simple separation of galactonic acid (pKa 3.60), galacturonic acid (pKa 3.42) and glucuronic acid (pKa 3.20) on this resin was also reported.[56]

All eight inositol isomers have been separated on a Ca^{2+}-form cation-exchange resin eluted under pressure with water. The method was applied to the separation of the six inositols and the range of other unknown products formed on reaction of myo-inositol with Raney nickel.[57]

Gentamicin C_1, C_{1a} and C_2, the three major components of the antibiotic from Micromonospora purpurea culture filtrates, were isolated by medium pressure chromatography on silica gel.[58]

A study on the separation of fructose, glucose and sucrose by continuous annular chromatography on a Ca^{2+}-form polystyrene-

based resin has been reported.[59]

Paper and Partition Chromatography.- Ternary solvent combinations have been re-examined for the paper chromatography of sugars, with rhamnose, arabinose and galactose being used as probes. A useful mixture (EtOAc-EtOH-H_2O) was promoted.[60]

Centrifugal liquid-liquid partition chromatography has been applied to separate efficiently flavonoid and triterpene glycosides that vary only in their sugar residues.[61]

2 Electrophoresis

A review on methods for analysis of urinary glycosaminoglycans has covered electrophoresis of enzymically produced di- and oligosaccharides.[25] Micellar electrokinetic capillary chromatography, which is equivalent to capillary zone electrophoresis with a surfactant added to the carrier electrolyte, has been used with u.v. detection for the simultaneous determination of seven water-soluble vitamins including vitamin C and riboflavin phosphate.[62] A fraction collector for use with capillary zone electrophoresis was demonstrated for isolation of adenosine and guanosine from their mixture.[63]

3 Other Analytical Methods

Several biosensors capable of detecting D-glucose have been detailed. Glucose oxidase chemically immobilized on a tin(IV) oxide electrode by various methods,[64,65] or simultaneously immobilized on an electrode with ferrocenecarboxylate as an electron relay in an electroconducting polypyrrole film,[66] have been used as amperometric sensors. At constant potential, they yield a current proportional to glucose concentration when immersed in test solutions. D-Glucose has been determined by reaction with immobilized glucose oxidase in a flow-through reactor (assay time 2 minutes), the H_2O_2 produced being quantified by its chemiluminescence reaction with luminol. For sucrose, maltose, lactose and fructose, a further appropriate immobilized enzyme *e.g.*, invertase for sucrose, was employed to convert these sugars to glucose.[67]

Electrochemical detection of carbohydrates (mono- to oligosaccharides, deoxysugars, and even polyols) has been achieved by use of a carbon electrode modified by addition of cobalt

phthalocyanine electrocatalyst. Oxidation occurred under very basic conditions at +0.4 to +0.5 V vs Ag/AgCl. No sample preparation was required other than dilution and particulate filtration of food products and physiological fluids, and a 10-50 pmole detection limit was attained.[68]

D-Fructose in concentrations up to 4.5M (81% w/v) has been determined by a method employing circular dichroism. Other compounds such as aldoses, sucrose and inulin did not affect the assay, although the method could be applied to other ketoses, e.g., D-tagatose, L-sorbose and turanose.[69]

Cyanogenic glucosides in food have been assayed by enzymic hydrolysis and isolation of the released hydrogen cyanide in a sealed diffusional apparatus.[70]

Sialic acids, released from human lymphocytes by hydrolysis, have been determined in the nanomolar range by a modified periodic acid - thiobarbituric acid assay.[24]

myo-Inositol has been determined using a flow-injection system. Passage of myo-inositol through a reactor containing inositol dehydrogenase, lactate dehydrogenase and lactate oxidase co-immobilized on porous glass produced an equivalent amount of hydrogen peroxide, which was used to convert hexacyanoferrate-(II) to hexacyanoferrate(III) in a second reactor containing immobilized peroxidase, the ferrate (III) being detected amperometrically.[71]

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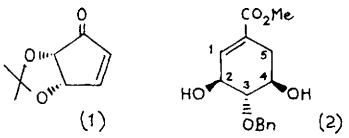
24
Synthesis of Enantiomerically Pure Non-carbohydrate Compounds

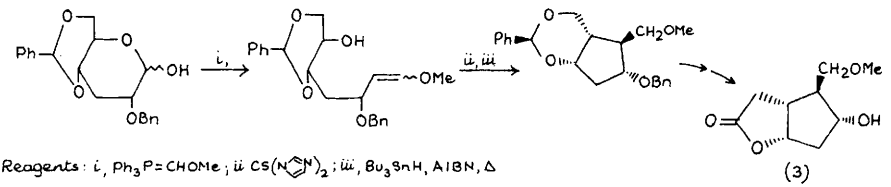
A review has appeared on the use of carbohydrates as chiral templates in synthesis.[1]

1 Carbocyclic Compounds

The cyclopentenone (1), a synthon for prostaglandins and related compounds, has been prepared from D-ribonolactone by chemistry similar to that reported by other workers last year (see Vol. 21 p.256),[2] and the 4-O-benzyl derivative of methyl 3-epi-shikimate (2) has been prepared from glucose by an intramolecular Wadsworth-Emmons reaction as used by earlier workers for shikimic acid itself (see Vol. 18, p.172).[3] The diagram indicates the sugar carbon atoms from which the ring atoms derive.



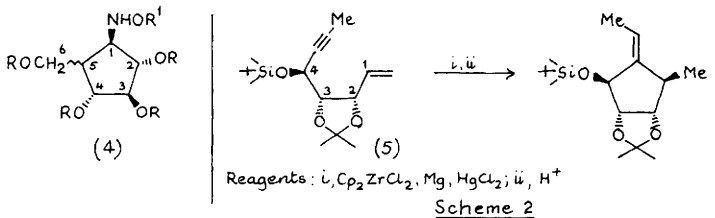
(1) (2)



Reagents: i, $Ph_3P{=}CHOMe$; ii $CS(N{\bigcirc}N)_2$; iii, Bu_3SnH, AIBN, Δ

(3)

Scheme 1



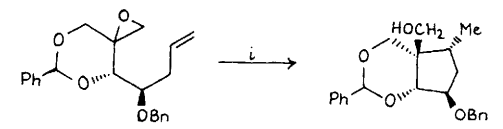
(4) (5)

Reagents: i, Cp_2ZrCl_2, Mg, $HgCl_2$; ii, H^+

Scheme 2

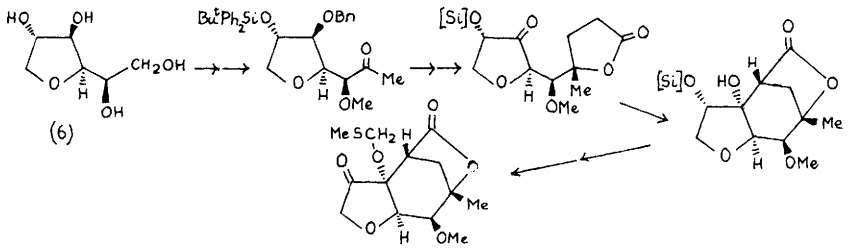
Free radical cyclization has been used as the key step in a synthesis of the 'Corey lactone' (3), as outlined in Scheme 1; the cyclization was stereospecific, and could be rationalized by invoking a boat-like transition

state.[4] In a similar way, cyclization of oxime ethers of 2,3,4,6-tetra-O-alkyl-D-glucose gave the products (4,R,R'=Me,Bn), as a mixture of the two diastereomers indicated.[5] The enyne (5), derived from D-ribonolactone (sugar carbons numbered) could be cyclized stereoselectively (Scheme 2) by a metallocene-mediated reaction,[6] and titanium (III) - induced cyclization of epoxyalkenes has been applied to carbohydrate examples, such as that in Scheme 3.[7]

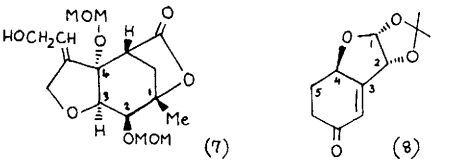


Scheme 3

A route has been developed for the synthesis of a chiral, functionalized, hexahydrobenzofuran unit as found in the avermectins by manipulating 1,4-anhydro-D-glucitol (6) as indicated in Scheme 4; the key intramolecular Claisen condensation was stereospecific.[8] The same group have also prepared the related intermediate (7) in a somewhat similar way from 2,3-O-isopropylidene L-erythrose (sugar atoms numbered), itself made from L-rhamnose.[9]



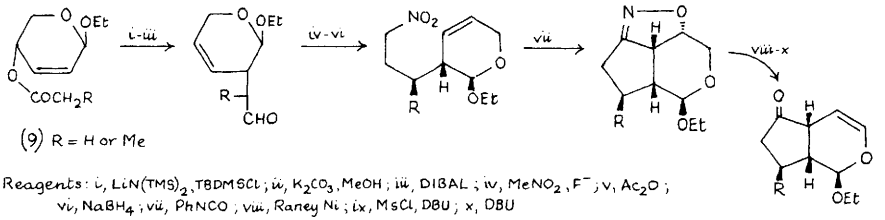
Scheme 4



The functionalized carbocycle (8) has been prepared from D-glucose (carbon atoms numbered) by Wittig chain extension and intramolecular aldol condensation.[10]

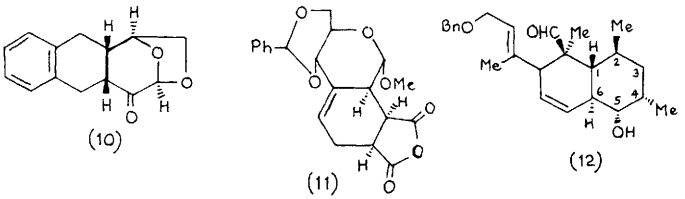
An ingenious approach to chiral iridoid aglycones involves the Ireland-Claisen rearrangement of the allylic ester (9) (Scheme 5) derived from diacetyl D-xylal, and subsequent annulation by intramolecular nitrile oxide

cyclization; these methods were applied to the synthesis of several natural products, including (-)-specionin.[11]

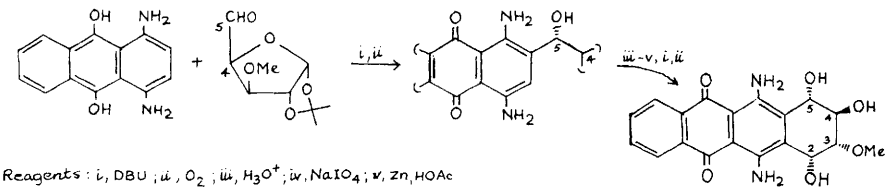


Scheme 5

Cycloaddition of o-diquinodimethane and levoglucosenone gave the adduct (10), potentially useful for making pyranonaphthoquinones.[12] Diels-Alder reactions of a glucose-derived diene with maleic anhydride and other dienophiles gave annulated systems, such as (11). These products are formed by approach of the dienophile form the face opposite to the anomeric substituent.[13] An intramolecular Diels-Alder reaction was used to establish the reduced naphthalene unit (12) of kijanolide, the carbons of a trideoxy-doubly branched hexose being incorporated as indicated.[14]



A diaminoanthacyclinone has been prepared by Marschalk-type chemistry as indicated in Scheme 6.[15]



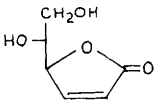
Scheme 6

2 γ- and δ- lactones

Efficient routes have been described for the synthesis of butenolide (13), its L-threo-isomer, and related compounds from L-ascorbic and D-isoascorbic acids.[16]

A full and extended account has been given of the syntheses from L-ascorbic acid of delesserine, leucodrin, and related metabolites (see Vol.21,

p.259).[17] Other workers have prepared sawaranin (14) by decarboxylative hydrolysis of one of the intermediates in this work.[18]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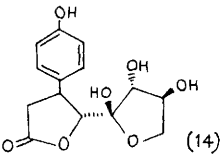
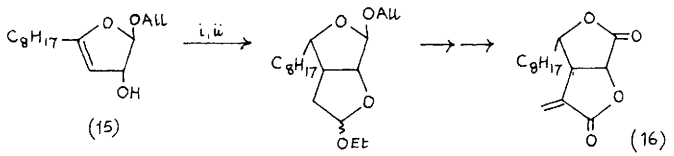

(14)

D-Ribose has been used to prepare the enol ether (15) (Scheme 7) which was then converted to (-)-isoavenaciolide (16), an antifungal mould metabolite, with the key step being the indicated free-radical process.[19]

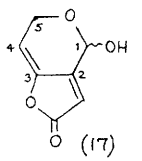

(15) (16)

Reagents: i, $BrCH_2CHBr(OEt)$; ii, Bu_3SnH, AIBN

Scheme 7

Arabinose has been used to prepare the racemic metabolite patulin (17), by removal of all the chiral centres except for the anomeric position (sugar carbons indicated).[20]

(5S)-Hydroxymethyl-δ–valerolactone (18) has been made from D-mannitol via isopropylidene-D-glyceraldehyde.[21] Epoxides of type (19) can be made in a few steps from triacetyl-D-glucal, and provide intermediates for the lactone ring of the mevinic acids, as demonstrated by their conversion to (20) with benzyl magnesium chloride.[22]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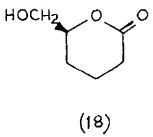
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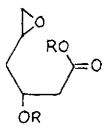
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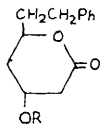
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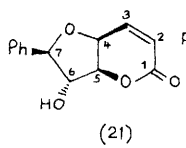
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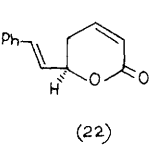
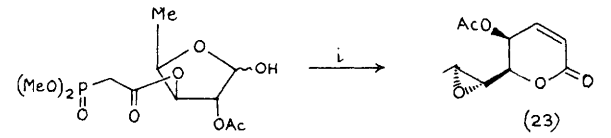

(22)

Two further syntheses of (+)-altholactone (21) (See Vol.21, p.259) have been reported; in one approach, carbons 1-4 of L-arabinose provided C(3) to C(6) of (21),[23] whilst in the other, D-gluconolactone was the precursor, C(1)-C(5) of the sugar becoming C(7)-C(3) of the target.[24] Another route to the related goniothalamin (22) has been published, in which the chiral centre corresponds to C(2) of D-glucose.[25] The antibiotic asperlin has been shown to have (6S, 7R)-stereochemistry as a result of a synthesis of the diastereomeric (6R, 7S)-isomer (23), the key step in which is an ingenious tandem epoxide formation and intramolecular Wadsworth-Emmons reaction (Scheme 8) of a glucose-derived precursor.[26]



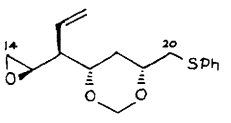
Scheme 8

3 Macrolides and their constituent segments

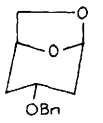
Two xylose-derived chiral synthons reported last year (Vol.21, p.261-2) for the polyene macrolide amphotericin B have been incorporated into the synthetic aglycone, amphoteronolide B.[27] The C(14)-C(20) building block (24) for amphoteronolide B has been prepared from isopropylidene L-glyceraldehyde, with the glyceraldehyde carbons providing C(14)-C(16);[28] the vinyl group was introduced by a [2,3]-Wittig rearrangement discussed in Chapter 14. The C(1)-C(6) and C(7)-C(12) synthons (25) and (26) have both been prepared from levoglucosan.[29]

A full account has been given of the synthesis of the macrodiolide elaiophylin (see Vol.20, p.264).[30]

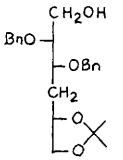
The unit (27) has been prepared from tri-O-acetyl-D-glucal via intermediate (28), the C(2)-methyl group being introduced by alkylation of the SAMP-hydrazone. Synthon (27) was subsequently converted into the C(1)-C(15) segment (29) of the immunosuppressant macrolide FK506 (which these authors have renamed tsukubaenolide).[31]



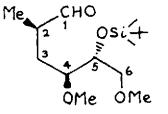
(24)



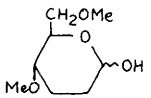
(25)



(26)



(27)



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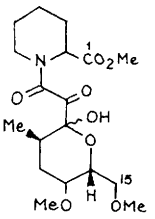

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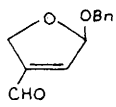
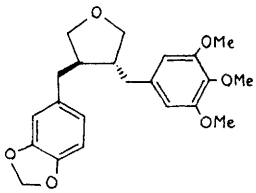


(30)



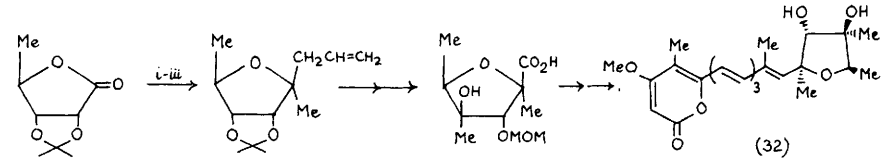
(31)

4 Other Oxygen Heterocycles

A major achievement in this area has been the completion of a carbohydrate-based synthesis of the spiroacetal-polyether antibiotic salinomycin (see Vol.21,

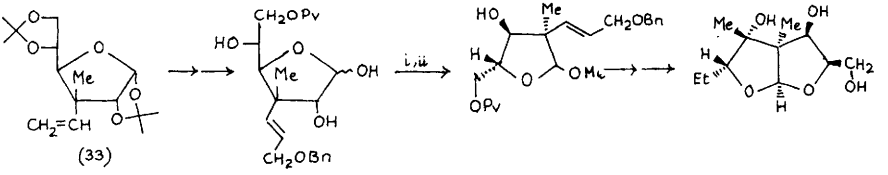
p.263-4 for a previous report).[32] A full account has been given of the synthesis of aurovertin B from D-glucose (see Vol.20, p.265).[33]

The intermediate (30) (see Vol.20, p.266) has been used for the chiral synthesis of the lignan (-)-burseran (31) and the related (-)-cubebin and (-)-hinokinin; the enantiomer of (30) was used to make (+)-burseran.[34] The mycotoxin (-)-citreoviridin (32) and the related (+)-citreoviral have been synthesized from D-ribonolactone via the key intermediates shown in Scheme 9; the method for introduction of two alkyl groups at the anomeric centre is a noteworthy point.[35] The bis(tetrahydrofuran) moiety of another pyrone mycotoxin, (+)-asteltoxin, has been prepared from the known glucose-derived intermediate (33) (see Vol.19, p.145) as outlined in Scheme 10.[36]



Reagents: i, MeLi; ii, MeOH, TsOH, $Me_2C(OMe)_2$; iii, ⌒TMS; $ZnBr_2$, $(CH_2Cl)_2$

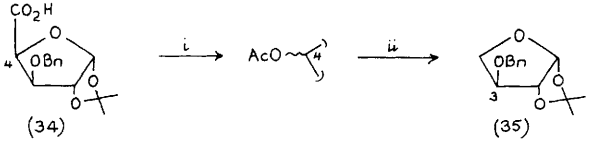
Scheme 9



Reagents: i, $NaIO_4$; ii, MeOH, IR-120(H^+)

Scheme 10

When the glucose-derived acid (34) was treated as shown in Scheme 11, the L-threose derivative (35) was obtained; the C(3)-epimer was similarly prepared, and both compounds were advocated as useful 4-carbon chiral synthons.[37] Some chiral 3-benzyloxytetrahydrofurans suitable for synthesis of active herbicides have been made from diacetone glucose.[38]

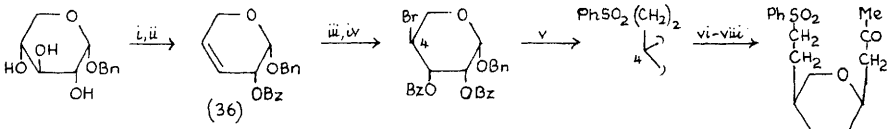


Reagents: i, $Pb(OAc)_4$; ii, Et_3SiH, $MgBr_2$

Scheme 11

A further carbohydrate-based approach to the pseudomonic acids has been reported; in this work, somewhat similar conceptually to an earlier route (Vol.18, p.247), benzyl α-D-xylopyranoside was converted (Scheme 12) into

the alkene (36) which was then manipulated as shown to introduce the two carbon chains.[39]



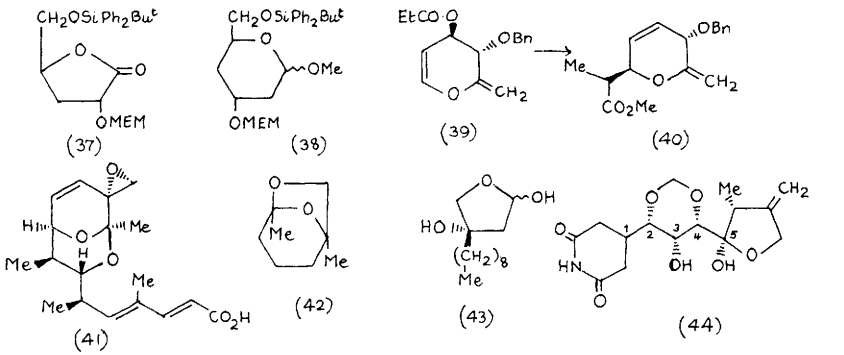
Reagents: i, BzCl·Py (−40°); ii, Ph_3P, CHI_3, imidazole; iii, NBS, H_2O; iv, BzCl, Py; v, CH_2=CH·SO_2Ph, Bu_3SnH; vi, Pd/C, cyclohexene; vii, Ph_3P=$CHCOMe$; viii, DBU

Scheme 12

A one-carbon ring expansion of γ-lactone (37) was used in a synthesis of the intermediate (38) required for mevinic acid syntheses.[40] An ester enolate Claisen rearrangement of the glucose-derived bis(enol ether) (39) gave product (40), used for the synthesis of (+)-streptolic acid (41).[41]

A full account has been given of the synthesis of natural (S)-(-)-frontalin from α-D-isosaccharinolactone, and by manipulation of the same starting material in a different way, the (R)-(+)-isomer (42) could also be made, as could the known synthon (43) for (-)-malyngolide.[42]

Some papers on nogalamycin congeners (see Vol.19, p.257) are mentioned in Chapter 19; papers on sesbanimide are referred to in section 5, and a reference dealing with the epoxide leukotriene A_4 is discussed with related systems in Section 6.

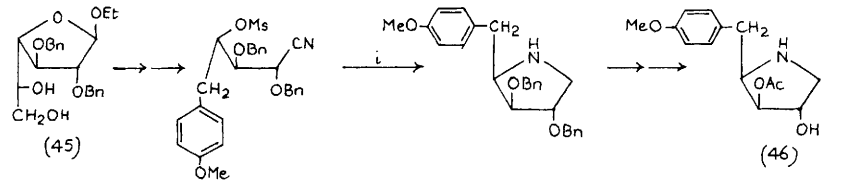


5 Nitrogen Heterocycles

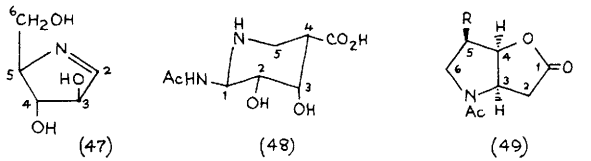
A further synthesis of the bioactive (+)-enantiomer (44) of sesbanimide has been reported, with the carbon framework of D-glucose being incorporated as shown,[43] and a full account has been given of an alternative route to (44) and its (-)-enantiomer from the enantiomeric xyloses (see Vol.19, p.261, and Vol.20, p.268).[44]

The antiprotozoal agent anisomycin (46) has been prepared from the D-galactose derivative (45) as outlined in Scheme 13,[45] and the unsaturated

fungal metabolite (47) has been synthesized from D-glucose (sugar carbons indicated).[46]

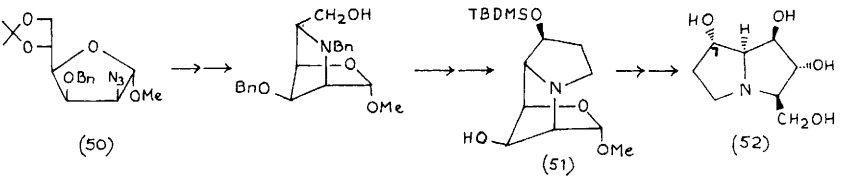


Scheme 13



In order to clarify its absolute stereochemistry, both enantiomers of the naturally-occurring sialidase inhibitor siastatin B were prepared from the enantiomers of ribose in multistep sequences, and the natural product was shown to have structure (48), the carbons of the precursor L-ribose being indicated.[47] Compounds (49, R=H and OBn) have been prepared from D-glucose (carbons indicated) as potential precursors for the pyrrolizidine alkaloids retronecine and crotanecine respectively.[48] Some other references to the synthesis of hydroxylated pyrrolidines and piperidines appear in Chapter 18.

The D-glucose-derived 2-azido-2-deoxy-α–D-mannofuranoside (50) (see Vol.19, p.169) could be employed as a precursor for the highly functionalized pyrrolizidine alexine (52) (Scheme 14); since the new chiral centre in intermediate (51) was not created stereospecifically, the 7-epimer of alexine was also accessible.[49]

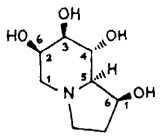


Scheme 14

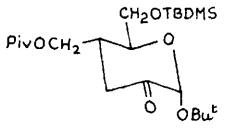
6-Epicastanospermine (53) and 1,6-diepicastanospermine (see exocyclic numbering) have been prepared from L-gulonolactone (sugar numbering endocyclic); use of D-gulonolactone gave the enantiomers of these two compounds. As a result of this work, it was demonstrated that the naturally-occurring 6-epicastanospermine has absolute configuration (53), and

a report to the contrary last year (see Vol.21, p.268) must therefore be in error.[50] Full accounts have been given of the synthesis of 1-deoxycastanospermine[51] and some related di- and trihydroxyindolizidines.[52] (see Vol.21, p.268)

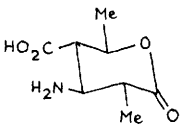
Amination of branched-chain hexopyranosidulose (54) via reaction of its enolate with dibenzyl azodicarboxylate led ultimately to the δ–lactone (55), a key intermediate for chiral synthesis of 1β–methylcarbapenems of type (56).[53]



(53)



(54)



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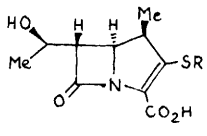
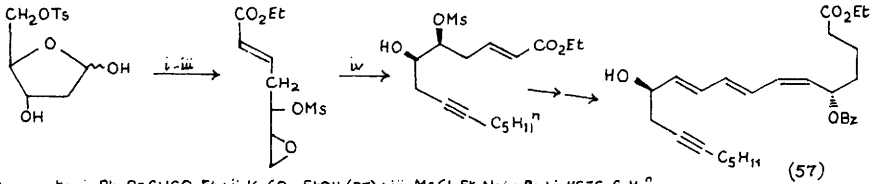


(56)

6 Acyclic compounds

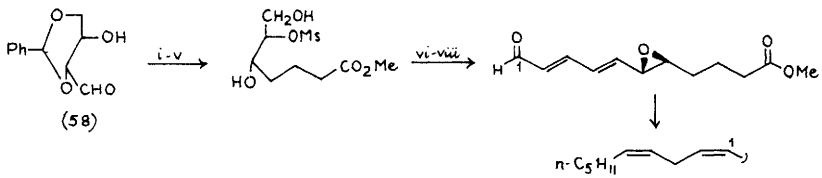
Metabolites of arachidonic acid continue to attract attention. The derivative (57) of 14,15-didehydroleukotriene B_4, and its 20-hydroxy analogue, potential precursors of labelled leukotrienes, have been prepared from 2-deoxy-D-ribose (sugar carbons numbered) as outlined in Scheme 15.[54] The chemistry



Reagents: i, $Ph_3P{=}CHCO_2Et$; ii, K_2CO_3, EtOH (RT); iii, MsCl, Et_3N; iv, BuLi, $HC{\equiv}C\text{-}C_5H_{11}{}^n$

Scheme 15

used is reminiscent of that used by the same group for the synthesis of LTB_4 itself (see Vol.16, p.269), work which has now been presented in full and extended to a number of analogues.[55] An approach used previously for the synthesis of LTB_4 (see Vol.19, p.263-4 and Vol.20, p.270) has been modified as a route to 19-hydroxy-LTB_4[56] whilst a high-yielding route to leukotriene A_4 methyl ester has been reported, proceeding from the periodate cleavage product (58) of 4,6-O-benzylidene D-glucose as outlined in Scheme 16.[57]

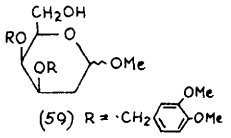


(58)

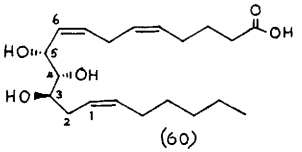
Reagents: i, $Ph_3P{=}CHCH_2CO_2^-$; ii, H_2, Pd/C; iii, C_2H_2; iv, MsCl; v, H^+; vi, K_2CO_3, MeOH; vii, CrO_3, Py; viii, viii, $Ph_3P{=}$ 

Scheme 16

Trihydroxylated arachidonate metabolites of the hepoxilin/trioxilin pathway have been prepared. The derivative (59) of 2-deoxy-D-galactose was used to produce both C-10 diastereomers of trioxilin B_3, namely (60) (sugar carbons numbered), and its isomer at C-10 (sugar C-5) made by Mitsunolu inversion of an appropriate intermediate.[58] The 8,9,12-trihydroxylation pattern has also been synthesized; the 8S, 9R, 12S-isomer (61) was available from 2-deoxy-D-ribose (sugar carbons indicated), and the three other stereomers with 12S-configuration, and the 12R-epimer of (61), were made by appropriate inversion steps.[59]



(59) R = $\cdot CH_2$



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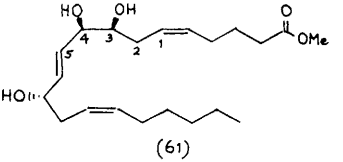

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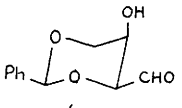
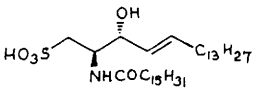
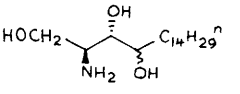


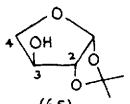
(62)



(63)



(64)



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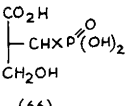

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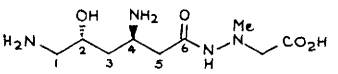


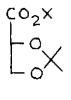
(67)

2,4-Q-Benzylidene-D-threose (62) obtained by periodate degradation of 4,6-Q-benzylidene-D-galactose, has been converted into the sulpholipid (63), found in the alkali-stable lipids of a diatom, by chemistry similar to that reported by other workers for the synthesis of sphingosine (see Vol.20, p.269).[60] Grignard addition to (62) was used to prepare the separate isomers of phytosphingosine (64).[61] The enantiomer of (62) (from L-arabinitol) was convertible by acidic acetone into (65), and thence, by Wittig reactions at C-3, into the phosphonate analogues (66, X=H,F) of 2-phosphoglyceric acid.[62]

The antibiotic (+)-negamycin (67) has been prepared from mono-Q-isopropylidene glucose in nine steps (sugar carbons numbered).[63]

Various papers have appeared on the preparation of potentially-useful chiral synthons. Electrolysis of 2,3:5,6-di-Q-isopropylidene-D-mannitol at an oxide-coated nickel electrode gave derivatives (68, X=Me,K) of isopropylidene D-glyceric acid, and similar treatment of isopropylidene L-ascorbic acid gave the enantiomers.[64] Ester (69) could be prepared from L-ascorbic acid by deoxygenation of an L-threonic acid derivative previously reported (Vol.19, p.260), and reduced to the (R)- butanetriol derivative; this now becomes

readily available (35% from ascorbic acid), the enantiomer being available from L-malic acid.[65] Degradation of a previously-reported branched-chain compound (Vol.16, p.145) has led to 2,3-O-isopropylidene-2-C-methyl-L-glyceraldehyde (70) and related systems.[66] The α,β-unsaturated aldehyde (71), or its enantiomer, are available by treatment of the appropriate enantiomer of dibenzylarabinal with mild aqueous acid and mercuric ions.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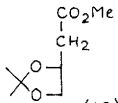
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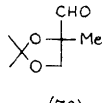
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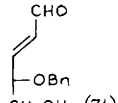
(71)

A paper on the use of a glycosylamine derivative as a chiral auxiliary is mentioned in Chapter 10.

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